PTO/AIA/15 (10-17)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	42534-708.304
First Named Inventor	Helmy ELTOUKHY
Title	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 91] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✔] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 11]
6. **Inventor's Oath or Declaration** [*Total Pages* ____] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee ____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [ ] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✔] **Other:** Track One Request

***Note**: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[✘] The address associated with Customer Number: 115823 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Timothy A. Hott/	Date	2019-11-01
Name (Print/Type)	Timothy A. Hott	Registration No. (Attorney/Agent)	67740

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Helmy		ELTOUKHY	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Atherton	CA	US

Mailing Address of Inventor:

Address 1	505 Penobscot Drive
Address 2	
City	Redwood City
State/Province	CA
Postal Code	94063
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	AmirAli		TALASAZ	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Atherton	CA	US

Mailing Address of Inventor:

Address 1	505 Penobscot Drive
Address 2	
City	Redwood City
State/Province	CA
Postal Code	94063
Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	115823		
Email Address	patents@guardanthealth.com	Add Email	Remove Email
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		
Attorney Docket Number	42534-708.304	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	11	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	115823		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
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Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16601168	2019-10-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16601168	Continuation of	15892178	2018-02-08
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15892178	Continuation of	14861989	2015-09-22	9920366	2018-03-20

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14861989	Continuation of	PCTUS2014072383	2014-12-24
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2014072383	Claims benefit of provisional	61948509	2014-03-05
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2014072383	Claims benefit of provisional	61921456	2013-12-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	GUARDANT HEALTH, INC.		
Mailing Address Information For Applicant:			
Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	**State/Province**	CA
Country	US	Postal Code	94063
Phone Number		Fax Number	
Email Address	patents@guardanthealth.com		

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Timothy A. Hott/			Date (YYYY-MM-DD)	2019-11-01
First Name	Timothy	Last Name	Hott	Registration Number	67740

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Helmy ELTOUKHY	Nonprovisional Application Number (if known):	
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Timothy A. Hott/	Date 2019-11-01
Name (Print/Typed) Timothy A. Hott	Practitioner Registration Number 67740

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/61 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/861,989

filed on September 22, 2015.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

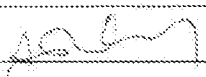
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: AmirAli Talasaz Date (Optional): 11/10/15

Signature: 

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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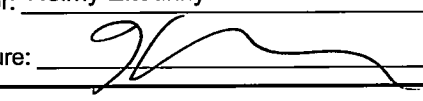
LEGAL NAME OF INVENTOR

Inventor: Helmy Eltoukhy Date (Optional): 11/10/15

Signature: 

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

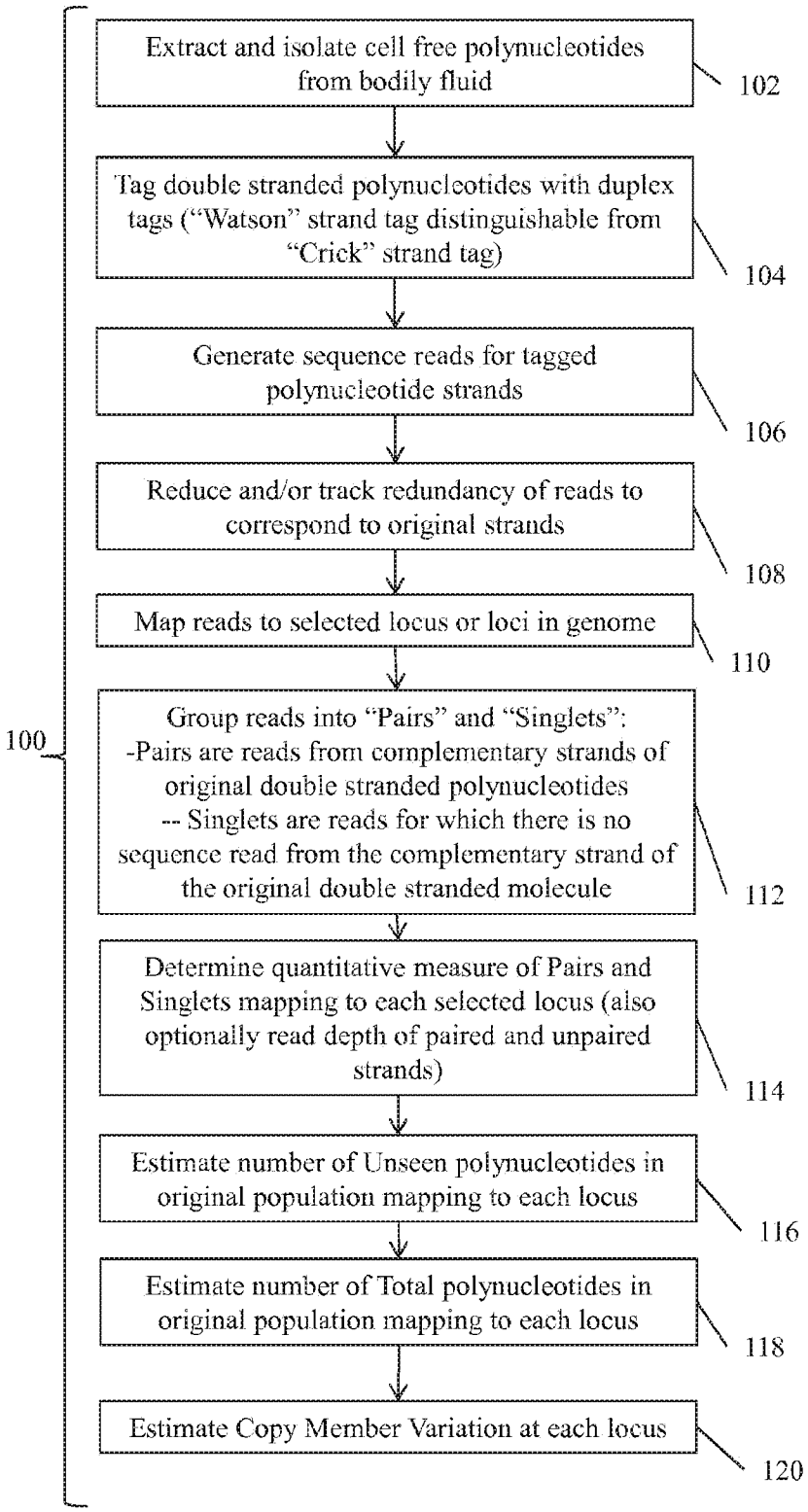

Extract and isolate cell free polynucleotides from bodily fluid
102
Tag double stranded polynucleotides with duplex tags ("Watson" strand tag distinguishable from "Crick" strand tag)
104
Generate sequence reads for tagged polynucleotide strands
106
Reduce and/or track redundancy of reads to correspond to original strands
108
Map reads to selected locus or loci in genome
110
Group reads into "Pairs" and "Singlets":
-Pairs are reads from complementary strands of original double stranded polynucleotides
-- Singlets are reads for which there is no sequence read from the complementary strand of the original double stranded molecule
112
Determine quantitative measure of Pairs and Singlets mapping to each selected locus (also optionally read depth of paired and unpaired strands)
114
Estimate number of Unseen polynucleotides in original population mapping to each locus
116
Estimate number of Total polynucleotides in original population mapping to each locus
118
Estimate Copy Member Variation at each locus
120
100

Fig. 1

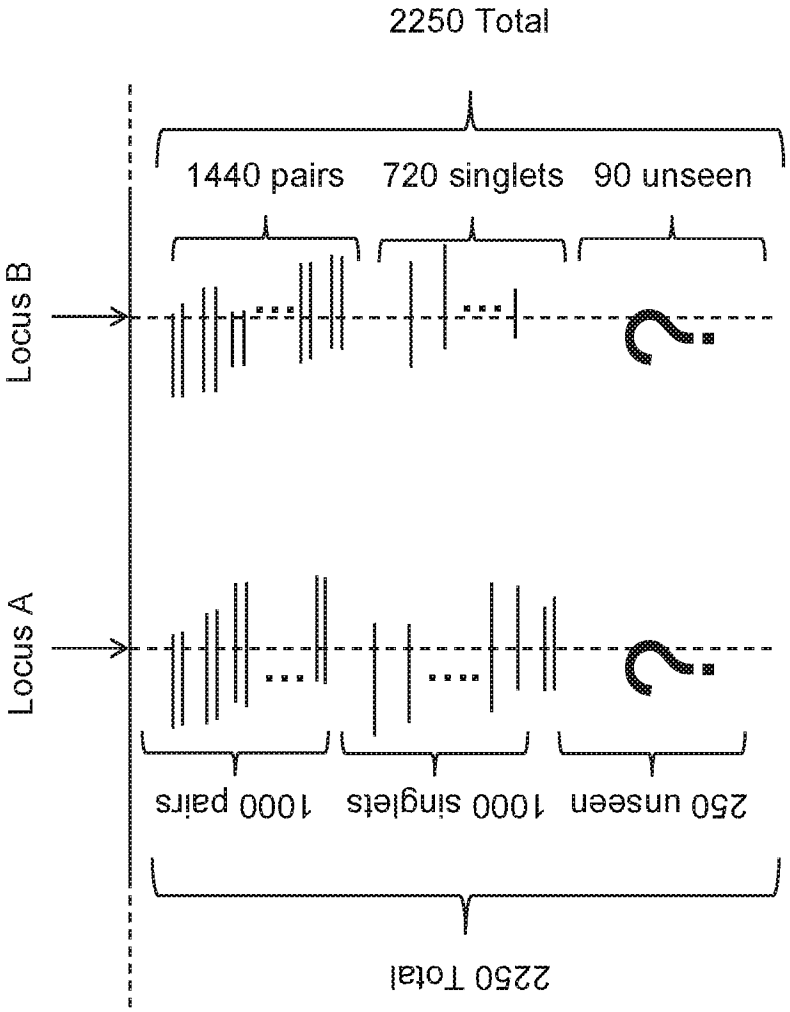

2250 Total
1440 pairs
720 singlets
90 unseen
Locus B
Locus A
1000 pairs
1000 singlets
250 unseen
2250 Total

Fig. 2

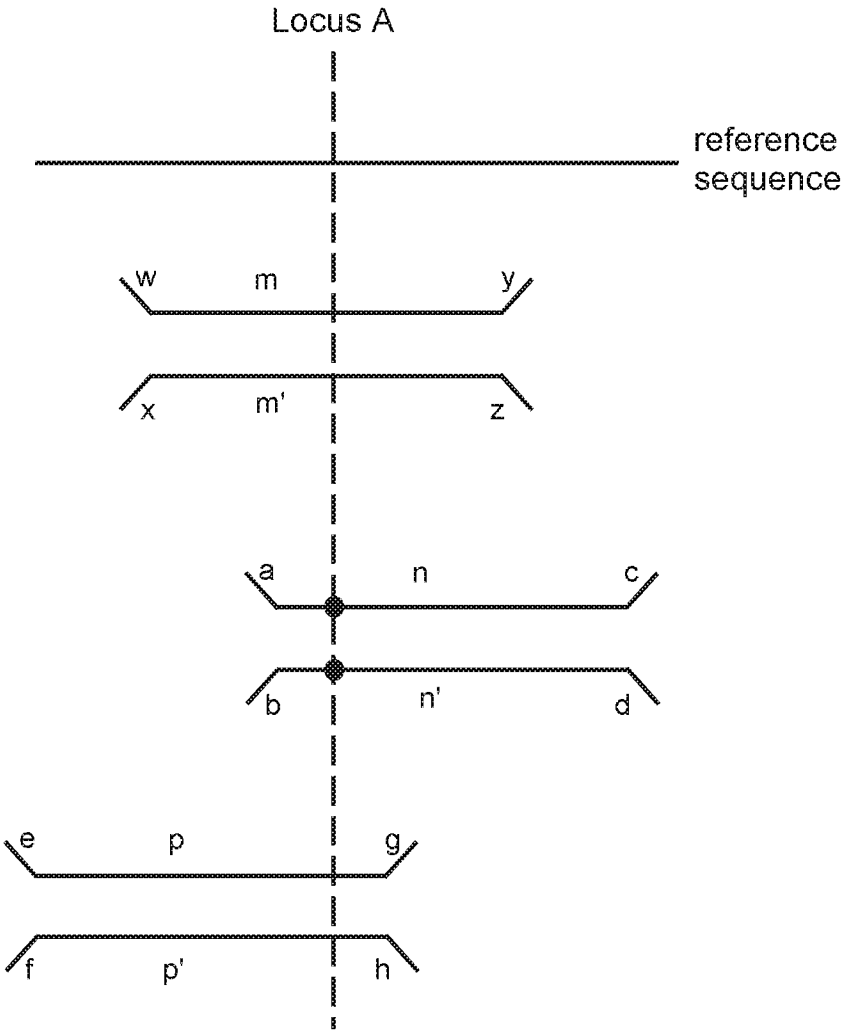


Fig. 3

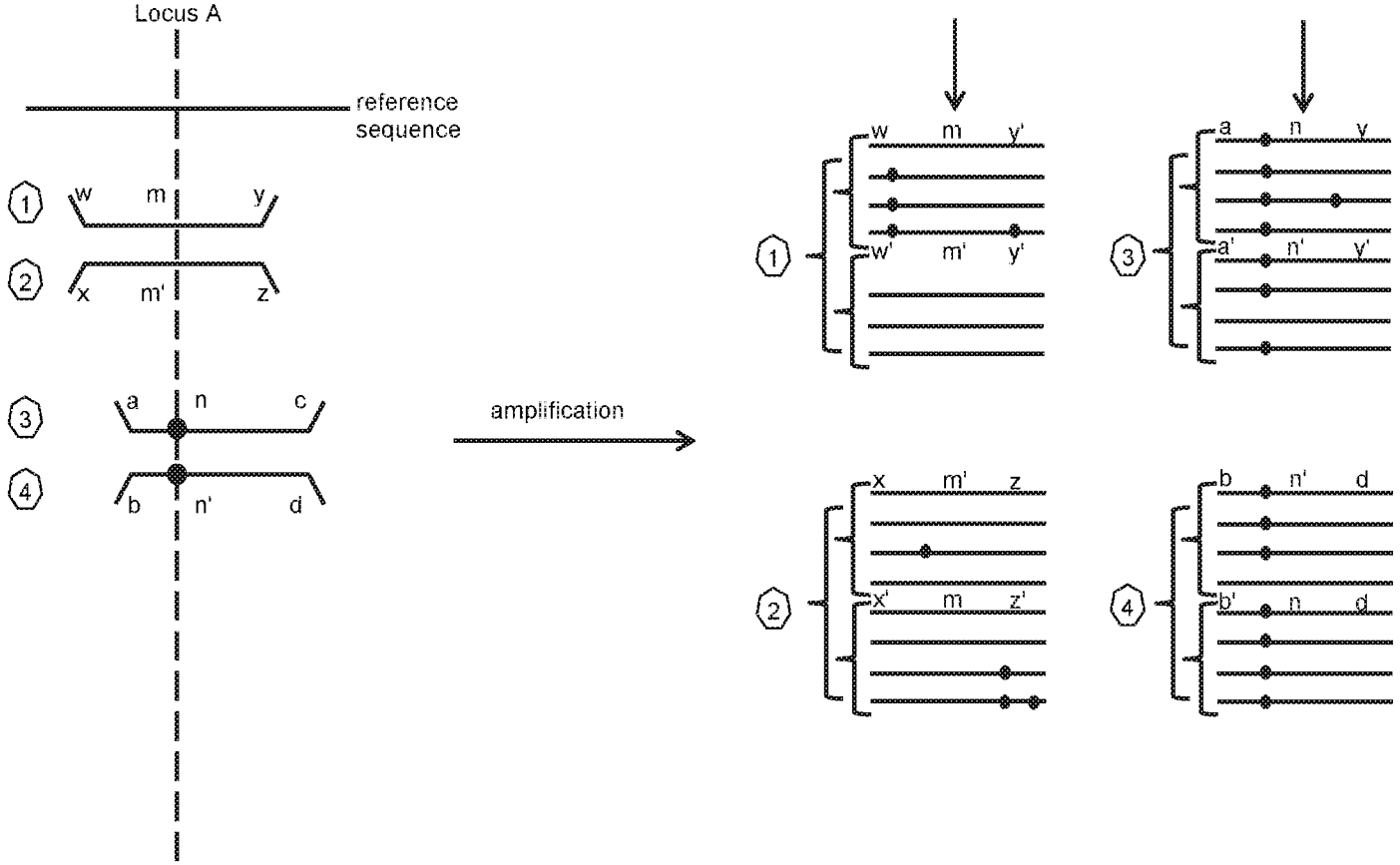

Locus A
reference sequence
1
w m y
2
x m' z
3
a n c
4
b n' d
amplification
w m y'
w' m' y'
a n y
a' n' y'
x m' z
x' m z'
b n' d
b' n d

Fig. 4A

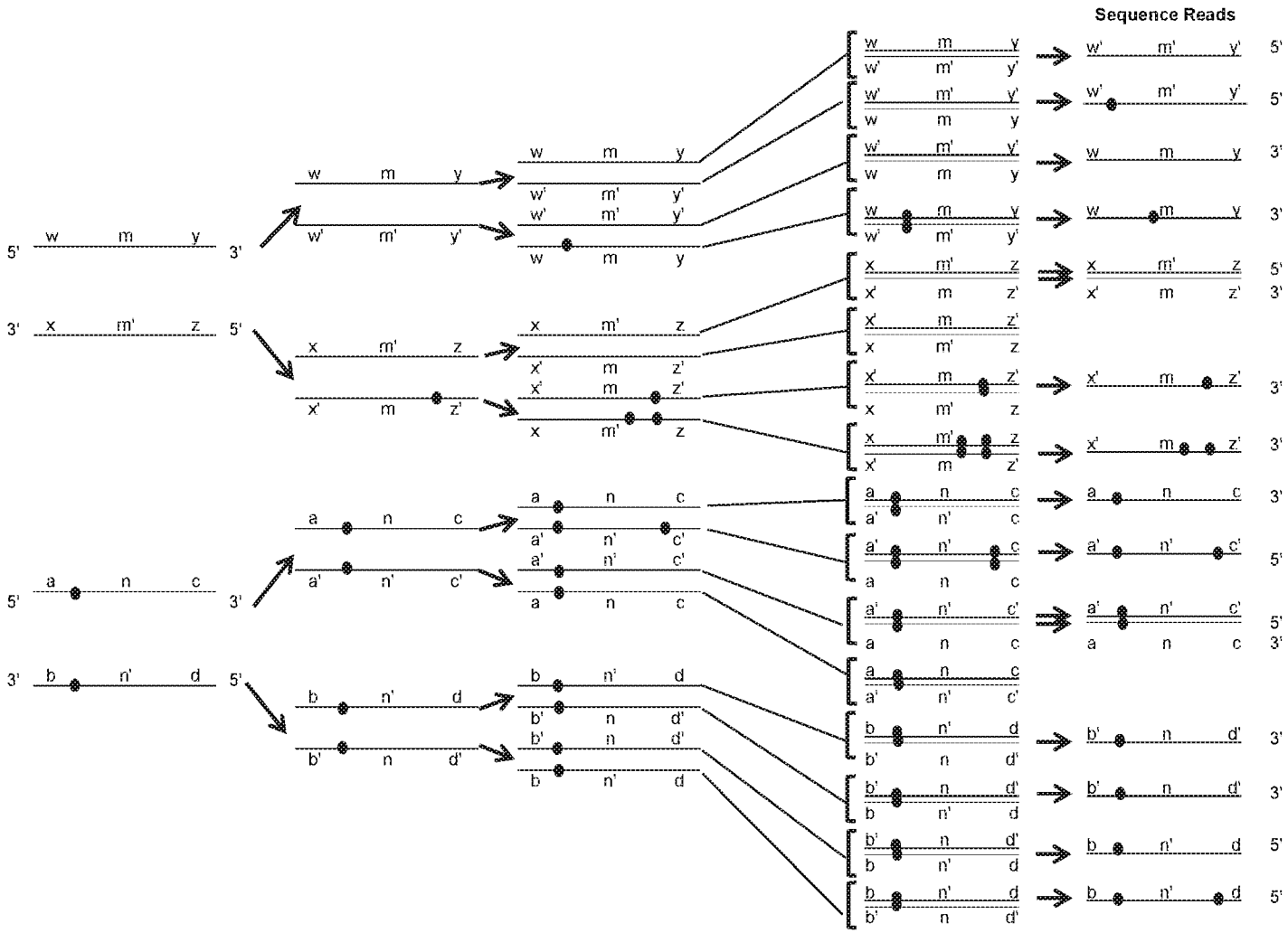


Fig. 4B

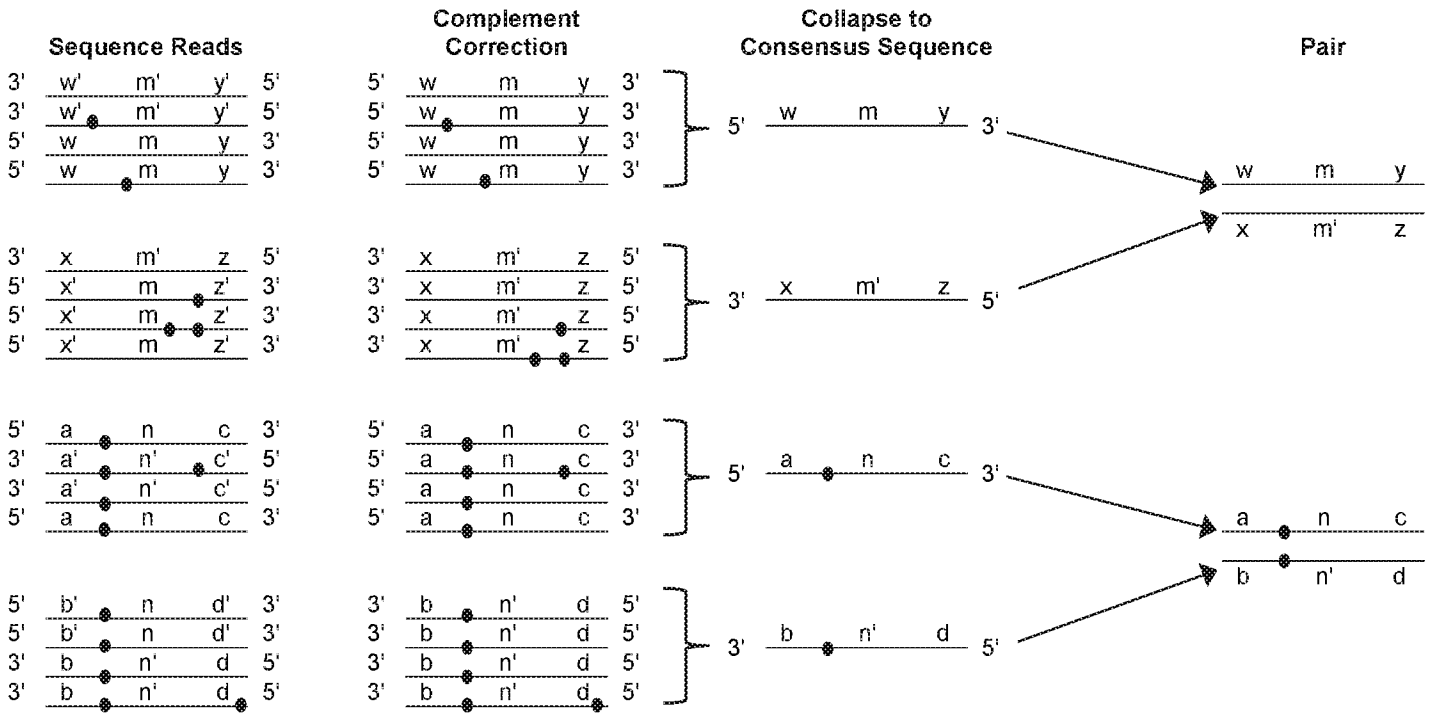

Sequence Reads
Complement Correction
Collapse to Consensus Sequence
Pair
3' w' m' y' 5'
3' w' m' y' 5'
5' w m y 3'
5' w m y 3'
5' w m y 3'
5' w m y 3'
5' w m y 3'
3' x m' z 5'
5' x' m z' 3'
5' x' m z' 3'
5' x' m z' 3'
3' x m' z 5'
3' x m' z 5'
3' x m' z 5'
3' x m' z 5'
3' x m' z 5'
5' a n c 3'
3' a' n' c' 5'
3' a' n' c' 5'
5' a n c 3'
5' a n c 3'
5' a n c 3'
5' a n c 3'
5' a n c 3'
5' b' n d' 3'
5' b' n d' 3'
3' b n' d 5'
3' b n' d 5'
3' b n' d 5'
3' b n' d 5'
3' b n' d 5'

Fig. 4C

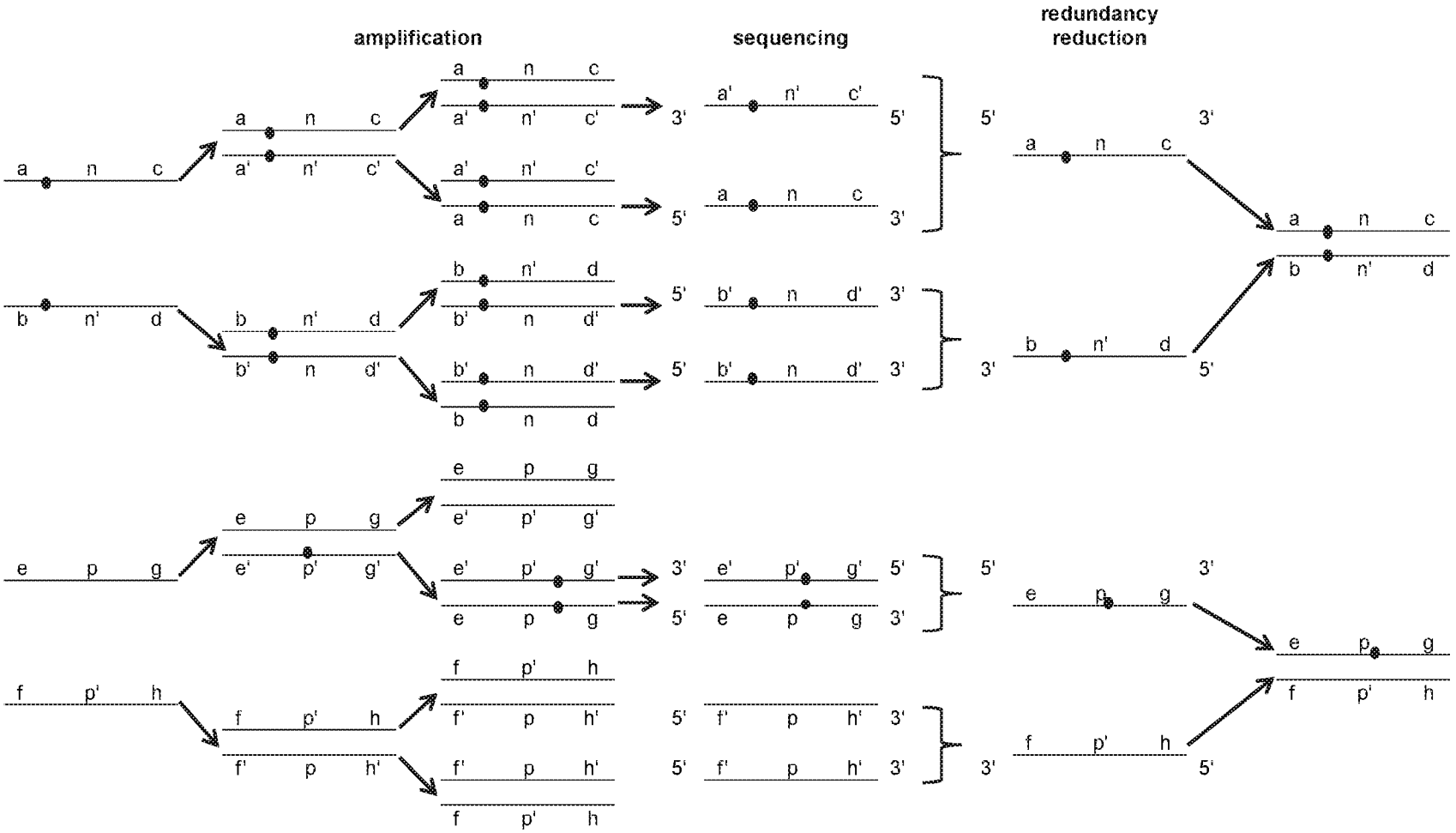

amplification
sequencing
redundancy reduction
a n c
a' n' c'
b n' d
b' n d'
b n d
e p g
e' p' g'
f p' h
f' p h'
3'
5'

Fig. 5

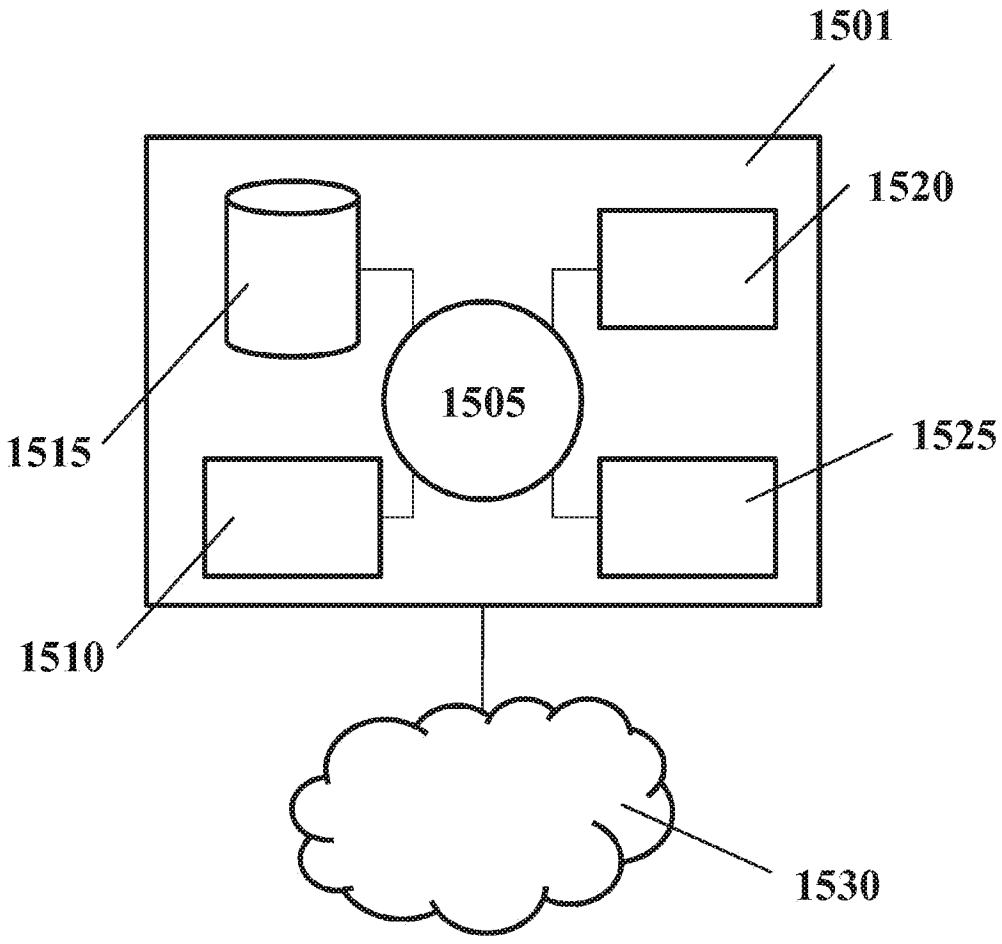


Fig. 6

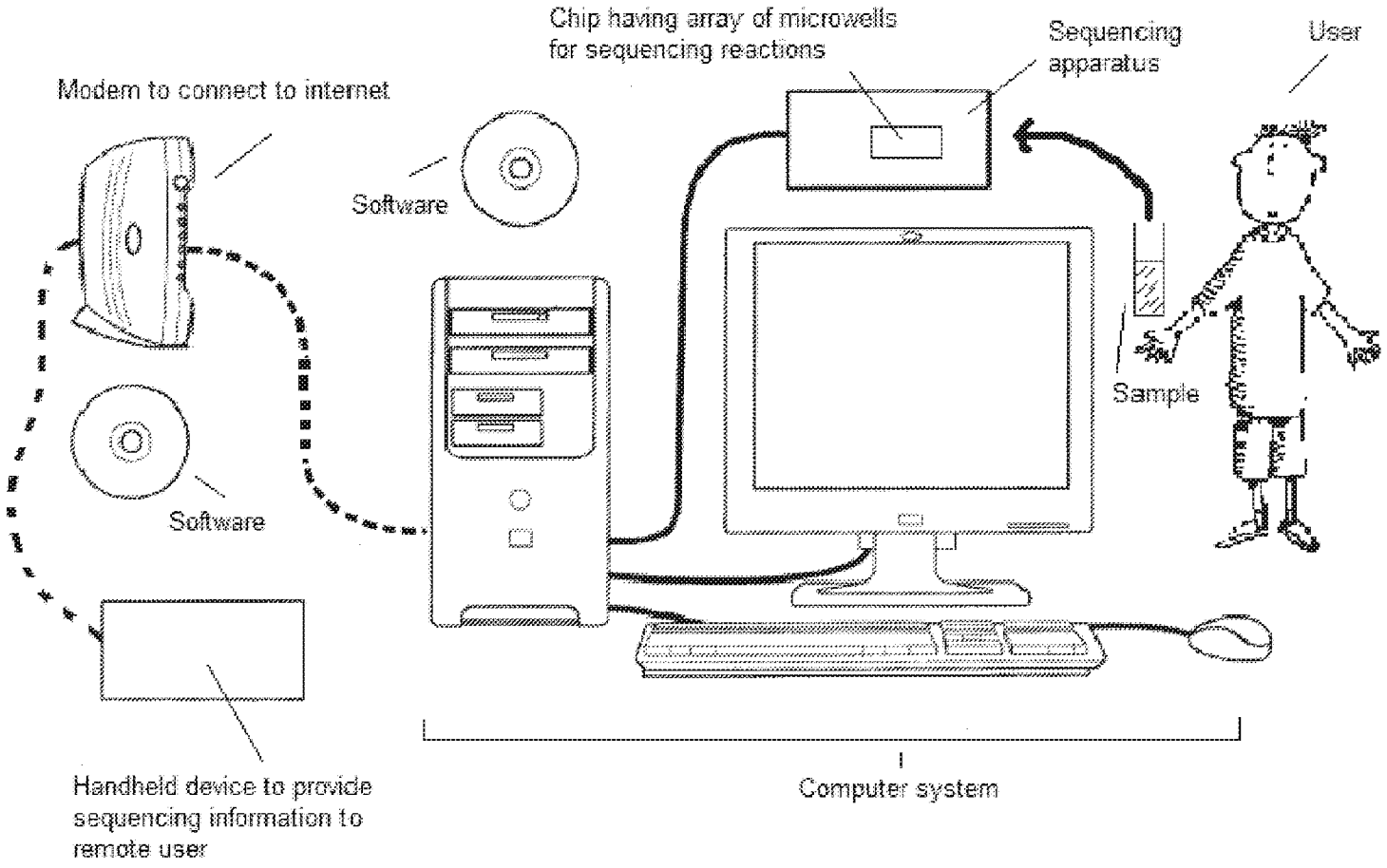

Chip having array of microwells for sequencing reactions
Sequencing apparatus
User
Modem to connect to internet
Software
Software
Sample
Handheld device to provide sequencing information to remote user
Computer system

Fig. 7

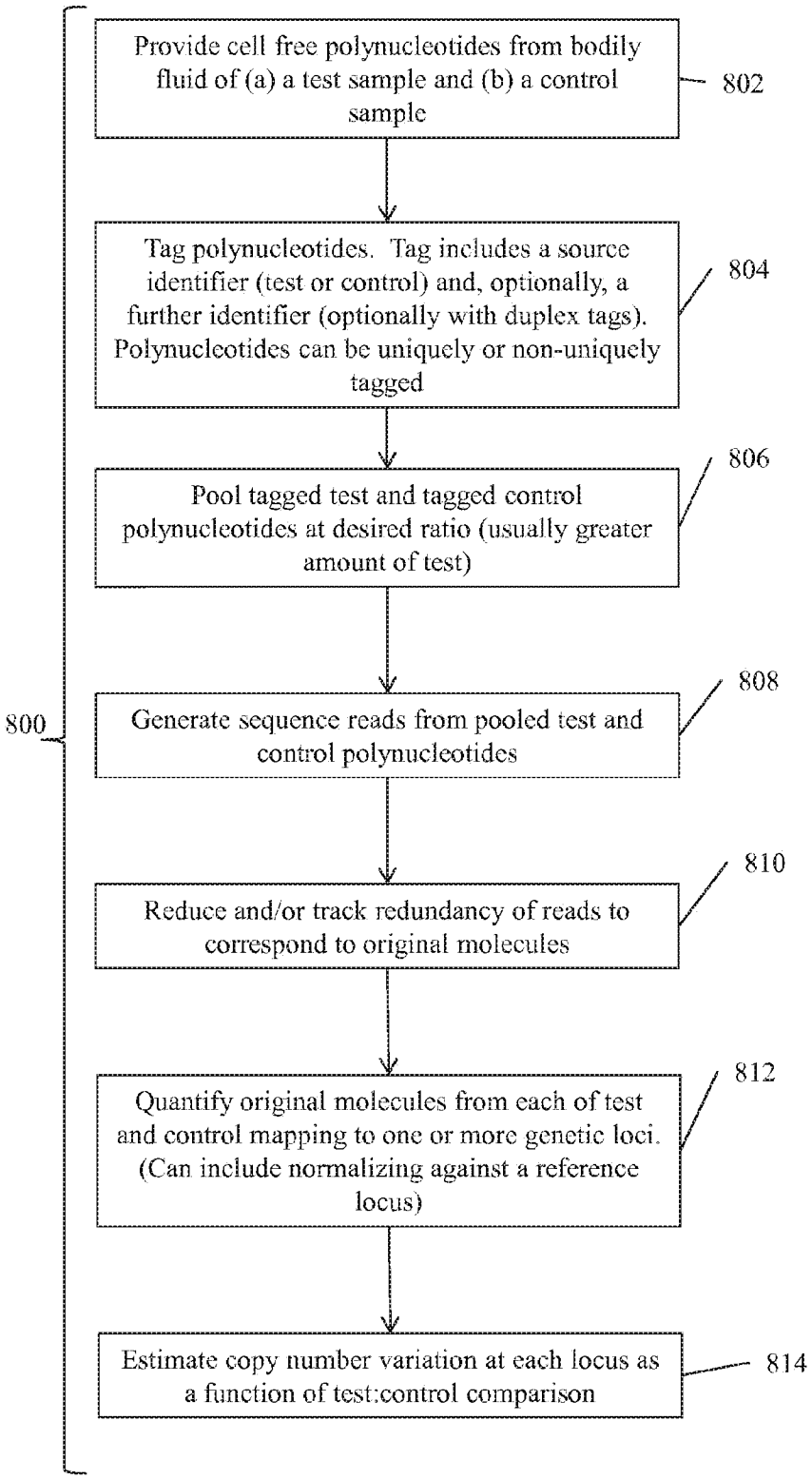

Provide cell free polynucleotides from bodily fluid of (a) a test sample and (b) a control sample
802
Tag polynucleotides. Tag includes a source identifier (test or control) and, optionally, a further identifier (optionally with duplex tags). Polynucleotides can be uniquely or non-uniquely tagged
804
Pool tagged test and tagged control polynucleotides at desired ratio (usually greater amount of test)
806
Generate sequence reads from pooled test and control polynucleotides
808
800
Reduce and/or track redundancy of reads to correspond to original molecules
810
Quantify original molecules from each of test and control mapping to one or more genetic loci. (Can include normalizing against a reference locus)
812
Estimate copy number variation at each locus as a function of test:control comparison
814

Fig. 8

Fig. 9A

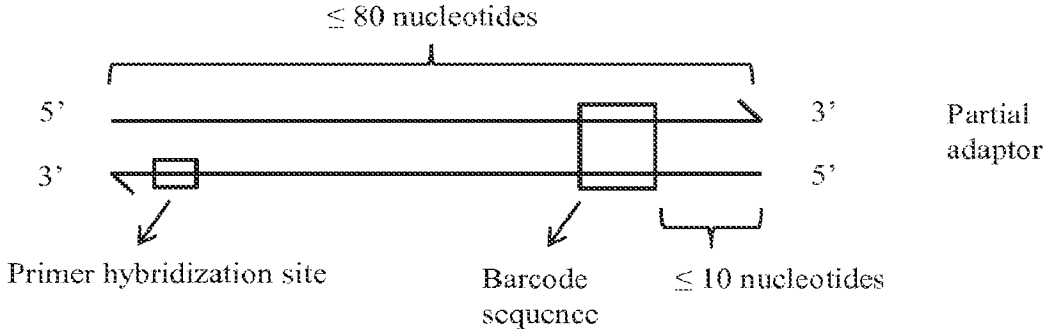


Fig. 9B

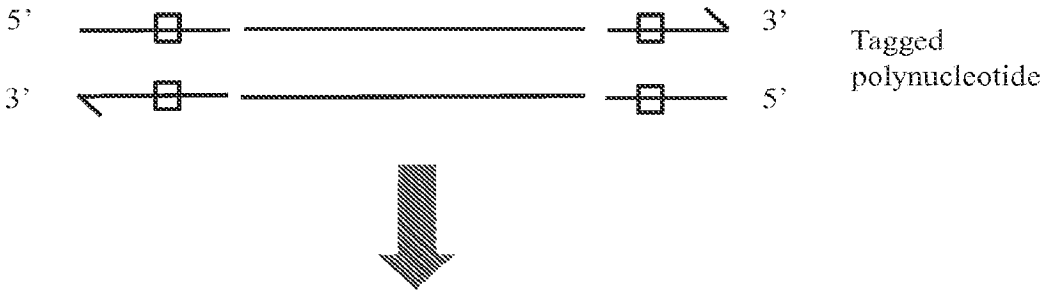
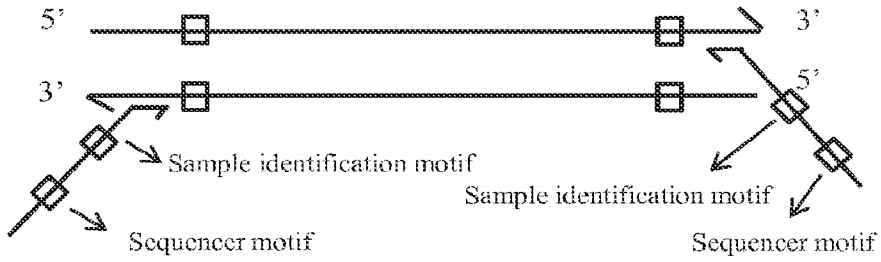


Fig. 9C



Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	Helmy ELTOUKHY
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	GH0004USCON3-42534708304

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	10	100	1000
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140

Petition:	
Patent-Appeals-and-Interference:	
Post-Allowance-and-Post-Issuance:	
Extension-of-Time:	
Miscellaneous:	
Total in USD ($)	**6860**

Electronic Acknowledgement Receipt

EFS ID:	37638219
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	Helmy ELTOUKHY
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	GH0004USCON3-42534708304
Receipt Date:	01-NOV-2019
Filing Date:	
Time Stamp:	18:52:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$6860
RAM confirmation Number	E2019A1I53532535
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00029

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	2019-11-01_GH0004US-CON3_AppTrans.pdf	293300 140db9de51acf0bc0b0631924c5e9da8889e0af3	no	2
Warnings:					
Information:					
2	Application Data Sheet	2019-11-01_GH0004US-CON3_ADS.pdf	1874460 a59c5d1c3123485293daac0cec2d50b0c3356644	no	9
Warnings:					
Information:					
3	TrackOne Request	2019-11-01_GH0004US-CON3_T1Request.pdf	129462 fa4d64aea2af12439fbb7da2b51e95eaff675d76	no	2
Warnings:					
Information:					
4	Oath or Declaration filed	2019-11-01_GH0004US-CON3_ParentDec.pdf	198149 9b1fdd215bf3349ea7dfbe0758e33756228765fb	no	2
Warnings:					
Information:					
5	Drawings-only black and white line drawings	2019-11-01_GH0004US-CON3_Figs.pdf	2550181 97cf1eb2e8fae70ef9de5a96fb471e6f046d9975	no	11
Warnings:					
Information:					
6	Power of Attorney	2019-11-01_GH0004US-CON3_ParentPoA.pdf	190194 ff69efd3f616ea4d4f0569e8551fc9e7bce85453	no	3
Warnings:					
Information:					

7	Fee Worksheet (SB06)	fee-info.pdf	41675 573cbc46d858f766b5f90459f4159f37ad79c9a8	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	5277421

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒ Practitioners associated with Customer Number: 115823

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☒ The address associated with Customer Number: 115823

OR

☐

Firm or Individual Name			
Address			
City			
Country			
Telephone		Email	

Assignee
Guardant Health, Inc.
2686 Middlefield Rd, Suite D
Redwood City, CA 94063

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	/[signature]/	Date *	9/5/13
Name	Helmy Eltoukhy	Telephone	
Title	CEO		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Guardant Health, Inc.

Application No./Patent No.: 14/861,989 Filed/Issue Date: September 22, 2015

Titled: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Guardant Health, Inc., a corporation of the State of Delaware

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is ___%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 037444, Frame 0265, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at Reel ___, Frame ___, or for which a COPY thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at Reel ___, Frame ___, or for which a copy thereof is attached.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel ___, Frame ___, or for which a COPY thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel ___, Frame ___, or for which a COPY thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel ___, Frame ___, or for which a COPY thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel ___, Frame ___, or for which a COPY thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Ali Alemozafar/	February 22, 2016
Signature	Date
Ali R. Alemozafar	68,180
Printed or Typed Name	Title or Registration Number

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/672,267	Filing Date 01/07/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/06/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LDRC
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/EVA V GILLIS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: To be assigned Examiner: To be assigned

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

Applicant respectfully requests consideration of the above-referenced application in view of the following amendments and remarks:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1-30. (Cancelled).

31. (New): A method for preparing a population of cell-free nucleic acid molecules obtained from a bodily fluid sample of a subject for sequencing, the method comprising:

(a) attaching molecular barcodes from a set of molecular barcodes to a plurality of cell-free nucleic acid molecules from the population to produce tagged parent polynucleotides,

wherein attaching comprises ligating a molecular barcode from the set of molecular barcodes to both ends of a molecule of the cell-free nucleic acid molecules,

wherein ligating comprises using more than a 30X molar excess of molecular barcodes as compared to the cell-free nucleic acid molecules, and

wherein at least 20% of the cell-free nucleic acid molecules from the population of cell-free nucleic acid molecules are attached to molecular barcodes;

(b) amplifying a plurality of the tagged parent polynucleotides to generate amplified progeny polynucleotides; and

(c) selectively enriching a subset of the amplified progeny polynucleotides for a plurality of genomic regions of interest.

32. (New): The method of claim 31, wherein the bodily fluid sample is selected from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, and tears.

33. (New): The method of claim 31, wherein the population comprises 1 nanogram (ng) to 100 ng of cell-free nucleic acid molecules.

34. (New): The method of claim 31, wherein the subject has cancer or is suspected of having cancer.
35. (New): The method of claim 31, wherein the cell-free nucleic acid molecules are selected from the group consisting of double-stranded deoxyribonucleic acid (DNA), single-stranded DNA, ribonucleic acid (RNA), cDNA, and any combination of these.
36. (New): The method of claim 31, wherein the molecular barcodes are ligated to the cell-free nucleic acid molecules by blunt-end ligation or sticky-end ligation.
37. (New): The method of claim 31, wherein the molecular barcodes of the set of molecular barcodes have 2 to 100,000 different molecular barcode sequences that are from 5 to 20 nucleotides in length.
38. (New): The method of claim 31, wherein ligating comprises using more than a 100X molar excess of molecular barcodes as compared to the cell-free nucleic acid molecules.
39. (New): The method of claim 31, wherein at least 40% of the cell-free nucleic acid molecules from the population of cell-free nucleic acid molecules are attached to molecular barcodes.
40. (New): The method of claim 31, wherein the genomic regions of interest comprise sequences from one or more genes selected from the group consisting of:
ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.
41. (New): The method of claim 31, where selectively enriching the subset of amplified progeny polynucleotides for a plurality of genomic regions of interest comprises using a set of probes that hybridize to the plurality of genomic regions of interest.
42. (New): The method of claim 41, wherein the plurality of genomic regions of interest comprises exon sequences.
43. (New): The method of claim 31, wherein molecular barcodes of the set of molecular barcodes are part of adapters.

44. (New): The method of claim 43, wherein the adapters are Y-shaped adapters.
45. (New): The method of claim 31, further comprising attaching sample identifiers to a plurality of the cell-free nucleic acid molecules in the population or the enriched amplified progeny polynucleotides.
46. (New): The method of claim 31, further comprising amplifying a plurality of enriched amplified progeny polynucleotides.
47. (New): A method for generating a cell-free deoxyribonucleic acid (cfDNA) sequencing library from a blood sample of a subject to conduct cancer testing, the method comprising:
    (a) performing a ligation reaction using more than a 30X molar excess of adapters comprising molecular barcodes as compared to cfDNA molecules in a population of cfDNA molecules obtained from the blood sample to produce tagged parent polynucleotides,
        wherein the molecular barcodes are members of a set of molecular barcodes comprising between 2 to 1,000 different molecular barcode sequences,
        wherein each end of a tagged parent polynucleotide has ligated thereon a respective molecular barcode from among the set of molecular barcodes, and
        wherein the efficiency of the ligation is more than 20%;
    (b) amplifying a plurality of the tagged parent polynucleotides to generate amplified progeny polynucleotides;
    (c) selectively enriching the amplified progeny polynucleotides for a plurality of cancer-associated genomic regions of interest; and
    (d) amplifying a subset of enriched amplified progeny polynucleotides, thereby generating the cell-free nucleic acid sequencing library.
48. (New): The method of claim 47, wherein the cfDNA molecules are double-stranded.
49. (New): The method of claim 47, wherein the population of cfDNA molecules is between 1 ng and 100 ng.
50. (New): The method of claim 47, wherein the ligation reaction is blunt-end ligation or sticky-end ligation.
51. (New): The method of claim 47, wherein the ligation reaction has a ligation efficiency of more than 30%.

52. (New): The method of claim 47, wherein the ligation reaction has a ligation efficiency of more than 50%.
53. (New): The method of claim 47, wherein the ligation reaction comprises using more than an 80X molar excess of adaptors as compared to the cfDNA molecules.
54. (New): The method of claim 47, wherein the ligation reaction comprises using more than a 100X molar excess of adapters as compared to the cfDNA molecules.
55. (New): The method of claim 47, wherein the ligation reaction has a ligation efficiency of more than 40% and comprises using more than a 60X molar excess of adaptors as compared to the cfDNA molecules.
56. (New): The method of claim 47, wherein the molecular barcodes in the set of molecular barcodes comprise 5 to 100 different molecular barcode sequences that are from 5 to 20 nucleotides in length.
57. (New): The method of claim 47, wherein the cancer-associated genomic regions of interest comprise sequences from one or more genes selected from the group consisting of: ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.
58. (New): The method of claim 47, where selectively enriching the subset of amplified progeny polynucleotides for a plurality of genomic regions of interest comprises using a set of probes that hybridize to the plurality of genomic regions of interest.
59. (New): The method of claim 57, wherein the cancer-associated genomic regions of interest comprise exon sequences.
60. (New): The method of claim 47, further comprising attaching sample identifiers to a plurality of the cell-free nucleic acid molecules in the population or the enriched amplified progeny polynucleotides.

REMARKS

Claims 1-30 were previously pending, but are hereby cancelled without disclaimer or prejudice. Claims 31-60 are newly added. Support for the new claims may be found throughout the application as filed. No new matter is added by these amendments. Thus, claims 31-60 are now pending and ready for examination.

CONCLUSION

Applicant believes that the present application is now in condition for examination and respectfully requests that the Examiner expedite the prosecution of this application to allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON2).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: December 6, 2019 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	To be assigned
Filing Date:	November 1, 2019	Examiner:	To be assigned
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☒ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure

statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☐ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: 15/892,178

Information Disclosure Statement(s) filed on: 11/7/19 and 11/27/19

AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON2).

Respectfully submitted,

Dated: December 6, 2019

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4725536	A	1988-02-16	Fritsch et al.	
	2	4942124	A	1990-07-17	Church	
	3	5124246	A	1992-06-23	Urdea et al.	
	4	5149625	A	1992-09-22	Church et al.	
	5	5200314	A	1993-04-06	Urdea	
	6	5424186	A	1995-06-13	Fodor et al.	
	7	5424413	A	1995-06-13	Hogan et al.	
	8	5445934		1995-08-01	Fodor et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	9	5604097	A	1997-02-18	Brenner	
	10	5635352	A	1997-06-03	Urdea et al.	
	11	5635400	A	1997-06-03	Brenner	
	12	5648245	A	1997-07-15	Fire et al.	
	13	5654413	A	1997-08-05	Brenner	
	14	5656731	A	1997-08-12	Urdea	
	15	5658737	A	1997-08-19	Nelson et al.	
	16	5714330	A	1998-02-03	Brenner et al.	
	17	5744305		1998-04-01	Fodor et al.	
	18	5759778	A	1998-06-02	Li et al.	
	19	5763175	A	1998-06-09	Brenner	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	20	5800992		1998-09-01	Fodor et al.	
	21	5846719	A	1998-12-08	Brenner et al.	
	22	5854033	A	1998-12-29	Lizardi	
	23	5871928	A	1999-02-16	Fodor et al.	
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Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

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	1	2013159035	WO	A2	2013-10-24	Mitchell et al.		
	2	2013173394	WO	A2	2013-11-21	Wang et al.		
	3	2013181170	WO	A1	2013-12-05	OTWINOWSKI et al.	Entire Document	

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	5	2013190441	WO	A2	2013-12-27	CHIU et al.	Entire Document	
	6	2014004726	WO	A1	2014-01-03	Chen et al.		
	7	2014014497	WO	A1	2014-01-23	Rava et al.		
	8	2014015319	WO	A1	2014-01-23	Rava		
	9	2014039556	WO	A1	2014-03-13	TALASAZ et al.	Entire Document	
	10	2014093330	WO	A1	2014-06-19	Raymond et al.		
	11	2014145078	WO	A1	2014-09-18	Srinivasan et al.		
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	14	2014152990	WO	A1	2014-09-25	SPENCE et al.		

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	15	2015159293	WO	A2	2015-10-22	DOR et al.	Entire Document	
	16	2016015058	WO	A2	2016-01-28	Shendure et al.	Entire Document	
	17	2016040901	WO	A1	2016-03-17	Diehn et al.	Entire Document	
	18	2017100441	WO	A1	2017-06-15	Loeb et al.	Entire Document	
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	38	Guardant Health vs. FMI 1st Amended Answer to Second Amended Complaint dated May 6, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	39	Guardant Health vs. FMI Invalidity Contentions dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	40	Guardant Health vs. FMI Invalidity Exhibit A-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	41	Guardant Health vs. FMI Invalidity Exhibit A-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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	43	Guardant Health vs. FMI Invalidity Exhibit A-8, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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	49	Guardant Health vs. FMI Invalidity Exhibit C-11, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)
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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
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	9	Guardant Health vs. FMI Suppl Invalidity References dated February 15, 2019 (C.A. No. 17-cv-1616-LPS-CJB)
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	12	Guardant Health vs. PGDx Invalidity Claim Chart A, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	13	Guardant Health vs. PGDx Invalidity Claim Chart B, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
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Name/Print	Timothy A. Hott	Registration Number	67740

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	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

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CERTIFICATION STATEMENT

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See attached certification statement.

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

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Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
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	1	NAWROZ, et al. Microsatellite alterations in serum DNA of head and neck cancer patients. Nat Med. 1996 Sep;2 (9):1035-7.	
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	39	Opposition Form and Statement to EP2893040 filed October 2, 2019 by Foundation Medicine Inc.	☐
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	42	Opposition Form and Statement to EP2893040 filed October 2, 2019 by Strawman Limited	☐
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See attached certification statement.

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

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Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

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	32	YANG, et al., EGFR gene copy number as a predictive biomarker for the treatment of metastatic colorectal cancer with anti-EGFR monoclonal antibodies: a meta-analysis.,J Hematol Oncol, 2012 Aug 16,5:52,1-9.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	34	YE, et al. Fluorescent microsphere-based readout technology for multiplexed human single nucleotide polymorphism analysis and bacterial identification. Human Mutation, 17(4): 305-316 (2001).	
	35	YOON, et al. Sensitive and accurate detection of copy number variants using read depth of coverage. Genome Res. 2009 Sep;19(9):1586-92. doi: 10.1101/gr.092981.109. Epub 2009 Aug 5.	
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	38	ZHAO, et al. Homozygous Deletions and Chromosome Amplifications in Human Lung Carcinomas Revealed by Single Nucleotide Polymorphism Array Analysis. Cancer Research, 65: 5561-5570 (2005).	
	39	ZHOU, et al. Counting alleles reveals a connection between chromosome 18q loss and vascularinvasion. Nature Biotechnology, 19: 78-81 (2001).	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: R48.REQ
Document Description: Request under Rule 48 correcting inventorship

PTO/AIA/40 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

Application Number	16/672,267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Practitioner Docket Number	42534-708.304

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby **requests that the inventorship be corrected or changed, or that the name of the inventor or a joint inventor, or the order of the names of joint inventors, be changed,** in the above-identified application. **Note**: 37 CFR 1.48 applies to any request to correct inventorship filed on or after September 16, 2012, regardless of the application filing date. **Do not submit this form after payment of the issue fee or if the application has been patented.** See 37 CFR 1.324 for correction of inventorship in a patent.

Please check the applicable box(es) below.

For a nonprovisional application:

☒ 1. This request is to correct or change the inventorship in a **nonprovisional** application (**under 37 CFR 1.48(a)**) and includes:

☒ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the Manual of Patent Examining Procedure (MPEP) section 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☒ The processing fee set forth in 37 CFR 1.17(i). $ 140

☒ An inventor is being added. An inventor's oath or declaration by any actual inventor who has not yet executed an oath or declaration is required (see 37 CFR 1.48(b)). See MPEP 602.01(a) for information about an inventor's oath or declaration for an application filed on/after September 16, 2012 (*e.g.*, form **PTO/AIA/01**). For information about an inventor's oath or declaration for an application filed before September 16, 2012 (*e.g.*, form **PTO/SB/01**), see MPEP 602.01(b).

☐ This request is being filed after the first Office action on the merits has been given or mailed (see 37 CFR 1.48(c) and 1.17(d)). Check one of the following:

☐ This request to correct or change the inventorship is due solely to the cancellation of claims in the application.

OR

☐ The fee set forth in 37 CFR 1.17(d) is due (in addition to the fee set forth in 37 CFR 1.17(i)). $ _____

PTO/AIA/40 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

☐ 2. This request is to correct or update the name of the inventor or a joint inventor, or the order of names of joint inventors, in a **nonprovisional** application (**under 37 CFR 1.48(f)**) and includes:

☐ An application data sheet in accordance with 37 CFR 1.76(c) identifying the complete inventive entity, including the corrected or updated name of the inventor, or the new order of names shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the MPEP 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☐ The processing fee set forth in 37 CFR 1.17(i). $ _____

For a provisional application:

☐ This request is to change or correct the inventorship, or correct or update the name of the inventor or a joint inventor, in a **provisional** application (**under 37 CFR 1.48(d)**) and includes:

☐ **Attached hereto** is a request, signed by a party set forth in 37 CFR 1.33(b), that identifies each inventor by his or her legal name, in the preferred order.

☐ The processing fee set forth in 37 CFR 1.17(q). $ _____

Fee Payment Information:

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 602231.

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ Applicant*

☒ attorney or agent of record
Registration number 67740

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Timothy A. Hott/

Typed or printed name Timothy A. Hott/

Date December 6, 2019

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☒ ** Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Helmy~~		~~ELTOUKHY~~	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	~~Atherton~~	State/Province	~~CA~~	Country of Residence	~~US~~

Mailing Address of Inventor:

Address 1	~~505 Penobscot Drive~~		
Address 2			
City	~~Redwood City~~	State/Province	~~CA~~
Postal Code	~~94063~~	Country	~~US~~

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	AmirAli		TALASAZ	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Atherton	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	State/Province	CA
Postal Code	94063	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stefanie	Ann Ward	MORTIMER	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

City	Morgan Hill	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2000 Willow Springs Road		
Address 2			
City	Morgan Hill	State/Province	CA
Postal Code	95037	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	115823		
Email Address	patents@guardanthealth.com	Add Email	Remove Email
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		
Attorney Docket Number	42534-708.304	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	11	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	115823		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16601168	2019-10-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16601168	Continuation of	15892178	2018-02-08
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15892178	Continuation of	14861989	2015-09-22	9920366	2018-03-20

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14861989	Continuation of	PCTUS2014072383	2014-12-24

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2014072383	Claims benefit of provisional	61948509	2014-03-05
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2014072383	Claims benefit of provisional	61921456	2013-12-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	GUARDANT HEALTH, INC.		
Mailing Address Information For Applicant:			
Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	**State/Province**	CA
Country	US	Postal Code	94063
Phone Number		Fax Number	
Email Address	patents@guardanthealth.com		

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Timothy A. Hott/			Date (YYYY-MM-DD)	2019-12-06
First Name	Timothy	Last Name	Hott	Registration Number	67740

Additional Signature may be generated within this form by selecting the Add button.

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	Helmy ELTOUKHY
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**140**

Electronic Acknowledgement Receipt

EFS ID:	37959288
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	Helmy ELTOUKHY
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	06-DEC-2019
Filing Date:	
Time Stamp:	17:23:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$140
RAM confirmation Number	E2019B6H24260686
Deposit Account	602231
Authorized User	Michelle Chan

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	2019-12-06_GH0004US-CON3_MortimerDec.pdf	2445268 0be2764e7021b8ee414393424ea79094e7a2aacc	no	1
Warnings:					
Information:					
2		2019-12-06_GH0004US-CON3_PA.pdf	117440 296ba0a3a6b96b76f73b4e381a1c996bea47a7f2	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
3	Transmittal Letter	2019-12-06_GH0004US-CON3_IDS.pdf	109572 1efd3240496703e214ddec4926c640e99d1ac0d4	no	4
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_1_OF_8.pdf	1067954 29e432c483ee56b4579da4fcf3cb289786911d9b	no	39
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_2_OF_8.pdf	1057315 ecb8fe3dddf5597314e86a1943731e90f7246ad7	no	10

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

6	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_3_OF_8.pdf	1055739 9d625fa4d65c234d3723dbf98e7046f7532b648f	no	8

Warnings:

Information:

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7	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_4_OF_8.pdf	1056441 bef232cb4a3ddd1261735350db8c34823564ee4c	no	8

Warnings:

Information:

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8	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_5_OF_8.pdf	1057806 f0b1b7cbd9df46b501dfaa303d6f00025de8cf55	no	8

Warnings:

Information:

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9	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_6_OF_8.pdf	1055469 60eefae1ed14b3bb6f3e24ed2ea63a9608822577	no	8

Warnings:

Information:

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Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
10	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_7_OF_8.pdf	1057627 1a92217a66ad32d556dd3b51e084b5c58cbf6133	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
11	Information Disclosure Statement (IDS) Form (SB08)	2019-12-06_GH0004US-CON3_SB08_8_OF_8.pdf	1056621 b420d20a7c046b0bb21b30c15803493a2944507e	no	7
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
12	Request under Rule 48 correcting inventorship	2019-12-06_GH0004US-CON3_ReqCorrInv.pdf	159195 c881c7303b3e66fcdd71ee85e5ff3b65e14a3834	no	3
Warnings:					
Information:					
13	Application Data Sheet	2019-12-06_GH0004US-CON3_CorrADS.pdf	1048091 6d8e36928f5c0ce9eddc79aee6cc9c6beea54f2c	no	8
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
14	Fee Worksheet (SB06)	fee-info.pdf	30281 6d9a0698784e1c83f7d170171ead0a0ce969735f	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	12374819	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/601,168

filed on 2019-10-14.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Stefanie Ann Ward MORTIMER Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/672,267	11/01/2019	AmirAli TALASAZ	42534-708.304

CONFIRMATION NO. 3448

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

FORMALITIES LETTER

OC000000113443757

Date Mailed: 12/19/2019

NOTICE OF INCOMPLETE NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

A filing date has NOT been accorded to the above-identified application papers for the reason(s) indicated below.

All of the items noted below **must** be submitted within **TWO MONTHS** of the date of this Notice, unless otherwise indicated, or proceedings on the application will be terminated *(37 CFR 1.53(e))*. Replies should be mailed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450. **Extensions of time under 37 CFR 1.136 are NOT available.**

The filing date will be the date of receipt of all items required below, unless otherwise indicated. Any assertions that the item(s) required below were submitted, or are not necessary for a filing date, must be by way of petition directed to the attention of the Office of Petitions accompanied by the petition fee set forth in 37 CFR 1.17(f). If the petition states that the application is entitled to a filing date, a request for a refund of the petition fee may be included in the petition.

If the above-identified application contains a priority claim under 37 CFR 1.55 or benefit claim under 37 CFR 1.78 of a prior-filed application that was present on the filing date of the application and applicant wants to rely on 37 CFR 1.57(b) to add inadvertently omitted material to the above-identified application, applicant must file a petition under 37 CFR 1.53(e) accompanied by the petition fee set forth in 37 CFR 1.17(f) within **TWO MONTHS** of the date of this Notice. Petitions should be mailed to: Mail Stop Petitions, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

- The specification is missing.
  A complete specification as prescribed by 35 U.S.C. 112 is required.

Applicant is cautioned that submission of the above items by a means other than the USPTO's electronic filing system, EFS-Web, may cause the application to be subject to the non-electronic filing fee of $400 ($200 for a small or micro entity). Section 10(h) of the Leahy-Smith America Invents Act (Public Law 112-29) requires an additional non-electronic filing fee of $400 ($200 for a small or micro entity) for any nonprovisional application filed on or after November 15, 2011, other than by the USPTO's electronic filing system (EFS-Web), except for a reissue, design, or plant application. See also 37 CFR 1.16(t).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/fhadera/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/672,267	11/01/2019	AmirAli TALASAZ	42534-708.304

CONFIRMATION NO. 3448

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000113443763

Date Mailed: 12/19/2019

NOTICE OF ACCEPTANCE OF AUTHORIZATION TO PERMIT ACCESS TO SEARCH RESULTS

This is in response to the applicant's authorization to permit access to the search results from the instant application under 37 CFR 1.14(h)(2) submitted on 11/01/2019.

The authorization to permit access to the search results under 37 CFR 1.14(h)(2) is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/fhadera/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/672,267	11/01/2019	AmirAli TALASAZ	42534-708.304

CONFIRMATION NO. 3448

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000113443760

Date Mailed: 12/19/2019

NOTICE OF ACCEPTANCE OF AUTHORIZATION TO PERMIT ACCESS TO APPLICATION VIA PRIORITY DOCUMENT EXCHANGE

This is in response to the applicant's authorization to permit access to the application-as-filed by participating offices under 37 CFR 1.14(h)(1) submitted on 11/01/2019.

The authorization to permit access to the application under 37 CFR 1.14(h)(1) is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/fhadera/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/672,267

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2720

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/672,267		AmirAli TALASAZ	42534-708.304

CONFIRMATION NO. 3448

115823
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37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000113444482

Date Mailed: 12/19/2019

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 12/06/2019.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/llvuong/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: To be assigned Examiner: To be assigned

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF INCOMPLETE APPLICATION AND PETITION UNDER 37 CFR 1.53(e) TO ADD INADVERTENTLY OMITTED ITEM

Sir:

This paper is in response to the Notice of Incomplete Nonprovisional Application mailed December 19, 2019, having a two-month response deadline of February 19, 2020. Accordingly, this response is timely filed.

The Notice of Incomplete Nonprovisional Application indicated the specification was missing from the original filing. The above-identified application claims benefit under 37 CFR 1.78 of USSN 16/601,168 as listed on the Application Data Sheet submitted on November 1, 2019. Applicant hereby petitions the Commissioner to add the inadvertently omitted specification to the above-identified application. Applicant submits herewith the petition fee under 37 CFR 1.17(f) and the inadvertently omitted specification. No new matter is being introduced.

The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,

GUARDANT HEALTH, INC.

Date: January 7, 2020 By: /Timothy A. Hott/

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ABSTRACT OF THE DISCLOSURE

Disclosed herein in are methods and systems for determining genetic variants (e.g., copy number variation) in a polynucleotide sample. A method for determining copy number variations includes tagging double-stranded polynucleotides with duplex tags, sequencing polynucleotides from the sample and estimating total number of polynucleotides mapping to selected genetic loci. The estimate of total number of polynucleotides can involve estimating the number of double-stranded polynucleotides in the original sample for which no sequence reads are generated. This number can be generated using the number of polynucleotides for which reads for both complementary strands are detected and reads for which only one of the two complementary strands is detected.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for estimating a total number of double-stranded deoxyribonucleic acid (DNA) molecules in a sample, comprising:

(a) determining a quantitative measure of individual DNA molecules for which both strands are detected;

(b) determining a quantitative measure of individual DNA molecules for which only one strand is detected;

(c) using said quantitative measures determined in (a) and (b) to estimate a total number of double-stranded DNA molecules in the sample, wherein said total number comprises individual DNA molecules for which neither DNA strand is detected.

2. The method of Claim 1, further comprising inferring, from said quantitative measures determined in (a) and (b), a quantitative measure of individual DNA molecules for which neither strand is detected.

3. The method of Claim 1, further comprising determining a normalized quantitative measure of one or more genetic loci to determine copy number variation in said sample.

4. The method of Claim 1, wherein said sample comprises double-stranded polynucleotide molecules sourced substantially from cell-free nucleic acids.

5. The method of Claim 1, wherein determining said quantitative measure of individual DNA molecules comprises tagging said DNA molecules with a set of duplex tags, wherein each duplex tag differently tags complementary strands of a double-stranded DNA molecule in said sample to provide tagged strands.

6. The method of Claim 5, further comprising sequencing at least some of said tagged strands to produce a set of sequence reads.

7. The method of Claim 6, further comprising sorting sequence reads into paired reads and unpaired reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from a double-stranded polynucleotide molecule in said set, and (ii) each

unpaired read represents a first tagged strand having no second differently tagged complementary strand derived from a double-stranded polynucleotide molecule represented among said sequence reads in said set of sequence reads.

8. The method of Claim 7, further comprising determining quantitative measures of (i) said paired reads and (ii) said unpaired reads that map to each of one or more genetic loci to determine a quantitative measure of total double-stranded DNA molecules in said sample that map to each of said one or more genetic loci based on said quantitative measure of paired reads and unpaired reads mapping to each locus.

9. A method, comprising:

(a) providing a sample comprising a set of double-stranded polynucleotide molecules, each double-stranded polynucleotide molecule including first and second complementary strands;

(b) tagging said double-stranded polynucleotide molecules with a set of duplex tags, wherein each duplex tag differently tags said first and second complementary strands of a double-stranded polynucleotide molecule in said set;

(c) sequencing at least some of said tagged strands to produce a set of sequence reads;

(d) reducing and/or tracking redundancy in said set of sequence reads;

(e) sorting sequence reads into paired reads and unpaired reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from a double-stranded polynucleotide molecule in said set, and (ii) each unpaired read represents a first tagged strand having no second differently tag complementary strand derived from a double-stranded polynucleotide molecule represented among said sequence reads in said set of sequence reads;

(f) determining quantitative measures of at least two of (i) said paired reads, (ii) said unpaired reads that map to each of one or more genetic loci, (iii) read depth of said paired reads and (iv) read depth of said unpaired reads; and

(g) estimating with a programmed computer processor a quantitative measure of total double-stranded polynucleotide molecules in said set that map to each of said one or

more genetic loci based on said quantitative measures of said at least two of (i) said paired reads, (ii) said unpaired reads mapping to each locus, (iii) said read depth of said paired reads and (iv) said read depth of said unpaired reads.

10. The method of Claim 9, further comprising detecting copy number variation in said sample by determining a normalized total quantitative measure determined in (g) at each of said one or more genetic loci and determining copy number variation based on the normalized measure.

11. The method of Claim 9, wherein said sample comprises double-stranded polynucleotide molecules sourced substantially from cell-free nucleic acids.

12. The method of Claim 9, wherein said duplex tags are not sequencing adaptors.

13. The method of claim 9, wherein (f) comprises determining quantitative measures of said paired reads and said unpaired reads, and wherein in (g), said quantitative measure of total double-stranded polynucleotide molecules in said set that map to each of said one or more genetic loci is determined based on said quantitative measures of said paired reads and said unpaired reads.

14. The method of Claim 9, wherein reducing redundancy in said set of sequence reads comprises collapsing sequence reads produced from amplified products of an original polynucleotide molecule in said sample back to said original polynucleotide molecule.

15. The method of Claim 14, further comprising determining a consensus sequence for said original polynucleotide molecule.

16. The method of Claim 15, further comprising identifying polynucleotide molecules at one or more genetic loci comprising a sequence variant.

17. The method of Claim 15, further comprising determining a quantitative measure of paired reads that map to a locus, wherein both strands of said pair comprise a sequence variant.

18. The method of Claim 15, further comprising determining a quantitative measure of paired molecules in which only one member of said pair bears a sequence variant and/or determining a quantitative measure of unpaired molecules bearing a sequence variant.

19. A method for detecting copy number variation in deoxyribonucleic acid (DNA) molecules in a biological sample of a subject, comprising:

(a) attaching adapters to ends of fragments generated from said DNA molecules in said biological sample of said subject, wherein said adapters tag a 5' end of a strand of an individual fragment among said fragments with a first tag and a 3' end of a complementary strand of said individual fragment with a second tag, thereby providing tagged fragment molecules;

(b) sequencing at least a portion of each of said tagged fragment molecules to provide a plurality of sequencing reads;

(c) mapping said plurality of sequencing reads to a first genetic locus and at least one second genetic locus in a reference genome, wherein said first tag and said second tag are indicative of which strand of said tagged fragment molecules each of said plurality of sequencing reads is derived;

(d) using a programmed computer to determine a first total number of tagged fragment molecules for said first genetic locus and a second total number of tagged fragment molecules for said at least one second genetic locus, wherein each of said first total number and second total number is based on (i) a number of tagged fragments for which sequencing reads from both strands of said tagged fragment molecules are detected and (ii) a number of tagged fragment for which sequencing reads from only one strand of said tagged fragment molecules are detected, and wherein said first total

number and said second total number comprises tagged fragment molecules for which neither strand was sequenced; and

(e) comparing said first total number of tagged fragment molecules to said second total number of tagged fragment molecules to determine copy number variation in said DNA molecules.

20. The method of claim 19, further comprising detecting sequencing errors by comparing said sequencing reads derived from different strands of said tagged fragment molecules.

21. The method of claim 19, further comprising amplifying said tagged fragment molecules prior to said sequencing and, subsequent to (b), collapsing said sequencing reads.

22. The method of claim 21, further comprising detecting amplification errors by comparing said sequencing reads derived from different strands of said tagged fragment molecules.

23. The method of claim 19, wherein said copy number variation is determined if said first total number is different from said second total number.

24. The method of claim 19, wherein said biological sample is a cell-free biological sample.

25. The method of claim 19, wherein said adapters comprise molecular barcodes.

26. The method of claim 25, wherein said molecular barcodes are non-unique.

27. The method of claim 26, wherein said molecular barcodes are non-unique and at least 50% of said tagged fragment molecules comprise a given molecular barcode that is shared by at least one other tagged fragment molecule.

28. The method of claim 25, wherein said molecular barcodes are unique.

29. The method of claim 25, further comprising amplifying said tagged fragment molecules prior to said sequencing and, subsequent to (b), collapsing said sequencing reads based at least in part on said molecular barcodes.

30. The method of claim 19, wherein said copy-number variation in said DNA molecules is indicative of copy-number variation within genomes of cells in a tumor.

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Application No. 16/601,168, filed October 14, 2019, which is a continuation of U.S. Application No. 15/892,178, filed February 8, 2018, which is a continuation of U.S. Application No. 14/861,989, filed September 22, 2015 (now U.S. Patent 9,920,366), which is a continuation application of International Application No. PCT/US2014/072383, filed December 24, 2014, which application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 61/921,456, filed December 28, 2013, and U.S. Provisional Application No. 61/948,509, filed March 5, 2014, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] The detection and quantification of polynucleotides is important for molecular biology and medical applications, such as diagnostics. Genetic testing is particularly useful for a number of diagnostic methods. For example, disorders that are caused by rare genetic alterations (*e.g.*, sequence variants) or changes in epigenetic markers, such as cancer and partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information.

[0003] Early detection and monitoring of genetic diseases, such as cancer, is often useful and needed in the successful treatment or management of the disease. One approach may include the monitoring of a sample derived from cell-free nucleic acids, a population of polynucleotides that can be found in different types of bodily fluids. In some cases, disease may be characterized or detected based on detection of genetic aberrations, such as copy number variation and/or sequence variation of one or more nucleic acid sequences, or the development of other certain rare genetic alterations. Cell-free DNA (cfDNA) may contain genetic aberrations associated with a particular disease. With improvements in sequencing and techniques to manipulate nucleic acids, there is a need in the art for improved methods and systems for using cell-free DNA to detect and monitor disease.

[0004] In particular, many methods have been developed for accurate copy number variation estimation, especially for heterogeneous genomic samples, such as tumor-derived gDNA or for

cfDNA for many applications (*e.g.*, prenatal, transplant, immune, metagenomics or cancer diagnostics). Most of these methods include sample preparation whereby the original nucleic acids are converted into a sequenceable library, followed by massively parallel sequencing, and finally bioinformatics to estimate copy number variation at one or more loci.

SUMMARY

[0005] Although many of these methods are able to reduce or combat the errors introduced by the sample preparation and sequencing processes for all molecules that are converted and sequenced, these methods are not able to infer the counts of molecules that were converted but not sequenced. Since this count of converted by unsequenced molecules can be highly variable from genomic region to region, these counts can dramatically and adversely affect the sensitivity that can be achieved.

[0006] To address this issue, input double-stranded deoxyribonucleic acid (DNA) can be converted by a process that tags both halves of the individual double-stranded molecule, in some cases differently. This can be performed using a variety of techniques, including ligation of hairpin, bubble, or forked adapters or other adaptors having double-stranded and single stranded segments (the unhybridized portion of a bubble, forked or hairpin adapter are deemed single-stranded herein). If tagged correctly, each original Watson and Crick (i.e., strand) side of the input double-stranded DNA molecule can be differently tagged and identified by the sequencer and subsequent bioinformatics. For all molecules in a particular region, counts of molecules where both Watson and Crick sides were recovered ("Pairs") versus those where only one half was recovered ("Singlets") can be recorded. The number of unseen molecules can be estimated based on the number of Pairs and Singlets detected.

[0007] An aspect of the present disclosure provides a method for detecting and/or quantifying rare deoxyribonucleic acid (DNA) in a heterogeneous population of original DNA fragments, comprising tagging the original DNA fragments in a single reaction using a library of a plurality of different tags such that greater than 30% of the fragments are tagged at both ends, wherein each of the tags comprises a molecular barcode. The single reaction can be in a single reaction vessel. Greater than 50% of the fragments can be tagged at both ends. The plurality of different tags can be no more than any of 100, 500, 1000, 10,000 or 100,000 different tags.

[0008] Another aspect provides a set of library adaptors that can be used to tag the molecules of interest (e.g., by ligation, hybridization, etc.). The set of library adaptors can comprise plurality of polynucleotide molecules with molecular barcodes, wherein the plurality of polynucleotide molecules are less than or equal to 80 nucleotide bases in length, wherein the molecular barcodes are at least 4 nucleotide bases in length, and wherein (a) the molecular barcodes are different from one another and have an edit distance of at least 1 between one another; (b) the molecular barcodes are located at least one nucleotide base away from a terminal end of their respective polynucleotide molecules; (c) optionally, at least one terminal base is identical in all of the polynucleotide molecules; and (d) none of the polynucleotide molecules contains a complete sequencer motif.

[0009] In some embodiments, the library adaptors (or adapters) are identical to one another but for the molecular barcodes. In some embodiments, each of the plurality of library adaptors comprises at least one double-stranded portion and at least one single-stranded portion (e.g., a non-complementary portion or an overhang). In some embodiments, the double-stranded portion has a molecular barcode selected from a collection of different molecular barcodes. In some embodiments, the given molecular barcode is a randomer. In some embodiments, each of the library adaptors further comprises a strand-identification barcode on the at least one single-stranded portion. In some embodiments, the strand-identification barcode includes at least 4 nucleotide bases. In some embodiments, the single-stranded portion has a partial sequencer motif. In some embodiments, the library adaptors do not include a complete sequencer motif.

[0010] In some embodiments, none of the library adaptors contains a sequence for hybridizing to a flow cell or forming a hairpin for sequencing.

[0011] In some embodiments, all of the library adaptors have a terminal end with nucleotide(s) that are the same. In some embodiments, the identical terminal nucleotide(s) are over two or more nucleotide bases in length.

[0012] In some embodiments, each of the library adapters is Y-shaped, bubble shaped or hairpin shaped. In some embodiments, none of the library adapters contains a sample identification motif. In some embodiments, each of the library adapters comprises a sequence that is selectively hybridizable to a universal primer. In some embodiments, each of the library adapters comprises a molecular barcode that is at least 5, 6, 7, 8, 9 and 10 nucleotide bases in

length. In some embodiments, each of the library adapters is from 10 nucleotide bases to 80 in length, or 30 to 70 nucleotide bases in length, or 40 to 60 nucleotide bases in length. In some embodiments, at least 1, 2, 3, or 4 terminal bases are identical in all of the library adaptors. In some embodiments, at least 4 terminal bases are identical in all of the library adaptors.

[0013] In some embodiments, the edit distance of the molecular barcodes of the library adapters is a Hamming distance. In some embodiments, the edit distance is at least 1, 2, 3, 4 or 5. In some embodiments, the edit distance is with respect to individual bases of the plurality of polynucleotide molecules. In some embodiments, the molecular barcodes are located at least 10 nucleotide base away from a terminal end of an adapter. In some embodiments, the plurality of library adapters includes at least 2, 4, 6, 8, 10, 20, 30, 40 or 50 different molecular barcodes, or from 2-100, 4-80, 6-60 or 8-40 different molecular barcodes. In any of the embodiments herein, there are more polynucleotides (e.g., cfDNA fragments) to be tagged than there are different molecular barcodes such that the tagging is not unique.

[0014] In some embodiments, the terminal end of an adaptor is configured for ligation (e.g., to a target nucleic acid molecule). In some embodiments, the terminal end of an adaptor is a blunt end.

[0015] In some embodiments, the adaptors are purified and isolated. In some embodiments, the library comprises one or more non-naturally occurring bases.

[0016] In some embodiments, the polynucleotide molecules comprise a primer sequence positioned 5' with respect to the molecular barcodes.

[0017] In some embodiments, the set of library adaptors consists essentially of the plurality of polynucleotide molecules.

[0018] In another aspect, a method comprises (a) tagging a collection of polynucleotides with a plurality of polynucleotide molecules from a library of adaptors to create a collection of tagged polynucleotides; and (b) amplifying the collection of tagged polynucleotides in the presence of sequencing adaptors, wherein the sequencing adaptors have primers with nucleotide sequences that are selectively hybridizable to complementary sequences in the plurality of polynucleotide molecules. The library of adaptors may be as described above or elsewhere herein. In some embodiments, each of the sequencer adaptors further comprises an index tag, which can be a sample identification motif.

[0019] Another aspect, provides a method for detecting and/or quantifying rare DNA in a heterogeneous population of original DNA fragments, wherein the rare DNA has a concentration that is less than 1%, the method comprising (a) tagging the original DNA fragments in a single reaction such that greater than 30% of the original DNA fragments are tagged at both ends with library adaptors that comprise molecular barcodes, thereby providing tagged DNA fragments; (b) performing high-fidelity amplification on the tagged DNA fragments; (c) optionally, selectively enriching a subset of the tagged DNA fragments; (d) sequencing one or both strands of the tagged, amplified and optionally selectively enriched DNA fragments to obtain sequence reads comprising nucleotide sequences of the molecular barcodes and at least a portion of the original DNA fragments; (e) from the sequence reads, determining consensus reads that are representative of single-strands of the original DNA fragments; and (f) quantifying the consensus reads to detect and/or quantify the rare DNA at a specificity that is greater than 99.9%.

[0020] In some embodiments, (e) comprises comparing sequence reads having the same or similar molecular barcodes and the same or similar end of fragment sequences. In some embodiments, the comparing further comprises performing a phylogentic analysis on the sequence reads having the same or similar molecular barcodes. In some embodiments, the molecular barcodes include a barcode having an edit distance of up to 3. In some embodiments, the end of fragment sequence includes fragment sequences having an edit distance of up to 3.

[0021] In some embodiments, the method further comprises sorting sequence reads into paired reads and unpaired reads, and quantifying a number of paired reads and unpaired reads that map to each of one or more genetic loci.

[0022] In some embodiments, the tagging occurs by having an excess amount of library adaptors as compared to original DNA fragments. In some embodiments, n the excess is at least a 5-fold excess. In some embodiments, the tagging comprises using a ligase. In some embodiments, the tagging comprises attachment to blunt ends.

[0023] In some embodiments, the method further comprises binning the sequence reads according to the molecular barcodes and sequence information from at least one end of each of the original DNA fragments to create bins of single stranded reads. In some embodiments, the method further comprises, in each bin, determining a sequence of a given original DNA fragment among the original DNA fragments by analyzing sequence reads. In some embodiments, the

method further comprises detecting and/or quantifying the rare DNA by comparing a number of times each base occurs at each position of a genome represented by the tagged, amplified, and optionally enriched DNA fragments.

[0024] In some embodiments, the library adaptors do not contain complete sequencer motifs. In some embodiments, the method further comprises selectively enriching a subset of the tagged DNA fragments. In some embodiments, the method further comprises, after enriching, amplifying the enriched tagged DNA fragments in the presence of sequencing adaptors comprising primers. In some embodiments, (a) provides tagged DNA fragments having from 2 to 1000 different combinations of molecular barcodes.

[0025] In some embodiments, the DNA fragments are tagged with polynucleotide molecules from a library of adaptors as described above or elsewhere herein.

[0026] In another aspect, a method for processing and/or analyzing a nucleic acid sample of a subject comprises (a) exposing polynucleotide fragments from the nucleic acid sample to a set of library adaptors to generate tagged polynucleotide fragments; and (b) subjecting the tagged polynucleotide fragments to nucleic acid amplification reactions under conditions that yield amplified polynucleotide fragments as amplification products of the tagged polynucleotide fragments. The set of library adaptors comprises a plurality of polynucleotide molecules with molecular barcodes, wherein the plurality of polynucleotide molecules are less than or equal to 80 nucleotide bases in length, wherein the molecular barcodes are at least 4 nucleotide bases in length, and wherein (1) the molecular barcodes are different from one another and have an edit distance of at least 1 between one another; (2) the molecular barcodes are located at least one nucleotide base away from a terminal end of their respective polynucleotide molecules; (3) optionally, at least one terminal base is identical in all of the polynucleotide molecules; and (4) none of the polynucleotide molecules contains a complete sequencer motif.

[0027] In some embodiments, the method further comprises determining nucleotide sequences of the amplified tagged polynucleotide fragments. In some embodiments, the nucleotide sequences of the amplified tagged polynucleotide fragments are determined without polymerase chain reaction (PCR). In some embodiments, the method further comprises analyzing the nucleotide sequences with a programmed computer processor to identify one or more genetic variants in the nucleotide sample of the subject. In some embodiments, the one or

more genetic variants are selected from the group consisting of base change(s), insertion(s), repeat(s), deletion(s), copy number variation(s) and transversion(s). In some embodiments, the one or more genetic variants include one or more tumor associated genetic alterations.

[0028] In some embodiments, the subject has or is suspected of having a disease. In some embodiments, the disease is cancer. In some embodiments, the method further comprises collecting the nucleic acid sample from the subject. In some embodiments, the nucleic acid sample is collected from a location selected from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, cerebral spinal fluid and tears of the subject. In some embodiments, the nucleic acid sample is a cell-free nucleic acid sample. In some embodiments, the nucleic acid sample is collected from no more than 100 nanograms (ng) of double-stranded polynucleotide molecules of the subject.

[0029] In some embodiments, the polynucleotide fragments comprise double-stranded polynucleotide molecules. In some embodiments, in (a), the plurality of polynucleotide molecules couple to the polynucleotide fragments via blunt end ligation, sticky end ligation, molecular inversion probes, PCR, ligation-based PCR, multiplex PCR, single stranded ligation, and single stranded circularization. In some embodiments, exposing the polynucleotide fragments of the nucleic acid sample to the plurality of polynucleotide molecules yields the tagged polynucleotide fragments with a conversion efficiency of at least 10%. In some embodiments, any of at least 5%, 6%, 7%, 8%, 9%, 10%, 20%, or 25% of the tagged polynucleotide fragments share a common polynucleotide molecule or sequence. In some embodiments, the method further comprises generating the polynucleotide fragments from the nucleic acid sample.

[0030] In some embodiments, the subjecting comprises amplifying the tagged polynucleotide fragments from sequences corresponding to genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1,

CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

[0031] In another aspect, a method comprises (a) generating a plurality of sequence reads from a plurality of polynucleotide molecules, wherein the plurality of polynucleotide molecules cover genomic loci of a target genome, wherein the genomic loci correspond to a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1; (b) grouping with a computer processor the plurality of sequence reads into families, wherein each family comprises sequence reads from one of the template polynucleotides; (c) for each of the families, merging sequence reads to generate a consensus sequence; (d) calling the consensus sequence at a given genomic locus among the genomic loci; and (e) detecting at the given genomic locus any of genetic variants among the calls, frequency of a genetic alteration among the calls, total number of calls, and total number of alterations among the calls.

[0032] In some embodiments, each family comprises sequence reads from only one of the template polynucleotides. In some embodiments, the given genomic locus comprises at least one nucleic acid base. In some embodiments, the given genomic locus comprises a plurality of nucleic acid bases. In some embodiments, the calling comprises calling at least one nucleic acid base at the given genomic locus. In some embodiments, the calling comprises calling a plurality of nucleic acid bases at the given genomic locus. In some embodiments, the calling comprises any one of phylogenetic analysis, voting, weighing, assigning a probability to each read at the locus in a family and calling the base with the highest probability.

[0033] In some embodiments, the method further comprises performing (d)-(e) at an additional genomic locus among the genomic loci. In some embodiments, the method further comprises determining a variation in copy number at one of the given genomic locus and

additional genomic locus based on counts at the given genomic locus and additional genomic locus.

[0034] In some embodiments, the grouping comprises classifying the plurality of sequence reads into families by identifying (i) different molecular barcodes coupled to the plurality of polynucleotide molecules and (ii) similarities between the plurality of sequence reads, wherein each family includes a plurality of nucleic acid sequences that are associated with a different combination of molecular barcodes and similar or identical sequence reads. Different molecular barcodes have different sequences.

[0035] In some embodiments, the consensus sequence is generated by evaluating a quantitative measure or a statistical significance level for each of the sequence reads. In some embodiments, the quantitative measure comprises use of a binomial distribution, exponential distribution, beta distribution, or empirical distribution. In some embodiments, the method further comprises mapping the consensus sequence to the target genome. In some embodiments, the plurality of genes includes at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50 or all of the plurality of genes selected from the group.

[0036] Another aspect of the present disclosure provides a method, comprising (a) providing template polynucleotide molecules and a set of library adaptors in a single reaction vessel, wherein the library adaptors are polynucleotide molecules that have different molecular barcodes (e.g., from 2 to 1,000 different molecular barcodes), and wherein none of the library adaptors contains a complete sequencer motif; (b) in the single reaction vessel, coupling the library adaptors to the template polynucleotide molecules at an efficiency of at least 10%, thereby tagging each template polynucleotide with a tagging combination that is among a plurality of different tagging combinations (e.g., 4 to 1,000,000 different tagging combinations), to produce tagged polynucleotide molecules; (c) subjecting the tagged polynucleotide molecules to an amplification reaction under conditions that yield amplified polynucleotide molecules as amplification products of the tagged polynucleotide molecules; and (d) sequencing the amplified polynucleotide molecules.

[0037] In some embodiments, the template polynucleotide molecules are blunt ended or sticky-ended. In some embodiments, the library adaptors are identical but for the molecular barcodes. In some embodiments, each of the library adaptors has a double stranded portion and

at least one single-stranded portion. In some embodiments, the double-stranded portion has a molecular barcode among the molecular barcodes. In some embodiments, each of the library adaptors further comprises a strand-identification barcode on the at least one single-stranded portion. In some embodiments, the single-stranded portion has a partial sequencer motif. In some embodiments, the library adaptors have a sequence of terminal nucleotides that are the same. In some embodiments, the template polynucleotide molecules are double-stranded. In some embodiments, the library adaptors couple to both ends of the template polynucleotide molecules.

[0038] In some embodiments, subjecting the tagged polynucleotide molecules to the amplification reaction comprises non-specifically amplifying the tagged polynucleotide molecules.

[0039] In some embodiments, the amplification reaction comprises use of a priming site to amplify each of the tagged polynucleotide molecules. In some embodiments, the priming site is a primer. In some embodiments, the primer is a universal primer. In some embodiments, the priming site is a nick.

[0040] In some embodiments, the method further comprises, prior to (e), (i) separating polynucleotide molecules comprising one or more given sequences from the amplified polynucleotide molecules, to produce enriched polynucleotide molecules; and (ii) amplifying the enriched polynucleotide molecules with sequencing adaptors.

[0041] In some embodiments, the efficiency is at least 30%, 40%, or 50%. In some embodiments, the method further comprises identifying genetic variants upon sequencing the amplified polynucleotide molecules. In some embodiments, the sequencing comprises (i) subjecting the amplified polynucleotide molecules to an additional amplification reaction under conditions that yield additional amplified polynucleotide molecules as amplification products of the amplified polynucleotide molecules, and (ii) sequencing the additional amplified polynucleotide molecules. In some embodiments, the additional amplification is performed in the presence of sequencing adaptors.

[0042] In some embodiments, (b) and (c) are performed without aliquoting the tagged polynucleotide molecules. In some embodiments, the tagging is non-unique tagging.

[0043] Another aspect, provides a system for analyzing a target nucleic acid molecule of a subject, comprising a communication interface that receives nucleic acid sequence reads for a plurality of polynucleotide molecules that cover genomic loci of a target genome; computer memory that stores the nucleic acid sequence reads for the plurality of polynucleotide molecules received by the communication interface; and a computer processor operatively coupled to the communication interface and the memory and programmed to (i) group the plurality of sequence reads into families, wherein each family comprises sequence reads from one of the template polynucleotides, (ii) for each of the families, merge sequence reads to generate a consensus sequence, (iii) call the consensus sequence at a given genomic locus among the genomic loci, and (iv) detect at the given genomic locus any of genetic variants among the calls, frequency of a genetic alteration among the calls, total number of calls; and total number of alterations among the calls, wherein the genomic loci correspond to a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

[0044] In another aspect, a set of oligonucleotide molecules that selectively hybridize to at least 5 genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

[0045] In some embodiments, the oligonucleotide molecules are from 10-200 bases in length. In some embodiments, the oligonucleotide molecules selectively hybridize to exon

regions of the at least 5 genes. In some embodiments, the oligonucleotide molecules selectively hybridize to at least 30 exons in the at least 5 genes. In some embodiments, multiple oligonucleotide molecules selectively hybridize to each of the at least 30 exons. In some embodiments, the oligonucleotide molecules that hybridize to each exon have sequences that overlap with at least 1 other oligonucleotide molecule.

[0046] In another aspect, a kit comprises a first container containing a plurality of library adaptors each having a different molecular barcode; and a second container containing a plurality of sequencing adaptors, each sequencing adaptor comprising at least a portion of a sequencer motif and optionally a sample barcode. The library adaptors can be as described above or elsewhere herein.

[0047] In some embodiments, the sequencing adaptor comprises the sample barcode. In some embodiments, the library adaptors are blunt ended and Y-shaped, and are less than or equal to 80 nucleic acid bases in length. In some embodiments, the sequencing adaptor is up to 70 bases from end to end.

[0048] In another aspect, a method for detecting sequence variants in a cell free DNA sample, comprising detecting rare DNA at a concentration less than 1% with a specificity that is greater than 99.9%.

[0049] In another aspect, a method comprises detecting genetic variants in a sample comprising DNA with a detection limit of at least 1% and specificity greater than 99.9%. In some embodiments, the method further comprises converting cDNA (e.g. cfDNA) into adaptor tagged DNA with a conversion efficiency of at least 30%, 40%, or 50% and reducing sequencing noise (or distortion) by eliminating false positive sequence reads.

[0050] Another aspect provides a method, comprising (a) providing a sample comprising a set of double-stranded polynucleotide molecules, each double-stranded polynucleotide molecule including first and second complementary strands; (b) tagging the double-stranded polynucleotide molecules with a set of duplex tags, wherein each duplex tag differently tags the first and second complementary strands of a double-stranded polynucleotide molecule in the set; (c) sequencing at least some of the tagged strands to produce a set of sequence reads; (d) reducing and/or tracking redundancy in the set of sequence reads; (e) sorting sequence reads into paired reads and unpaired reads, wherein (i) each paired read corresponds to sequence reads

generated from a first tagged strand and a second differently tagged complementary strand derived from a double-stranded polynucleotide molecule in the set, and (ii) each unpaired read represents a first tagged strand having no second differently tag complementary strand derived from a double-stranded polynucleotide molecule represented among the sequence reads in the set of sequence reads; (f) determining quantitative measures of (i) the paired reads and (ii) the unpaired reads that map to each of one or more genetic loci; and (g) estimating with a programmed computer processor a quantitative measure of total double-stranded polynucleotide molecules in the set that map to each of the one or more genetic loci based on the quantitative measure of paired reads and unpaired reads mapping to each locus.

[0051] In some embodiments, the method further comprises (h) detecting copy number variation in the sample by determining a normalized total quantitative measure determined in step (g) at each of the one or more genetic loci and determining copy number variation based on the normalized measure. In some embodiments, the sample comprises double-stranded polynucleotide molecules sourced substantially from cell-free nucleic acids. In some embodiments, the duplex tags are not sequencing adaptors.

[0052] In some embodiments, reducing redundancy in the set of sequence reads comprises collapsing sequence reads produced from amplified products of an original polynucleotide molecule in the sample back to the original polynucleotide molecule. In some embodiments, the method further comprises determining a consensus sequence for the original polynucleotide molecule. In some embodiments, the method further comprises identifying polynucleotide molecules at one or more genetic loci comprising a sequence variant. In some embodiments, the method further comprises determining a quantitative measure of paired reads that map to a locus, wherein both strands of the pair comprise a sequence variant. In some embodiments, the method further comprises determining a quantitative measure of paired molecules in which only one member of the pair bears a sequence variant and/or determining a quantitative measure of unpaired molecules bearing a sequence variant. In some embodiments, the sequence variant is selected from the group consisting of a single nucleotide variant, an indel, a transversion, a translocation, an inversion, a deletion, a chromosomal structure alteration, a gene fusion, a chromosome fusion, a gene truncation, a gene amplification, a gene duplication and a chromosomal lesion.

[0053] Another aspect provides a system comprising a computer readable medium comprising machine-executable code that, upon execution by a computer processor, implements a method comprising (a) receiving into memory a set of sequence reads of polynucleotides tagged with duplex tags; (b) reducing and/or tracking redundancy in the set of sequence reads; (c) sorting sequence reads into paired reads and unpaired reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from a double-stranded polynucleotide molecule in the set, and (ii) each unpaired read represents a first tagged strand having no second differently tag complementary strand derived from a double-stranded polynucleotide molecule represented among the sequence reads in the set of sequence reads; (d) determining quantitative measures of (i) the paired reads and (ii) the unpaired reads that map to each of one or more genetic loci; and (e) estimating a quantitative measure of total double-stranded polynucleotide molecules in the set that map to each of the one or more genetic loci based on the quantitative measure of paired reads and unpaired reads mapping to each locus.

[0054] Another aspect provides a method, comprising (a) providing a sample comprising a set of double-stranded polynucleotide molecules, each double-stranded polynucleotide molecule including first and second complementary strands; (b) tagging the double-stranded polynucleotide molecules with a set of duplex tags, wherein each duplex tag differently tags the first and second complementary strands of a double-stranded polynucleotide molecule in the set; (c) sequencing at least some of the tagged strands to produce a set of sequence reads; (d) reducing and/or tracking redundancy in the set of sequence reads; (e) sorting sequence reads into paired reads and unpaired reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from a double-stranded polynucleotide molecule in the set, and (ii) each unpaired read represents a first tagged strand having no second differently tag complementary strand derived from a double-stranded polynucleotide molecule represented among the sequence reads in the set of sequence reads; and (f) determining quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads that map to each of one or more genetic loci, (iii) read depth of the paired reads and (iv) read depth of unpaired reads.

[0055] In some embodiments, (f) comprises determining quantitative measures of at least three of (i)-(iv). In some embodiments, (f) comprises determining quantitative measures of all of (i)-(iv). In some embodiments, the method further comprises (g) estimating with a programmed computer processor a quantitative measure of total double-stranded polynucleotide molecules in the set that map to each of the one or more genetic loci based on the quantitative measure of paired reads and unpaired reads and their read depths mapping to each locus.

[0056] In another aspect, a method comprises (a) tagging control parent polynucleotides with a first tag set to produce tagged control parent polynucleotides, wherein the first tag set comprises a plurality of tags, wherein each tag in the first tag set comprises a same control tag and an identifying tag, and wherein the tag set comprises a plurality of different identifying tags; (b) tagging test parent polynucleotides with a second tag set to produce tagged test parent polynucleotides, wherein the second tag set comprises a plurality of tags, wherein each tag in the second tag set comprises a same test tag that is distinguishable from the control tag and an identifying tag, and wherein the second tag set comprises a plurality of different identifying tags; (c) mixing tagged control parent polynucleotides with tagged test parent polynucleotides to form a pool; (d) amplifying tagged parent polynucleotides in the pool to form a pool of amplified, tagged polynucleotides; (e) sequencing amplified, tagged polynucleotides in the amplified pool to produce a plurality of sequence reads; (f) grouping sequence reads into families, each family comprising sequence reads generated from a same parent polynucleotide, which grouping is optionally based on information from an identifying tag and from start/end sequences of the parent polynucleotides, and, optionally, determining a consensus sequence for each of a plurality of parent polynucleotides from the plurality of sequence reads in a group; (g) classifying each family or consensus sequence as a control parent polynucleotide or as a test parent polynucleotide based on having a test tag or a control tag; (h) determining a quantitative measure of control parent polynucleotides and control test polynucleotides mapping to each of at least two genetic loci; and (i) determining copy number variation in the test parent polynucleotides at at least one locus based on relative quantity of test parent polynucleotides and control parent polynucleotides mapping to the at least one locus.

[0057] In another aspect, a method comprises (a) generating a plurality of sequence reads from a plurality of template polynucleotides, each polynucleotide mapped to a genomic locus;

(b) grouping the sequence reads into families, each family comprising sequence reads generated from one of the template polynucleotides; (c) calling a base (or sequence) at the genomic locus for each of the families; (d) detecting at the genomic locus any of genomic alterations among the calls, frequency of a genetic alteration among the calls, total number of calls and total number of alterations among the calls.

[0058] In some embodiments, calling comprises any of phylogenetic analysis, voting, weighing, assigning a probability to each read at the locus in a family, and calling the base with the highest probability. In some embodiments, the method is performed at two loci, comprising determining CNV at one of the loci based on counts at each of the loci.

[0059] Another aspect provides a method for determining a quantitative measure indicative of a number of individual double-stranded DNA fragments in a sample comprising (a) determining a quantitative measure of individual DNA molecules for which both strands are detected; (b) determining a quantitative measure of individual DNA molecules for which only one of the DNA strands are detected; (c) inferring from (a) and (b) above a quantitative measure of individual DNA molecules for which neither strand was detected; and (d) using (a)-(c) determining the quantitative measure indicative of a number of individual double-stranded DNA fragments in the sample.

[0060] In some embodiments, the method further comprises detecting copy number variation in the sample by determining a normalized quantitative measure determined in step (d) at each of one or more genetic loci and determining copy number variation based on the normalized measure. In some embodiments, the sample comprises double-stranded polynucleotide molecules sourced substantially from cell-free nucleic acids.

[0061] In some embodiments, determining the quantitative measure of individual DNA molecules comprises tagging the DNA molecules with a set of duplex tags, wherein each duplex tag differently tags complementary strands of a double-stranded DNA molecule in the sample to provide tagged strands. In some embodiments, the method further comprises sequencing at least some of the tagged strands to produce a set of sequence reads. In some embodiments, the method further comprises sorting sequence reads into paired reads and unpaired reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from a double-stranded polynucleotide

molecule in the set, and (ii) each unpaired read represents a first tagged strand having no second differently tag complementary strand derived from a double-stranded polynucleotide molecule represented among the sequence reads in the set of sequence reads. In some embodiments, the method further comprises determining quantitative measures of (i) the paired reads and (ii) the unpaired reads that map to each of one or more genetic loci to determine a quantitative measure of total double-stranded DNA molecules in the sample that map to each of the one or more genetic loci based on the quantitative measure of paired reads and unpaired reads mapping to each locus.

[0062] In another aspect, a method for reducing distortion in a sequencing assay, comprises (a) tagging control parent polynucleotides with a first tag set to produce tagged control parent polynucleotides; (b) tagging test parent polynucleotides with a second tag set to produce tagged test parent polynucleotides; (c) mixing tagged control parent polynucleotides with tagged test parent polynucleotides to form a pool; (d) determining quantities of tagged control parent polynucleotides and tagged test parent polynucleotides; and (e) using the quantities of tagged control parent polynucleotides to reduce distortion in the quantities of tagged test parent polynucleotides.

[0063] In some embodiments, the first tag set comprises a plurality of tags, wherein each tag in the first tag set comprises a same control tag and an identifying tag, and wherein the first tag set comprises a plurality of different identifying tags. In some embodiments, the second tag set comprises a plurality of tags, wherein each tag in the second tag set comprises a same test tag and an identifying tag, wherein the test tag is distinguishable from the control tag, and wherein the second tag set comprises a plurality of different identifying tags. In some embodiments, (d) comprises amplifying tagged parent polynucleotides in the pool to form a pool of amplified, tagged polynucleotides, and sequencing amplified, tagged polynucleotides in the amplified pool to produce a plurality of sequence reads. In some embodiments, the method further comprises grouping sequence reads into families, each family comprising sequence reads generated from a same parent polynucleotide, which grouping is optionally based on information from an identifying tag and from start/end sequences of the parent polynucleotides, and, optionally, determining a consensus sequence for each of a plurality of parent polynucleotides from the plurality of sequence reads in a group.

[0064] In some embodiments, (d) comprises determining copy number variation in the test parent polynucleotides at greater than or equal to one locus based on relative quantity of test parent polynucleotides and control parent polynucleotides mapping to the locus.

[0065] Another aspect provides a method comprising (a) ligating adaptors to double-stranded DNA polynucleotides, wherein ligating is performed in a single reaction vessel, and wherein the adaptors comprise molecular barcodes, to produce a tagged library comprising an insert from the double-stranded DNA polynucleotides, and having between 4 and 1 million different tags; (b) generating a plurality of sequence reads for each of the double-stranded DNA polynucleotides in the tagged library; (c) grouping sequence reads into families, each family comprising sequence reads generated from a single DNA polynucleotide among the double-stranded DNA polynucleotides, based on information in a tag and information at an end of the insert; and (d) calling bases at each position in the double-stranded DNA molecule based on bases at the position in members of a family. In some embodiments, (b) comprises amplifying each of the double-stranded DNA polynucleotide molecules in the tagged library to generate amplification products, and sequencing the amplification products. In some embodiments, the method further comprises sequencing the double-stranded DNA polynucleotide molecules a plurality of times. In some embodiments, (b) comprises sequencing the entire insert. In some embodiments, (c) further comprises collapsing sequence reads in each family to generate a consensus sequence. In some embodiments, (d) comprises calling a plurality of sequential bases from at least a subset of the sequence reads to identify single nucleotide variations (SNV) in the double-stranded DNA molecule.

[0066] Another aspect provides a method of detecting disease cell heterogeneity from a sample comprising polynucleotides from somatic cells and disease cells. The method comprises quantifying polynucleotides in the sample bearing a nucleotide sequence variant at each of a plurality of genetic loci; determining copy number variation (CNV) at each of the plurality of genetic loci, wherein the CNV indicates a genetic dose of a locus in the disease cell polynucleotides; determining with a programmed computer processor a relative measure of quantity of polynucleotides bearing a sequence variant at a locus per the genetic dose at the locus for each of a plurality of the loci; and comparing the relative measures at each of the plurality of loci, wherein different relative measures is indicative of tumor heterogeneity.

[0067] In another aspect, a method comprises subjecting a subject to one or more pulsed therapy cycles, each pulsed therapy cycle comprising (a) a first period during which a drug is administered at a first amount; and (b) a second period during which the drug is administered at a second, reduced amount, wherein (i) the first period is characterized by a tumor burden detected above a first clinical level; and (ii) the second period is characterized by a tumor burden detected below a second clinical level.

[0068] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0069] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0001] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "figure" and "FIG." herein), of which:

[0070] **FIG. 1** is a flowchart representation of a method of the present disclosure for determining copy number variation (CNV);

[0071] **FIG. 2** depicts mapping of pairs and singlets to Locus A and Locus B in a genome;

[0072] **FIG. 3** shows a reference sequence encoding a genetic Locus A;

[0073] **FIGs. 4A-C** shows amplification, sequencing, redundancy reduction and pairing of complementary molecules;

[0074] **FIG. 5** shows increased confidence in detecting sequence variants by pairing reads from Watson and Crick strands;

[0075] **FIG. 6** shows a computer system that is programmed or otherwise configured to implement various methods of the present disclosure;

[0076] **FIG. 7** is schematic representation of a system for analyzing a sample comprising nucleic acids from a user, including a sequencer; bioinformatic software and internet connection for report analysis by, for example, a hand held device or a desk top computer;

[0077] **FIG. 8** is a flowchart representation of a method of this invention for determining CNV using pooled test and control pools; and

[0078] **FIGs. 9A-9C** schematically illustrate a method for tagging a polynucleotide molecule with a library adaptor and subsequently a sequencing adaptor.

DETAILED DESCRIPTION

[0079] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

[0080] The term "genetic variant," as used herein, generally refers to an alteration, variant or polymorphism in a nucleic acid sample or genome of a subject. Such alteration, variant or polymorphism can be with respect to a reference genome, which may be a reference genome of the subject or other individual. Single nucleotide polymorphisms (SNPs) are a form of polymorphisms. In some examples, one or more polymorphisms comprise one or more single nucleotide variations (SNVs), insertions, deletions, repeats, small insertions, small deletions, small repeats, structural variant junctions, variable length tandem repeats, and/or flanking sequences,. Copy number variants (CNVs), transversions and other rearrangements are also forms of genetic variation. A genomic alternation may be a base change, insertion, deletion, repeat, copy number variation, or transversion.

[0081] The term "polynucleotide," as used herein, generally refers to a molecule comprising one or more nucleic acid subunits. A polynucleotide can include one or more subunits selected from adenosine (A), cytosine (C), guanine (G), thymine (T) and uracil (U), or variants thereof. A

nucleotide can include A, C, G, T or U, or variants thereof. A nucleotide can include any subunit that can be incorporated into a growing nucleic acid strand. Such subunit can be an A, C, G, T, or U, or any other subunit that is specific to one or more complementary A, C, G, T or U, or complementary to a purine (i.e., A or G, or variant thereof) or a pyrimidine (i.e., C, T or U, or variant thereof). A subunit can enable individual nucleic acid bases or groups of bases (*e.g.*, AA, TA, AT, GC, CG, CT, TC, GT, TG, AC, CA, or uracil-counterparts thereof) to be resolved. In some examples, a polynucleotide is deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), or derivatives thereof. A polynucleotide can be single-stranded or double stranded.

[0082] The term "subject," as used herein, generally refers to an animal, such as a mammalian species (*e.g.*, human) or avian (*e.g.*, bird) species, or other organism, such as a plant. More specifically, the subject can be a vertebrate, a mammal, a mouse, a primate, a simian or a human. Animals include, but are not limited to, farm animals, sport animals, and pets. A subject can be a healthy individual, an individual that has or is suspected of having a disease or a pre-disposition to the disease, or an individual that is in need of therapy or suspected of needing therapy. A subject can be a patient.

[0083] The term "genome" generally refers to an entirety of an organism's hereditary information. A genome can be encoded either in DNA or in RNA. A genome can comprise coding regions that code for proteins as well as non-coding regions. A genome can include the sequence of all chromosomes together in an organism. For example, the human genome has a total of 46 chromosomes. The sequence of all of these together constitutes a human genome.

[0084] The terms "adaptor(s)", "adapter(s)" and "tag(s)" are used synonymously throughout this specification. An adaptor or tag can be coupled to a polynucleotide sequence to be "tagged" by any approach including ligation, hybridization, or other approaches.

[0085] The term "library adaptor" or "library adapter" as used herein, generally refers to a molecule (e.g., polynucleotide) whose identity (e.g., sequence) can be used to differentiate polynucleotides in a biological sample (also "sample" herein).

[0086] The term "sequencing adaptor," as used herein, generally refers to a molecule (e.g., polynucleotide) that is adapted to permit a sequencing instrument to sequence a target polynucleotide, such as by interacting with the target polynucleotide to enable sequencing. The sequencing adaptor permits the target polynucleotide to be sequenced by the sequencing

instrument. In an example, the sequencing adaptor comprises a nucleotide sequence that hybridizes or binds to a capture polynucleotide attached to a solid support of a sequencing system, such as a flow cell. In another example, the sequencing adaptor comprises a nucleotide sequence that hybridizes or binds to a polynucleotide to generate a hairpin loop, which permits the target polynucleotide to be sequenced by a sequencing system. The sequencing adaptor can include a sequencer motif, which can be a nucleotide sequence that is complementary to a flow cell sequence of other molecule (e.g., polynucleotide) and usable by the sequencing system to sequence the target polynucleotide. The sequencer motif can also include a primer sequence for use in sequencing, such as sequencing by synthesis. The sequencer motif can include the sequence(s) needed to couple a library adaptor to a sequencing system and sequence the target polynucleotide.

[0087] As used herein the terms "at least", "at most" or "about", when preceding a series, refers to each member of the series, unless otherwise identified.

[0088] The term *"about"* and its grammatical equivalents in relation to a reference numerical value can include a range of values up to plus or minus 10% from that value. For example, the amount *"about 10"* can include amounts from 9 to 11. In other embodiments, the term *"about"* in relation to a reference numerical value can include a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value.

[0089] The term "at least" and its grammatical equivalents in relation to a reference numerical value can include the reference numerical value and greater than that value. For example, the amount "at least 10" can include the value 10 and any numerical value above 10, such as 11, 100, and 1,000.

[0090] The term "at most" and its grammatical equivalents in relation to a reference numerical value can include the reference numerical value and less than that value. For example, the amount "at most 10" can include the value 10 and any numerical value under 10, such as 9, 8, 5, 1, 0.5, and 0.1.

[0091] **1. <u>Methods for processing and/or analyzing a nucleic acid sample</u>**

[0092] An aspect of the present disclosure provides methods for determining a genomic alternation in a nucleic acid sample of a subject. **FIG. 1** shows a method of determining copy

number variation (CNV). The method can be implemented to determine other genomic alternations, such as SNVs.

[0093] **A. Polynucleotide Isolation**

[0094] Methods disclosed herein can comprise isolating one or more polynucleotides. A polynucleotide can comprise any type of nucleic acid, for example, a sequence of genomic nucleic acid, or an artificial sequence (*e.g.*, a sequence not found in genomic nucleic acid). For example, an artificial sequence can contain non-natural nucleotides. Also, a polynucleotide can comprise both genomic nucleic acid and an artificial sequence, in any portion. For example, a polynucleotide can comprise 1 to 99% of genomic nucleic acid and 99% to 1% of artificial sequence, where the total adds up to 100%. Thus, fractions of percentages are also contemplated. For example, a ratio of 99.1% to 0.9% is contemplated.

[0095] A polynucleotide can comprise any type of nucleic acids, such as DNA and/or RNA. For example, if a polynucleotide is DNA, it can be genomic DNA, complementary DNA (cDNA), or any other deoxyribonucleic acid. A polynucleotide can also be cell-free DNA (cfDNA). For example, the polynucleotide can be circulating DNA. The circulating DNA can comprise circulating tumor DNA (ctDNA). A polynucleotide can be double-stranded or single-stranded. Alternatively, a polynucleotide can comprise a combination of a double-stranded portion and a single-stranded portion.

[0096] Polynucleotides do not have to be cell-free. In some cases, the polynucleotides can be isolated from a sample. For example, in step (102) (**FIG. 1**), double-stranded polynucleotides are isolated from a sample. A sample can be any biological sample isolated from a subject. For example, a sample can comprise, without limitation, bodily fluid, whole blood, platelets, serum, plasma, stool, red blood cells, white blood cells or leucocytes, endothelial cells, tissue biopsies, synovial fluid, lymphatic fluid, ascites fluid, interstitial or extracellular fluid, the fluid in spaces between cells, including gingival crevicular fluid, bone marrow, cerebrospinal fluid, saliva, mucous, sputum, semen, sweat, urine, or any other bodily fluids. A bodily fluid can include saliva, blood, or serum. For example, a polynucleotide can be cell-free DNA isolated from a bodily fluid, *e.g.*, blood or serum. A sample can also be a tumor sample, which can be obtained from a subject by various approaches, including, but not limited to, venipuncture, excretion,

ejaculation, massage, biopsy, needle aspirate, lavage, scraping, surgical incision, or intervention or other approaches.

[0097] A sample can comprise various amount of nucleic acid that contains genome equivalents. For example, a sample of about 30 ng DNA can contain about 10,000 (10^4) haploid human genome equivalents and, in the case of cfDNA, about 200 billion ($2x10^{11}$) individual polynucleotide molecules. Similarly, a sample of about 100 ng of DNA can contain about 30,000 haploid human genome equivalents and, in the case of cfDNA, about 600 billion individual molecules.

[0098] A sample can comprise nucleic acids from different sources. For example, a sample can comprise germline DNA or somatic DNA. A sample can comprise nucleic acids carrying mutations. For example, a sample can comprise DNA carrying germline mutations and/orsomatic mutations, . A sample can also comprise DNA carrying cancer-associated mutations (*e.g.*, cancer-associated somatic mutations).

[0099] **B. Tagging**

[00100] Polynucleotides disclosed herein can be tagged. For example, in step (104) (**FIG. 1**) the double-stranded polynucleotides are tagged with duplex tags, tags that differently label the complementary strands (*i.e.*, the "Watson" and "Crick" strands) of a double-stranded molecule. In one embodiment the duplex tags are polynucleotides having complementary and non-complementary portions.

[00101] Tags can be any types of molecules attached to a polynucleotide, including, but not limited to, nucleic acids, chemical compounds, florescent probes, or radioactive probes. Tags can also be oligonucleotides (*e.g.*, DNA or RNA). Tags can comprise known sequences, unknown sequences, or both. A tag can comprise random sequences, pre-determined sequences, or both. A tag can be double-stranded or single-stranded. A double-stranded tag can be a duplex tag. A double-stranded tag can comprise two complementary strands. Alternatively, a double-stranded tag can comprise a hybridized portion and a non-hybridized portion. The double-stranded tag can be Y-shaped, *e.g.*, the hybridized portion is at one end of the tag and the non-hybridized portion is at the opposite end of the tag. One such example are the "Y adapters" used in Illumina sequencing. Other examples include hairpin shaped adapters or bubble shaped

adapters. Bubble shaped adapters have non-complementary sequences flanked on both sides by complementary sequences.

[00102] Tagging disclosed herein can be performed using any method. A polynucleotide can be tagged with an adaptor by hybridization. For example, the adaptor can have a nucleotide sequence that is complementary to at least a portion of a sequence of the polynucleotide. As an alternative, a polynucleotide can be tagged with an adaptor by ligation.

[00103] For example, tagging can comprise using one or more enzymes. The enzyme can be a ligase. The ligase can be a DNA ligase. For example, the DNA ligase can be a T4 DNA ligase, *E. coli* DNA ligase, and/or mammalian ligase. The mammalian ligase can be DNA ligase I, DNA ligase III, or DNA ligase IV. The ligase can also be a thermostable ligase. Tags can be ligated to a blunt-end of a polynucleotide (blunt-end ligation). Alternatively, tags can be ligated to a sticky end of a polynucleotide (sticky-end ligation). Efficiency of ligation can be increased by optimizing various conditions. Efficiency of ligation can be increased by optimizing the reaction time of ligation. For example, the reaction time of ligation can be less than 12 hours, *e.g.*, less than 1, less than 2, less than 3, less than 4, less than 5, less than 6, less than 7, less than 8, less than 9, less than 10, less than 11, less than 12, less than 13, less than 14, less than 15, less than 16, less than 17, less than 18, less than 19, or less than 20 hours. In a particular example, reaction time of ligation is less than 20 hours. Efficiency of ligation can be increased by optimizing the ligase concentration in the reaction. For example, the ligase concentration can be at least 10, at least 50, at least 100, at least 150, at least 200, at least 250, at least 300, at least 400, at least 500, or at least 600 unit/microliter. Efficiency can also be optimized by adding or varying the concentration of an enzyme suitable for ligation, enzyme cofactors or other additives, and/or optimizing a temperature of a solution having the enzyme. Efficiency can also be optimized by varying the addition order of various components of the reaction. The end of tag sequence can comprise dinucleotide to increase ligation efficiency. When the tag comprises a non-complementary portion (e.g., Y-shaped adaptor), the sequence on the complementary portion of the tag adaptor can comprise one or more selected sequences that promote ligation efficiency. Preferably such sequences are located at the terminal end of the tag. Such sequences can comprise 1, 2, 3, 4, 5, or 6 terminal bases. Reaction solution with high viscosity (*e.g.*, a low Reynolds number) can also be used to increase ligation efficiency. For example, solution can

have a Reynolds number less than 3000, less than 2000, less than 1000, less than 900, less than 800, less than 700, less than 600, less than 500, less than 400, less than 300, less than 200, less than 100, less than 50, less than 25, or less than 10. It is also contemplated that roughly unified distribution of fragments (*e.g.*, tight standard deviation) can be used to increase ligation efficiency. For example, the variation in fragment sizes can vary by less than 20%, less than 15%, less than 10%, less than 5%, or less than 1%. Tagging can also comprise primer extension, for example, by polymerase chain reaction (PCR). Tagging can also comprise any of ligation-based PCR, multiplex PCR, single strand ligation, or single strand circularization.

[00104] In some instances, the tags herein comprise molecular barcodes. Such molecular barcodes can be used to differentiate polynucleotides in a sample. Preferably molecular barcodes are different from one another. For example, molecular barcodes can have a difference between them that can be characterized by a predetermined edit distance or a Hamming distance. In some instances, the molecular barcodes herein have a minimum edit distance of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. To further improve efficiency of conversion (e.g., tagging) of untagged molecular to tagged molecules, one preferably utilizes short tags. For example, in some embodiments, a library adapter tag can be up to 65, 60, 55, 50, 45, 40, or 35 nucleotide bases in length. A collection of such short library barcodes preferably includes a number of different molecular barcodes, e.g., at least 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20 different barcodes with a minimum edit distance of 1, 2, 3 or more.

[00105] Thus, a collection of molecules can include one or more tags. In some instances, some molecules in a collection can include an identifying tag ("identifier") such as a molecular barcode that is not shared by any other molecule in the collection. For example, in some instances of a collection of molecules, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the molecules in the collection

can include an identifier or molecular barcode that is not shared by any other molecule in the collection. As used herein, a collection of molecules is considered to be "uniquely tagged" if each of at least 95% of the molecules in the collection bears an identifier that is not shared by any other molecule in the collection ("unique tag" or "unique identifier"). A collection of molecules is considered to be "non-uniquely tagged" if each of at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least or about 50% of the molecules in the collection bears an identifying tag or molecular barcode that is shared by at least one other molecule in the collection ("non-unique tag" or "non-unique identifier"). Accordingly, in a non-uniquely tagged population no more than 1% of the molecules are uniquely tagged. For example, in a non-uniquely tagged population, no more than 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the molecules can be uniquely tagged.

[00106] A number of different tags can be used based on the estimated number of molecules in a sample. In some tagging methods, the number of different tags can be at least the same as the estimated number of molecules in the sample. In other tagging methods, the number of different tags can be at least two, three, four, five, six, seven, eight, nine, ten, one hundred or one thousand times as many as the estimated number of molecules in the sample. In unique tagging, at least two times (or more) as many different tags can be used as the estimated number of molecules in the sample.

[00107] The molecules in the sample may be non-uniquely tagged. In such instances a fewer number of tags or molecular barcodes is used then the number of molecules in the sample to be tagged. For example, no more than 100, 50, 40, 30, 20 or 10 unique tags or molecular barcodes are used to tag a complex sample such as a cell free DNA sample with many more different fragments.

[00108] The polynucleotide to be tagged can be fragmented, such as either naturally or using other approaches, such as, for example, shearing. The polynucleotides can be fragmented by certain methods, including but not limited to, mechanical shearing, passing the sample through a syringe, sonication, heat treatment (*e.g.*, for 30 minutes at 90°C), and/or nuclease treatment (*e.g.*, using DNase, RNase, endonuclease, exonuclease, and/or restriction enzyme).

[00109] The polynucleotides fragments (prior to tagging) can comprise sequences of any length. For example, polynucleotide fragments (prior to tagging) can comprise at least 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000 or more nucleotides in length. The polynucleotide fragment are preferably about the average length of cell-free DNA. For example, the polynucleotide fragments can comprise about 160 bases in length. The polynucleotide fragment can also be fragmented from a larger fragment into smaller fragments about 160 bases in length.

[00110] Polynucleotides tagged can comprise sequences associated with cancer. The cancer-associated sequences can comprise single nucleotide variation (SNV), copy number variation (CNV), insertions, deletions, and/or rearrangements.

[00111] The polynucleotides can comprise sequences associated with cancer, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, Kaposi Sarcoma, anal cancer, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain stem glioma, brain cancer, craniopharyngioma, ependymoblastoma, ependymoma, medulloblastoma, medulloeptithelioma, pineal parenchymal tumor, breast cancer, bronchial tumor, Burkitt lymphoma, Non-Hodgkin lymphoma, carcinoid tumor, cervical cancer, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, cutaneous T-cell lymphoma, ductal carcinoma in situ, endometrial cancer, esophageal cancer, Ewing Sarcoma, eye cancer, intraocular melanoma, retinoblastoma, fibrous histiocytoma, gallbladder cancer, gastric cancer, glioma, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, kidney cancer, laryngeal cancer, lip cancer, oral cavity cancer, lung cancer, non-small cell carcinoma, small cell carcinoma, melanoma, mouth cancer, myelodysplastic syndromes, multiple myeloma, medulloblastoma, nasal cavity cancer, paranasal sinus cancer, neuroblastoma, nasopharyngeal cancer, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, parathyroid cancer, penile cancer, pharyngeal cancer, pituitary tumor, plasma

cell neoplasm, prostate cancer, rectal cancer, renal cell cancer, rhabdomyosarcoma, salivary gland cancer, Sezary syndrome, skin cancer, nonmelanoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, testicular cancer, throat cancer, thymoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and/or Wilms Tumor.

[00112] A haploid human genome equivalent has about 3 picograms of DNA. A sample of about 1 microgram of DNA contains about 300,000 haploid human genome equivalents. Improvements in sequencing can be achieved as long as at least some of the duplicate or cognate polynucleotides bear unique identifiers with respect to each other, that is, bear different tags. However, in certain embodiments, the number of tags used is selected so that there is at least a 95% chance that all duplicate molecules starting at any one position bear unique identifiers. For example, in a sample comprising about 10,000 haploid human genome equivalents of fragmented genomic DNA, *e.g.*, cfDNA, z is expected to be between 2 and 8. Such a population can be tagged with between about 10 and 100 different identifiers, for example, about 2 identifiers, about 4 identifiers, about 9 identifiers, about 16 identifiers, about 25 identifiers, about 36 different identifiers, about 49 different identifiers, about 64 different identifiers, about 81 different identifiers, or about 100 different identifiers.

[00113] Nucleic acid barcodes having identifiable sequences including molecular barcodes, can be used for tagging. For example, a plurality of DNA barcodes can comprise various numbers of sequences of nucleotides. A plurality of DNA barcodes having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more identifiable sequences of nucleotides can be used. When attached to only one end of a polynucleotide, the plurality of DNA barcodes can produce 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more different identifiers. Alternatively, when attached to both ends of a polynucleotide, the plurality DNA barcodes can produce 4, 9, 16, 25, 36, 49, 64, 81, 100, 121, 144, 169, 196, 225, 256, 289, 324, 361, 400 or more different identifiers (which is the ^2 of when the DNA barcode is attached to only 1 end of a polynucleotide). In one example, a plurality of DNA barcodes having 6, 7, 8, 9 or 10 identifiable sequences of nucleotides can be used. When attached to both ends of a polynucleotide, they produce 36, 49, 64, 81 or 100 possible different identifiers, respectively. In

a particular example, the plurality of DNA barcodes can comprise 8 identifiable sequences of nucleotides. When attached to only one end of a polynucleotide, the plurality of DNA barcodes can produce 8 different identifiers. Alternatively, when attached to both ends of a polynucleotide, the plurality of DNA barcodes can produce 64 different identifiers. Samples tagged in such a way can be those with a range of about 10 ng to any of about 100 ng, about 1 μg, about 10 μg of fragmented polynucleotides, *e.g.*, genomic DNA, *e.g.*, cfDNA.

[00114] A polynucleotide can be uniquely identified in various ways. A polynucleotide can be uniquely identified by a unique DNA barcode. For example, any two polynucleotides in a sample are attached two different DNA barcodes. Alternatively, a polynucleotide can be uniquely identified by the combination of a DNA barcode and one or more endogenous sequences of the polynucleotide. For example, any two polynucleotides in a sample can be attached the same DNA barcode, but the two polynucleotides can still be identified by different endogenous sequences. The endogenous sequence can be on an end of a polynucleotide. For example, the endogenous sequence can be adjacent (*e.g.*, base in between) to the attached DNA barcode. In some instances the endogenous sequence can be at least 2, 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 bases in length. Preferably, the endogenous sequence is a terminal sequence of the fragment/polynucleotides to be analyzed. The endogenous sequence may be the length of the sequence. For example, a plurality of DNA barcodes comprising 8 different DNA barcodes can be attached to both ends of each polynucleotide in a sample. Each polynucleotide in the sample can be identified by the combination of the DNA barcodes and about 10 base pair endogenous sequence on an end of the polynucleotide. Without being bound by theory, the endogenous sequence of a polynucleotide can also be the entire polynucleotide sequence.

[00115] Also disclosed herein are compositions of tagged polynucleotides. The tagged polynucleotide can be single-stranded. Alternatively, the tagged polynucleotide can be double-stranded (*e.g.*, duplex-tagged polynucleotides). Accordingly, this invention also provides compositions of duplex-tagged polynucleotides. The polynucleotides can comprise any types of nucleic acids (DNA and/or RNA). The polynucleotides comprise any types of DNA disclosed herein. For example, the polynucleotides can comprise DNA, *e.g.*, fragmented DNA or cfDNA. A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least 2 and fewer

than the number of polynucleotides that map to the mappable base position. The number of different identifiers can also be at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25and fewer than the number of polynucleotides that map to the mappable base position.

[00116] In some instances, as a composition goes from about 1 ng to about 10 μg or higher, a larger set of different molecular barcodes can be used. For example, between 5 and 100 different library adaptors can be used to tag polynucleotides in a cfDNA sample.

[00117] The systems and methods disclosed herein may be used in applications that involve the assignment of molecular barcodes. The molecular barcodes can be assigned to any types of polynucleotides disclosed in this invention. For example, the molecular barcodes can be assigned to cell-free polynucleotides (*e.g.*, cfDNAs). Often, an identifier disclosed herein can be a barcode oligonucleotide that is used to tag the polynucleotide. The barcode identifier may be a nucleic acid oligonucleotide (*e.g.*, a DNA oligonucleotide). The barcode identifier can be single-stranded. Alternatively, the barcode identifier can be double-stranded. The barcode identifier can be attached to polynucleotides using any method disclosed herein. For example, the barcode identifier can be attached to the polynucleotide by ligation using an enzyme. The barcode identifier can also be incorporated into the polynucleotide through PCR. In other cases, the reaction may comprise addition of a metal isotope, either directly to the analyte or by a probe labeled with the isotope. Generally, assignment of unique or non-unique identifiers or molecular barcodes in reactions of this disclosure may follow methods and systems described by, for example, U.S. patent applications 2001/0053519, 2003/0152490, 2011/0160078 and U.S. Patent No. 6,582,908, each of which is entirely incorporated herein by reference.

[00118] Identifiers or molecular barcodes used herein may be completely endogenous whereby circular ligation of individual fragments may be performed followed by random shearing or targeted amplification. In this case, the combination of a new start and stop point of the molecule and the original intramolecular ligation point can form a specific identifier.

[00119] Identifiers or molecular barcodes used herein can comprise any types of oligonucleotides. In some cases, identifiers may be predetermined, random, or semi-random sequence oligonucleotides. Identifiers can be barcodes. For example, a plurality of barcodes may be used such that barcodes are not necessarily unique to one another in the plurality.

Alternatively, a plurality of barcodes may be used such that each barcode is unique to any other barcode in the plurality. The barcodes can comprise specific sequences (*e.g.*, predetermined sequences) that can be individually tracked. Further, barcodes may be attached (*e.g.*, by ligation) to individual molecules such that the combination of the barcode and the sequence it may be ligated to creates a specific sequence that may be individually tracked. As described herein, detection of barcodes in combination with sequence data of beginning (start) and/or end (stop) portions of sequence reads can allow assignment of a unique identity to a particular molecule. The length or number of base pairs of an individual sequence read may also be used to assign a unique identity to such a molecule. As described herein, fragments from a single strand of nucleic acid having been assigned a unique identity, may thereby permit subsequent identification of fragments from the parent strand. In this way the polynucleotides in the sample can be uniquely or substantially uniquely tagged. A duplex tag can include a degenerate or semi-degenerate nucleotide sequence, *e.g.*, a random degenerate sequence. The nucleotide sequence can comprise any number of nucleotides. For example, the nucleotide sequence can comprise 1 (if using a non-natural nucleotide), 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or more nucleotides. In a particular example, the sequence can comprise 7 nucleotides. In another example, the sequence can comprise 8 nucleotides. The sequence can also comprise 9 nucleotides. The sequence can comprise 10 nucleotides.

[00120] A barcode can comprise contiguous or non-contiguous sequences. A barcode that comprises at least 1, 2, 3, 4, 5 or more nucleotides is a contiguous sequence or non-contiguous sequence. if the 4 nucleotides are uninterrupted by any other nucleotide. For example, if a barcode comprises the sequence TTGC, a barcode is contiguous if the barcode is TTGC. On the other hand, a barcode is non-contiguous if the barcode is TTXGC, where X is a nucleic acid base.

[00121] An identifier or molecular barcode can have an n-mer sequence which may be 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or more nucleotides in length. A tag herein can comprise any range of nucleotides in length. For example, the sequence can be between 2 to 100, 10 to 90, 20 to 80, 30 to 70, 40 to 60, or about 50 nucleotides in length.

[00122] The tag can comprise a double-stranded fixed reference sequence downstream of the identifier or molecular barcode. Alternatively, the tag can comprise a double-stranded fixed reference sequence upstream or downstream of the identifier or molecular barcode. Each strand of a double-stranded fixed reference sequence can be, for example, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 nucleotides in length.

[00123] **C. Adaptors**

[00124] A library of polynucleotide molecules can be synthesized for use in sequencing. For example, a library of polynucleotides comprising a plurality of polynucleotide molecules that are each less than or equal to 100, 90, 80, 70, 60, 50, 45, 40, or 35 nucleic acid (or nucleotide) bases in length can be made. A plurality of polynucleotide molecules can be each less than or equal to 35 nucleic acid bases in length. A plurality of polynucleotide molecules can be each less than or equal to 30 nucleic acid bases in length. A plurality of polynucleotide molecules can also be less than or equal to 250, 200, 150, 100, or 50 nucleic acid bases. Additionally, the plurality of polynucleotide molecules can also be less than or equal to 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, or 10 nucleic acid bases.

[00125] A library of polynucleotides comprising a plurality of polynucleotide molecules can also have distinct (with respect to each other) molecular barcode sequences (or molecular barcodes) with respect to at least 4 nucleic acid bases. A molecular barcode (also "barcode" or "identifier" herein) sequence is a nucleotide sequence that distinguishes one polynucleotide from another. In other embodiments, the polynucleotide molecules can also have different barcode sequences with respect to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or more nucleic acid bases.

[00126] A library of polynucleotides comprising a plurality of polynucleotide molecules can also have a plurality of different barcode sequences. For example, a plurality of polynucleotide molecules can have at least 4 different molecular barcode sequences. In some cases, the plurality

of polynucleotide molecules has from 2-100, 4-50, 4-30, 4-20, or 4-10 different molecular barcode sequences. The plurality of polynucleotides molecules can also have other ranges of different barcode sequences such as, 1-4, 2-5, 3-6, 4-7, 5-8, 6-9, 7-10, 8-11, 9-12, 10-13, 11-14, 12-15, 13-16, 14-17, 15-18, 16-19, 17-20, 18-21, 19-22, 20-23, 21-24, or 22-25 different barcode sequences. In other cases, a plurality of polynucleotide molecules can have at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 more different barcode sequences. In a particular example, the plurality library adapters comprise at least 8 different sequences.

[00127] The location of the different barcode sequences can vary within the plurality of polynucleotides. For example, the different barcode sequences can be within 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, or 2 nucleic acid bases from a terminal end of a respective one of the plurality of polynucleotide molecules. In an example, a plurality of polynucleotide molecules has distinct barcode sequences that are within 10 nucleic acid bases from the terminal end. In another example, a plurality of polynucleotide molecules has distinct barcode sequences that are within 5 or 1 nucleic acid bases from the terminal end. In other instances, the distinct barcode sequences can be at the terminal end of a respective one of the plurality of polynucleotide molecules. Other variations include that the distinct molecular barcode sequences can be within 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, or more nucleic acid bases from a terminal end of a respective one of the plurality of polynucleotide molecules.

[00128] The terminal end of the plurality of polynucleotide molecules can be adapted for ligation to a target nucleic acid molecule. For example, the terminal end can be a blunt end. In some other cases, the terminal end is adapted for hybridization to a complementary sequence of a target nucleic acid molecule.

[00129] A library of polynucleotides comprising a plurality of polynucleotide molecules can also have an edit distance of at least 1. In some cases, the edit distance is with respect to individual bases of the plurality of polynucleotide molecules. In other cases, the plurality of polynucleotide molecules can have an edit distance of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or more. The edit distance can be a Hamming distance.

[00130] In some cases, the plurality of polynucleotides does not contain sequencing adaptors. A sequence adaptor can be a polynucleotide that comprises a sequence that hybridizes to one or more sequencing adaptors or primers. A sequencing adaptor can further comprise a sequence hybridizing to a solid support, *e.g.*, a flow cell sequence. The term "flow cell sequence" and its grammatical equivalents as used herein, refers to a sequence that permits hybridization to a substrate, for example, by way of a primer attached to the substrate. The substrate can be bead or a planar surface. In some embodiments, a flow cell sequence can allow a polynucleotide to attach to a flow cell or surface (e.g., surface of a bead, for example, an Illumina flow cell.

[00131] When a plurality of polynucleotide molecules does not contain sequencing adaptors or primers, each polynucleotide molecule of the plurality does not contain a nucleic acid sequence or other moiety that is adapted to permit sequencing of a target nucleic acid molecule with a given sequencing approach, such as Illumina, SOLiD, Pacific Biosciences, GeneReader, Oxford Nanopore, Complete Genomics, Gnu-Bio, Ion Torrent, Oxford Nanopore or Genia. In some examples, when a plurality of polynucleotide molecules does not contain sequencing adaptors or primers, the plurality of polynucleotide molecules does not contain flow cell sequences. For example, the plurality of polynucleotide molecules cannot bind to flow cells, such as used in Illumina flow cell sequencers. However, these flow cell sequences, if desired, can be added to the plurality of polynucleotide molecules by methods such as PCR amplification or ligation. At this point, Illumina flow cell sequencers can be used. Alternatively, when the

plurality of polynucleotide molecules does not contain sequencing adaptors or primers, the plurality of polynucleotide molecules does not contain hairpin shaped adaptors or adaptors for generating hairpin loops in a target nucleic acid molecule, such as Pacific Bioscience SMRTbell™ adaptors. However, these hairpin shaped adaptors, if desired, can be added to the plurality of polynucleotide molecules by methods such as PCR amplification or ligation. The plurality of polynucleotide molecules can be circular or linear.

[00132] A plurality of polynucleotide molecules can be double stranded. In some cases, the plurality of polynucleotide molecules can be single stranded, or can comprise hybridized and non-hybridized regions. A plurality of polynucleotide molecules can be non-naturally occurring polynucleotide molecules.

[00133] Adaptors can be polynucleotide molecules. The polynucleotide molecules can be Y-shaped, bubble-shaped or hairpin-shaped. A hairpin adaptor may contain a restriction site(s) or a Uracil containing base. Adaptors can comprise a complementary portion and a non-complementary portion. The non-complementary portion can have an edit distance (*e.g.*, Hamming distance). For example, the edit distance can be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or at least 30. The complementary portion of the adaptor can comprise sequences that are selected to enable and/or promote ligation to a polynucleotide, *e.g.*, a sequence to enable and/or promote ligation to a polynucleotide at a high yield.

[00134] A plurality of polynucleotide molecules as disclosed herein can be purified. In some cases, a plurality of polynucleotide molecules as disclosed herein can be isolated polynucleotide molecules. In other cases, a plurality of polynucleotide molecules as disclosed herein can be purified and isolated polynucleotide molecules.

[00135] In certain aspects, each of the plurality of polynucleotide molecules is Y-shaped or hairpin-shaped. Each of the plurality of polynucleotide molecules can comprise a different barcode. The different barcode can be a randomer in the complementary portion (*e.g.*, double stranded portion) of the Y-shaped or hairpin-shaped adaptor. Alternatively, the different barcode can be in one strand of the non-complementary portion (*e.g.*, one of the Y-shaped arms). As

discussed above, the different barcode can be at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more (or any length as described throughout) nucleic acid bases, *e.g.*, 7 bases. The barcode can be contiguous or non-contiguous sequences, as described above. The plurality of polynucleotide molecules is from 10 nucleic acid bases to 35 nucleic acid bases (or any length as described above) in length. Further, the plurality of polynucleotide molecules can comprise an edit distance (as described above), that is a Hamming distance. A plurality of polynucleotide molecules can have distinct barcode sequences that are within 10 nucleic acid bases from the terminal end.

[00136] In another aspect, a plurality of polynucleotide molecules can be sequencing adaptors. A sequencing adaptor can comprise a sequence hybridizing to one or more sequencing primers. A sequencing adaptor can further comprise a sequence hybridizing to a solid support, *e.g.*, a flow cell sequence. For example, a sequencing adaptor can be a flow cell adaptor. The sequencing adaptors can be attached to one or both ends of a polynucleotide fragment. In another example, a sequencing adaptor can be hairpin shaped. For example, the hairpin shaped adaptor can comprise a complementary double-stranded portion and a loop portion, where the double-stranded portion can be attached (*e.g.*, ligated) to a double-stranded polynucleotide. Hairpin shaped sequencing adaptors can be attached to both ends of a polynucleotide fragment to generate a circular molecule, which can be sequenced multiple times. A sequencing adaptor can be up to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, or more bases from end to end. For example, a sequencing adaptor can be up to 70 bases from end to end. The sequencing adaptor can comprise 20-30, 20-40, 30-50, 30-60, 40-60, 40-70, 50-60, 50-70, bases from end to end. In a particular example, the sequencing adaptor can comprise 20-30 bases from end to end. In another example, the sequencing adaptor can comprise 50-60 bases from end to end. A sequencing adaptor can comprise one or more barcodes. For example, a sequencing adaptor can comprise a sample barcode. The sample barcode can comprise a pre-determined sequence. The sample barcodes can be used to identify the source of the polynucleotides. The sample barcode can be at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,

or more (or any length as described throughout) nucleic acid bases, *e.g.*, at least 8 bases. The barcode can be contiguous or non-contiguous sequences, as described above.

[00137] The plurality of polynucleotide molecules as described herein can be used as adaptors. Adaptors can comprise one or more identifiers. An adaptor can comprise an identifier with a random sequence. Alternatively, an adaptor can comprise an identifier with pre-determined sequences. Some adaptors can comprise an identifier with a random sequence and another identifier with a pre-determined sequence. The adaptors comprising identifiers can be double-stranded or single-stranded adaptors. The adaptors comprising identifiers can be Y-shaped adaptors. A Y-shaped adaptor can comprise one or more identifiers with a random sequence. The one or more identifiers can be on the hybrid portion and/or non-hybridized portion of the Y-shaped adaptor. A Y-shaped adaptor can comprise one or more identifiers with a pre-determined sequence. The one or more identifiers with pre-determined sequence can be on the hybridized portion and/or non- hybridized portion of the Y-shaped adaptor. A Y-shaped adaptor can comprise one or more identifiers with a random sequence and one or more identifiers with a pre-determined sequence. For example, the one or more identifiers with a random sequence can be on the hybridized portion of the Y-shaped adaptor and/or the non- hybridized portion of the Y-shaped adaptor. The one or more identifiers with a pre-determined sequence can be on the hybridized portion of the Y-shaped adaptor and/or the non- hybridized portion of the Y-shaped adaptor. In a particular example, a Y-shaped adaptor can comprise an identifier with a random sequence on its hybridized portion and an identifier with a pre-determined sequence on its non- hybridized portion. The identifiers can be in any length disclosed herein. For example, a Y-shaped adaptor can comprise an identifier with a random sequence of 7 nucleotides on its hybridized portion and an identifier with a pre-determined sequence of 8 nucleotides on its non- hybridized portion.

[00138] An adaptor can include a double-stranded portion with a molecular barcode and at least one or two single-stranded portion. For example, the adaptor can be Y-shaped and include a double-stranded portion and two single-stranded portions. The single-stranded portions can include sequences that are not complementary to one another.

[00139] The adaptor can include a terminal end that has a sequence that is selected to permit the adaptor to be efficiently (e.g., at an efficiency of at least about 20%, 30%, 40%, 50%) ligated

or otherwise coupled to a polynucleotide. In some examples, terminal nucleotides in a double-stranded portion of an adaptor are selected from a combination of purines and pyrimidines to provide for efficient ligation.

[00140] In some examples, a set of library adaptors comprises a plurality of polynucleotide molecules (library adaptors) with molecular barcodes. The library adaptors are less than or equal to 80, 70, 60, 50, 45, or 40 nucleotide bases in length. The molecular barcodes can be at least 4 nucleotide bases in length, but may be from 4 to 20 nucleotide bases in length. The molecular barcodes can be different from one another and have an edit distance of at least 1, 2, 3, 4, or 5 between one another. The molecular barcodes are located at least 1, 2, 3, 4, 5, 10, or 20 nucleotide bases away from a terminal end of their respective library adaptors. In some cases, the at least one terminal base is identical in all of the library adaptors.

[00141] The library adaptors can be identical but for the molecular barcodes. For example, the library adaptors can have identical sequences but differ only with respect to nucleotide sequences of the molecular barcodes.

[00142] Each of the library adaptors can have a double stranded portion and at least one single-stranded portion. By "single stranded portion" is meant an area of non-complementarity or an overhang. In some cases, each of the library adaptors has a double-stranded portion and two single-stranded portions. The double-stranded portion can have a molecular barcode. In some cases, the molecular barcode is a randomer. Each of the library adaptors can further include a strand-identification barcode on a single-stranded portion. The strand-identification barcode can include at least 4 nucleotide bases, in some cases from 4 to 20 nucleotide bases.

[00143] In some examples, each of the library adaptors has a double-stranded portion with a molecular barcode and two single-stranded portions. The single-stranded portions may not hybridize to one another. The single-stranded portions may not be completely complementary to one another.

[00144] The library adaptors can have a sequence of terminal nucleotides in a double-stranded portion that are the same. The sequence of terminal nucleotides can be at least 2, 3, 4, 5 or 6 nucleotide bases in length. For example, one strand of a double-stranded portion of the library adaptor can have the sequence ACTT, TCGC, or TACC at the terminal end, while the other strand can have a complementary sequence. In some cases, such a sequence is selected to

optimize the efficiency at which the library adaptors ligate to target polynucleotides. Such sequences can be selected to optimize a binding interaction between the ends of the library adaptors and the target polynucleotides.

[00145] In some cases, none of the library adaptors contains a sample identification motif (or sample molecular barcode). Such sample identification motif can be provided via sequencing adaptors. A sample identification motif can include a sequencer of at least 4, 5, 6, 7, 8, 9, 10, 20, 30, or 40 nucleotide bases that permits the identification of polynucleotide molecules from a given sample from polynucleotide molecules from other samples. For example, this can permit polynucleotide molecules from two subjects to be sequenced in the same pool and sequence reads for the subjects subsequently identified.

[00146] A sequencer motif includes nucleotide sequence(s) needed to couple a library adaptor to a sequencing system and sequence a target polynucleotide coupled to the library adaptor. The sequencer motif can include a sequence that is complementary to a flow cell sequence and a sequence (sequencing initiation sequence) that is selectively hybridizable to a primer (or priming sequence) for use in sequencing. For example, such sequencing initiation sequence can be complementary to a primer that is employed for use in sequence by synthesis (e.g., Illumina). Such primer can be included in a sequencing adaptor. A sequencing initiation sequence can be a primer hybridization site.

[00147] In some cases, none of the library adaptors contains a complete sequencer motif. The library adaptors can contain partial or no sequencer motifs. In some cases, the library adaptors include a sequencing initiation sequence. The library adaptors can include a sequencing initiation sequence but no flow cell sequence. The sequence initiation sequence can be complementary to a primer for sequencing. The primer can be a sequence specific primer or a universal primer. Such sequencing initiation sequences may be situated on single-stranded portions of the library adaptors. As an alternative, such sequencing initiation sequences may be priming sites (e.g., kinks or nicks) to permit a polymerase to couple to the library adaptors during sequencing.

[00148] In some cases, partial or complete sequencer motifs are provided by sequencing adaptors. A sequencing adaptor can include a sample molecular barcode and a sequencer motif. The sequencing adaptors can be provided in a set that is separate from the library adaptors. The

sequencing adaptors in a given set can be identical – i.e., they contain the same sample barcode and sequencer motif.

[00149] Sequencing adaptors can include sample identification motifs and sequencer motifs. Sequencer motifs can include primers that are complementary to a sequencing initiation sequence. In some cases, sequencer motifs also include flow cell sequences or other sequences that permit a polynucleotide to a configured or arranged in a manner that permits the polynucleotide to be sequenced by a sequencer.

[00150] Library adaptors and sequencing adaptors can each be partial adaptors, that is, containing part but not all of the sequences necessary to enable sequencing by a sequencing platform. Together they provide complete adaptors. For example, library adaptors can include partial or no sequencer motifs, but such sequencer motifs are provided by sequencing adaptors.

[00151] **FIGs. 9A-9C** schematically illustrate a method for tagging a target polynucleotide molecule with library adaptors. **FIG. 9A** shows a library adaptor as a partial adaptor containing a primer hybridization site on one of the strands and a molecular barcode towards another end. The primer hybridization site can be a sequencing initiation sequence for subsequent sequencing. The library adaptor is less than or equal to 80 nucleotide bases in length. In **FIG. 9B**, the library adaptors are ligated at both ends of the target polynucleotide molecule to provide a tagged target polynucleotide molecule. The tagged target polynucleotide molecule may be subjected to nucleic acid amplification to generate copies of the target. Next, in **FIG. 9C**, sequencing adaptors containing sequencer motifs are provided and hybridized to the tagged target polynucleotide molecule. The sequencing adaptors contain sample identification motifs. The sequencing adaptors can contain sequences to permit sequencing of the tagged target with a given sequencer.

[00152] **D. <u>Sequencing</u>**

[00153] Tagged polynucleotides can be sequenced to generate sequence reads (*e.g.*, as shown in step (106), **FIG. 1**). For example, a tagged duplex polynucleotide can be sequenced. Sequence reads can be generated from only one strand of a tagged duplex polynucleotide. Alternatively, both strands of a tagged duplex polynucleotide can generate sequence reads. The two strands of the tagged duplex polynucleotide can comprise the same tags. Alternatively, the two strands of the tagged duplex polynucleotide can comprise different tags. When the two

strands of the tagged duplex polynucleotide are differently tagged, sequence reads generated from one strand (*e.g.*, a Watson strand) can be distinguished from sequence reads generated from the other strands (*e.g.*, a Crick strand). Sequencing can involve generating multiple sequence reads for each molecule. This occurs, for example, as a result the amplification of individual polynucleotide strands during the sequencing process, *e.g.*, by PCR.

[00154] Methods disclosed herein can comprise amplifying of polynucleotides. Polynucleotides amplification can result in the incorporation of nucleotides into a nucleic acid molecule or primer thereby forming a new nucleic acid molecule complementary to a template nucleic acid. The newly formed polynucleotide molecule and its template can be used as templates to synthesize additional polynucleotides. The polynucleotides being amplified can be any nucleic acids, for example, deoxyribonucleic acids, including genomic DNAs, cDNAs (complementary DNA), cfDNAs, and circulating tumor DNAs (ctDNAs). The polynucleotides being amplified can also be RNAs. As used herein, one amplification reaction may comprise many rounds of DNA replication. DNA amplification reactions can include, for example, polymerase chain reaction (PCR). One PCR reaction may comprise 2-100 "cycles" of denaturation, annealing, and synthesis of a DNA molecule. For example, 2-7, 5-10, 6-11, 7-12, 8-13, 9-14, 10-15, 11-16, 12-17, 13-18, 14-19, or 15-20 cycles can be performed during the amplification step. The condition of the PCR can be optimized based on the GC content of the sequences, including the primers.

[00155] Nucleic acid amplification techniques can be used with the assays described herein. Some amplification techniques are the PCR methodologies which can include, but are not limited to, solution PCR and *in situ* PCR. For example, amplification may comprise PCR-based amplification. Alternatively, amplification may comprise non PCR-based amplification. Amplification of the template nucleic acid may comprise use of one or more polymerases. For example, the polymerase may be a DNA polymerase or an RNA polymerase. In some cases, high fidelity amplification is performed such as with the use of high fidelity polymerase (e.g., Phusion® High-Fidelity DNA Polymerase) or PCR protocols. In some cases, the polymerase may be a high fidelity polymerase. For example, the polymerase may be KAPA HiFi DNA polymerase. The polymerase may also be Phusion DNA polymerase. The polymerase may be

used under reaction conditions that reduce or minimize amplification biases, e.g., due to fragment length, GC content, etc.

[00156] Amplification of a single strand of a polynucleotide by PCR will generate copies both of that strand and its complement. During sequencing, both the strand and its complement will generate sequence reads. However, sequence reads generated from the complement of, for example, the Watson strand, can be identified as such because they bear the complement of the portion of the duplex tag that tagged the original Watson strand. In contrast, a sequence read generated from a Crick strand or its amplification product will bear the portion of the duplex tag that tagged the original Crick strand. In this way, a sequence read generated from an amplified product of a complement of the Watson strand can be distinguished from a complement sequence read generated from an amplification product of the Crick strand of the original molecule.

[00157] All amplified polynucleotides can be submitted to a sequencing device for sequencing. Alternatively, a sampling, or subset, of all of the amplified polynucleotides is submitted to a sequencing device for sequencing. With respect to any original double-stranded polynucleotide there can be three results with respect to sequencing. First, sequence reads can be generated from both complementary strands of the original molecule (that is, from both the Watson strand and from the Crick strand). Second, sequence reads can be generated from only one of the two complementary strands (that is, either from the Watson strand or from the Crick strand, but not both). Third, no sequence read may be generated from either of the two complementary strands. Consequently, counting unique sequence reads mapping to a genetic locus will underestimate the number of double-stranded polynucleotides in the original sample mapping to the locus. Described herein are methods of estimating the unseen and uncounted polynucleotides.

[00158] The sequencing method can be massively parallel sequencing, that is, simultaneously (or in rapid succession) sequencing any of at least 100, 1000, 10,000, 100,000, 1 million, 10 million, 100 million, or 1 billion polynucleotide molecules. Sequencing methods may include, but are not limited to: high-throughput sequencing, pyrosequencing, sequencing-by-synthesis, single-molecule sequencing, nanopore sequencing, semiconductor sequencing, sequencing-by-ligation, sequencing-by-hybridization, RNA-Seq (Illumina), Digital Gene Expression (Helicos), Next generation sequencing, Single Molecule Sequencing by Synthesis (SMSS)(Helicos),

massively-parallel sequencing, Clonal Single Molecule Array (Solexa), shotgun sequencing, Maxam-Gilbert or Sanger sequencing, primer walking, sequencing using PacBio, SOLiD, Ion Torrent, or Nanopore platforms and any other sequencing methods known in the art.

[00159] For example, duplex-tagged polynucleotides can be amplified, by for example PCR (*see e.g.*, **FIG. 4A** duplex-tagged polynucleotides are referred to as mm' and nn'). In **Fig. 4A**, the strand of the duplex polynucleotide including sequence m bears sequence tags w and y, while the strand of the duplex polynucleotide including sequence m' bears sequence tags x and z. Similarly, the strand of the duplex polynucleotide including sequence n bears sequence tags a and c, while the strand of the duplex polynucleotide including sequence n' bears sequence tags b and d. During amplification, each strand produces itself and its complementary sequence. However, for example, an amplification progeny of original strand m that includes the complementary sequence, m', is distinguishable from an amplification progeny of original strand m' because the progeny from original strand m will have the sequence 5'-y'm'w'-3' and the progeny of the original m' strand one strand will have the sequence 5'-zm'x-3'. **FIG. 4B** shows amplification in more detail. During amplification, errors can be introduced into the amplification progeny, represented by dots. The application progeny are sampled for sequencing, so that not all strands produce sequence reads, resulting in the sequence reads indicated. Because sequence reads can come from either of a strand or its complement, both sequences and complement sequences will be included in the set of sequence reads. It should be noted that it is possible that a polynucleotide would bear the same tag on each end. Thus, for a tag "a", and polynucleotide "m", a first strand could be tagged a-m-a', and the complement could be tagged a-m'-a.

[00160] **E. <u>Determining consensus sequence reads</u>**

[00161] Methods disclosed herein can comprise determining consensus sequence reads in sequence reads (*e.g.*, as shown in step (108), **FIG. 1**), such as by reducing or tracking redundancy. Sequencing of amplified polynucleotides can produce reads of the several amplification products from the same original polynucleotide, referred to as "redundant reads". By identifying redundant reads, unique molecules in the original sample can be determined. If the molecules in a sample are uniquely tagged, then reads generated from amplification of a

single unique original molecule can be identified based on their distinct barcode. Ignoring barcodes, reads from unique original molecules can be determined based on sequences at the beginning and end of a read, optionally in combination with the length of the read. In certain cases, however, a sample may be expected to have a plurality of original molecules having the same start stop sequences and the same length. Without barcoding, these molecules are difficult to distinguish from one another. However, if a collection of polynucleotides is non-uniquely tagged (that is, an original molecule shares the same identifier with at least one other original molecule), combining information from a barcode with start/stop sequence and/or polynucleotide length significantly increases the probability that any sequence read can be traced back to an original polynucleotide. This is because, in part, even without unique tagging, it is unlikely that any two original polynucleotides having the same start/stop sequence and length also will be tagged with the same identifier.

[00162] **F. Collapsing**

[00163] Collapsing allows for reduction in noise (*i.e.*, background) that is generated at each step of the process. Methods disclosed herein can comprise collapsing, *e.g.*, generating a consensus sequence by comparing multiple sequence reads. For example, sequence reads generated from a single original polynucleotide can be used to generate a consensus sequence of that original polynucleotide. Iterative rounds of amplification can introduce errors into progeny polynucleotides. Also, sequencing typically may not be performed with perfect fidelity so sequencing errors are introduced at this stage as well. However, comparison of sequence reads of molecules derived from a single original molecule, including those that have sequence variants, can be analyzed so as to determine the original, or "consensus" sequence. This can be done phylogenetically. Consensus sequences can be generated from families of sequence reads by any of a variety of methods. Such methods include, for example, linear or non-linear methods of building consensus sequences (such as voting (*e.g.*, biased voting), averaging, statistical, maximum a posteriori or maximum likelihood detection, dynamic programming, Bayesian, hidden Markov or support vector machine methods, etc.) derived from digital communication theory, information theory, or bioinformatics. For example, if all or most of the sequence reads tracking back to an original molecule bear the same sequence variant, that variant probably existed in the original molecule. On the other hand, if a sequence variant exists in a subset of

redundant sequence reads, that variant may have been introduced during amplification/sequencing and represents an artifact not existing in the original. Furthermore, if only sequence reads derived from the Watson or Crick strand of an original polynucleotide contain the variant, the variant may have been introduced through single-sided DNA damage, first-cycle PCR error or through contaminating polynucleotides that were amplified from a different sample.

[00164] After fragments are amplified and the sequences of amplified fragments are read and aligned, the fragments are subjected to base calling, *e.g.*, determining for each locus the most likely nucleotide. However, variations in the number of amplified fragments and unseen amplified fragments (*e.g.*, those without being read their sequences; reasons could be too many such as amplification errors, sequencing reading errors, too long, too short, being chopped, etc.) may introduce errors in base calling. If there are too many unseen amplified fragments with respect to the seen amplified fragments (amplified fragments actually being read), the reliability of base calling may be diminished.

[00165] Therefore, disclosed herein is a method to correct for the number of unseen fragments in base calling. For example, when base calling for locus A (an arbitrary locus), it is first assumed that there are N amplified fragments. The sequence readouts can come from two types of fragments: double-strand fragments and single-strand fragments. Therefore, we assign N1, N2, and N3 as the numbers of double-strands, single-strands, and unseen fragments, respectively. Thus, N=N1+N2+N3 (N1 and N2 are known from the sequence readouts, and N and N3 are unknown). If the formula is solved for N (or N3), then N3 (or N) will be inferred.

[00166] Probability is used to estimate N. For example, we assign "p" to be the probability of having detected (or having read) a nucleotide of locus A in a sequence readout of a single-strand.

[00167] For sequence readouts from double-strands, the nucleotide call from a double-strand amplified fragment has a probability of p * p=p^2, seeing all N1 double-strands has the following equation: N1=N * (p^2).

[00168] For sequence readouts from a single-strand. Assuming that one of the 2 strands is seen, and the other is unseen, the probability of seeing one strand is "p", but the probability of missing the other strand is (1-p). Furthermore, by not distinguishing the single strand sourcing from 5-primer and sourcing from 3-primer, there is a factor of 2. Therefore, the nucleotide call

from a single-strand amplified fragment has a probability 2×p×(1-p). Thus, seeing all N2 single-strands has the following equation: N2=N×2×p×(1-p).

[00169] "p" is also unknown. To solve p, the ratio of N1 to N2 is used to solve for "p":

$$R = \frac{N1}{N2} = \frac{Np^2}{2Np(1-p)} = \frac{p^2}{2p(1-p)} = \frac{p}{2(1-p)}$$

Once "p" is found, N can be found. After N is found, can be found N3 = N − N1 − N2.

[00170] Besides the ratio of paired versus unpaired strands (which is a measure post-collapsing), there is useful information in the pre-collapsing read depth at each locus. This information can be used to further improve the call for total molecule count and/or increase confidence of calling variants.

[00171] For example, **FIG. 4C** demonstrates sequence reads corrected for complementary sequences. Sequences generated from an original Watson strand or an original Crick strand can be differentiated on the basis of their duplex tags. Sequences generated from the same original strand can be grouped. Examination of the sequences can allow one to infer the sequence of the original strand (the "consensus sequence"). In this case, for example, the sequence variant in the nn' molecule is included in the consensus sequence because it included in every sequence read while other variants are seen to be stray errors. After collapsing sequences, original polynucleotide pairs can be identified based on their complementary sequences and duplex tags.

[00172] **FIG. 5** demonstrates increased confidence in detecting sequence variants by pairing reads from Watson and Crick strands. Sequence nn' can include a sequence variant indicated by a dot. In some cases, sequence pp' does not include a sequence variant. Amplification, sequencing, redundancy reduction and pairing can result in both Watson and Crick strands of the same original molecule including the sequence variant. In contrast, as a result of errors introduced during amplification and sampling during sequencing, the consensus sequence of the Watson strand p can contain a sequence variant, while the consensus sequence of the Crick strand p' does not. It is less likely that amplification and sequencing will introduce the same variant into both strands (nn' sequence) of a duplex than onto one strand (pp' sequence). Therefore, the variant in the pp' sequence is more likely to be an artifact, and the variant in the nn' sequence is more likely to exist in the original molecule.

[00173] Methods disclosed herein can be used to correct errors resulted from experiments, *e.g.*, PCR, amplification, and/or sequencing. For example, such a method can comprises attaching one or more double stranded adaptors to both ends of a double stranded polynucleotide, thereby providing a tagged double stranded polynucleotide; amplifying the double stranded tagged polynucleotide; sequencing both strands of the tagged polynucleotide; comparing the sequence of one strand with its complement to determine any errors introduced during sequencing; and correcting errors in the sequence based on (d). The adaptors used in this method can be any adaptors disclosed herein, *e.g.*, Y-shaped adaptors. The adaptor can comprise any barcodes (*e.g.*, distinct barcodes) disclosed herein.

[00174] **G. Mapping**

[00175] Sequence reads or consensus sequences can be mapped to one or more selected genetic loci (*e.g.*, as shown step (110), **FIG. 1**). A genetic locus can be, for example, a specific nucleotide position in the genome, a sequence of nucleotides (for example, an open reading frame), a fragment of a chromosome, a whole chromosome, or an entire genome. A genetic locus can be a polymorphic locus. Polymorphic locus can be a locus at which sequence variation exists in the population and/or exists in a subject and/or a sample. A polymorphic locus can be generated by two or more distinct sequences coexisting at the same location of the genome. The distinct sequences can differ from one another by one or more nucleotide substitutions, a deletion/insertion, and/or a duplication of any number of nucleotides, generally a relatively small number of nucleotides, such as less than 50, 45, 40, 35, 30, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 nucleotide(s), among others. A polymorphic locus can be created by a single nucleotide position that varies within the population, *e.g.* a single nucleotide variation (SNV) or a single nucleotide polymorphism (SNP).

[00176] A reference genome for mapping can include the genome of any species of interest. Human genome sequences useful as references can include the hg19 assembly or any previous or available hg assembly. Such sequences can be interrogated using the genome browser available at genome.ucsc.edu/index.html. Other species genomes include, for example PanTro2 (chimp) and mm9 (mouse).

[00177] In methods disclosed herein, collapsing can be performed before or after mapping. In some aspects, collapsing can be performed before mapping. For example, sequence reads can be

grouped into families based on their tags and one or more endogenous sequences, without regard to where the reads map in the genome. Then, the members of a family can be collapsed into a consensus sequence. The consensus sequence can be generated using any collapsing method disclosed herein. Then the consensus sequence can be mapped to locations in the genome. Reads mapped to a locus can be quantified (*e.g.*, counted). Percentage of reads carrying a mutation at a locus can also be determined. Alternatively, collapsing can be performed after mapping. For example, all reads can first be mapped to the genome. Then the reads can be grouped into families based on their tags and one or more endogenous sequences. Since the reads have been mapped to the genome, consensus bases can be determined for each family at each locus. In other aspects, consensus sequence can be generated for one strand of a DNA molecule (*e.g.*, for a Watson strand or a Crick strand). Mapping can be performed before or after the consensus sequence for one strand of the DNA molecule is determined. Numbers of Doublets and Singlets can be determined. These numbers can be used to calculate unseen molecules. For example, the unseen molecules can be calculated using the following equation: N= D+S+U; D=Np(2), S=N2pq, where p=1-q, where p is the probability of seeing; q is the probability of missing a strand.

[00178] **H. <u>Grouping</u>**

[00179] Methods disclosed herein can also comprise grouping sequence reads. Sequence reads can be grouped based on various types of sequences, *e.g.*, sequences of an oligonucleotide tag (*e.g.*, a barcode), sequence of a polynucleotide fragments, or any combinations. For example, as shown in step (112) (**FIG. 1**), sequence reads can be grouped as follows: Sequence reads generated from a "Watson" strand and those generated from a "Crick" strand of a double-stranded polynucleotide in the sample are identifiable based on the duplex tags that they bear. In this way, a sequence read or consensus sequence from a Watson strand of a duplex polynucleotide can be paired with a sequence read or consensus sequence from its complementary Crick strand. Paired sequence reads are referred to as a "Pair".

[00180] Sequence reads for which no sequence read corresponding to a complementary strand can be found among the sequence reads are termed "Singlets".

[00181] Double-stranded polynucleotides for which a sequence read for neither of the two complementary strands has been generated are referred to as "Unseen" molecules.

[00182] **I. Quantifying**

[00183] Methods disclosed herein also comprise quantifying sequence reads. For example, as shown in step (114) (**FIG. 1**), Pairs and Singlets mapping to a selected genetic locus, or to each of a plurality of selected genetic loci, are quantified, *e.g.*, counted.

[00184] The quantifying can comprise estimating number of polynucleotides in the sample (*e.g.*, Pairs polynucleotides, Singlets polynucleotides, or Unseen polynucleotides. For example, as shown in step (116) (**FIG. 1**), the number of double-stranded polynucleotides in the sample for which no sequence reads were generated ("Unseen" polynucleotides) is estimated. The probability that a double strand polynucleotide generates no sequence reads can be determined based on the relative number of Pairs and Singlets at any locus. Using this probability, the number of Unseen polynucleotide can be estimated.

[00185] In step (118) an estimate for the total number of double-stranded polynucleotides in a sample mapping to a selected locus is the sum of the number of Pairs, the number of Singlets and the number of Unseen molecules mapping to the locus.

[00186] The number of Unseen original molecules in a sample can be estimated based on the relative number of Pairs and Singlets (**FIG. 2**). Referring to **FIG. 2**, as an example, counts for a particular genomic locus, Locus A, are recorded, where 1000 molecules are paired and 1000 molecules are unpaired. Assuming a uniform probability, p, for an individual Watson or Crick strand to make it through the process subsequent to conversion, one can calculate the proportion of molecules that fail to make it through the process (Unseen) as follows: Let R = ratio of paired to unpaired molecules = 1, so $R=1=p^2/(2p(1-p))$. This implies that $p=2/3$ and that the quantity of lost molecules is equal to $(1-p)^2 = 1/9$. Thus in this example, approximately 11% of converted molecules are lost and never detected. Consider another genomic locus, Locus B, in the same sample where 1440 molecules are paired and 720 are unpaired. Using the same method, we can infer the number of molecules that are lost, is only 4%. Comparing the two areas, it may be assumed that Locus A had 2000 unique molecules as compared to 2160 molecules in Locus B – a difference of almost 8%. However, by correctly adding in the lost molecules in each region, we infer there are 2000/(8/9)=2250 molecules in Locus A and 2160/.96=2250 molecules in Locus B. Hence, the counts in both regions are actually equal. This correction and thus much higher sensitivity can be achievable by converting the original double-stranded nucleic acid

molecules and bioinformatically keeping track of all those that are paired and unpaired at the end of the process. Similarly, the same procedure can be used to infer true copy number variations in regions that appear to have similar counts of observed unique molecules. By taking the number of unseen molecules into consideration in the two or more regions, the copy number variation becomes apparent.

[00187] In addition to using binomial distribution, other methods of estimating numbers of unseen molecules include exponential, beta, gamma or empirical distributions based on the redundancy of sequence reads observed. In the latter case, the distribution of read counts for paired and unpaired molecules can be derived from such redundancy to infer the underlying distribution of original polynucleotide molecules at a particular locus. This can often lead to a better estimation of the number of unseen molecules.

[00188] **J. <u>CNV Detection</u>**

[00189] Methods disclosed herein also comprise detecting CNV. For example, as shown in step (120) (**FIG. 1**), once the total number of polynucleotides mapping to a locus is determined, this number can be used in standard methods of determining CNV at the locus. A quantitative measure can be normalized against a standard. The standard can be an amount of any polynucleotides. In one method, a quantitative measure at a test locus can be standardized against a quantitative measure of polynucleotides mapping to a control locus in the genome, such as gene of known copy number. Quantitative measures can be compared against the amount of nucleic acid in any sample disclosed herein. For example, in another method, the quantitative measure can be compared against the amount of nucleic acid in the original sample. For example, if the original sample contained 10,000 haploid gene equivalents, the quantitative measure can be compared against an expected measure for diploidy. In another method, the quantitative measure can be normalized against a measure from a control sample, and normalized measures at different loci can be compared.

[00190] In some cases, in which copy number variation analysis is desired, sequence data may be: 1) aligned with a reference genome; 2) filtered and mapped; 3) partitioned into windows or bins of sequence; 4) coverage reads counted for each window; 5) coverage reads can then be normalized using a stochastic or statistical modeling algorithm; 6) and an output file can be generated reflecting discrete copy number states at various positions in the genome. In other

cases, in which rare mutation analysis is desired, sequence data may be 1) aligned with a reference genome; 2) filtered and mapped; 3) frequency of variant bases calculated based on coverage reads for that specific base; 4) variant base frequency normalized using a stochastic, statistical or probabilistic modeling algorithm; 5) and an output file can be generated reflecting mutation states at various positions in the genome.

[00191] After the sequence read coverage ratios have been determined, a stochastic modeling algorithm can be optionally applied to convert the normalized ratios for each window region into discrete copy number states. In some cases, this algorithm may comprise a Hidden Markov Model. In other cases, the stochastic model may comprise dynamic programming, support vector machine, Bayesian modeling, probabilistic modeling, trellis decoding, Viterbi decoding, expectation maximization, Kalman filtering methodologies, or neural networks.

[00192] Methods disclosed herein can comprise detecting SNVs, CNVs, insertions, deletions, and/or rearrangements at a specific region in a genome. The specific genomic region can comprise a sequence in a gene, such as ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, or NTRK1.

[00193] In some cases, the method uses a panel which comprises exons of one or more genes. The panel can comprise introns of one or more genes as well. The panel can also comprise exons and introns of one or more genes. The one or more genes can be those disclosed above. The panel can comprise about 80,000 bases which cover a panel of genes. The panel can comprise about 1000, 2000, 3000, 4000, 5000, 10000, 15000, 20000, 25000, 30000, 35000, 40000, 45000, 50000, 55000, 60000, 65000, 70000, 75000, 80000, 85000, 90000, 95000, 100000, 105000, 110000, 115000, 120000, 125000, or more bases.

[00194] In some aspects, copy number of a gene can be reflected in the frequency of a genetic form of the gene in a sample. For example, in a healthy individual, no copy number variation is

reflected in a variant in a gene in one chromosome (*e.g.*, heterozygosity) being detected in about 50% of detected molecules in a sample. Also, in a healthy individual, duplication of a gene bearing a variant can be reflected in the variant being detected in about 66% of detected molecules in a sample. Accordingly, if the tumor burden in a DNA sample is 10%, the frequency of a somatic mutation in a gene in one chromosome of cancer cells, without CNV, can be about 5%. The converse can be true in the case of aneuploidy.

[00195] The methods disclosed herein can be used to determine whether a sequence variant is more likely present in the germ line level or resulted from a somatic cell mutation, *e.g.*, in a cancer cell. For example, a sequence variant in a gene detected at levels arguably consistent with heterozygosity in the germ line is more likely the product of a somatic mutation if CNV is also detected in that gene. In some cases, to the extent we expect that a gene duplication in the germ line bears a variant consistent with genetic dose (*e.g.*, 66% for trisomy at a locus), detection gene amplification with a sequence variant dose that deviates significantly from this expected amount indicates that the CNV is more likely present as a result of somatic cell mutation.

[00196] The methods disclosed herein can also be used to infer tumor heterogeneity in a situation in which sequence variants in two genes are detected at different frequencies. For example, tumor heterogeneity can be inferred when two genes are detected at different frequencies but their copy numbers are relatively equal. Alternatively, tumor homogeneity can be inferred when the difference in frequency between two sequence variants is consistent with difference in copy number for the two genes. Thus, for example, if an EGFR variant is detected at 11% and a KRAS variant is detected at 5%, and no CNV is detected at these genes, the difference in frequency likely reflects tumor heterogeneity (*e.g.*, all tumor cells carry an EGFR mutant and half the tumor cells also carry a KRAS mutant). Alternatively, if the EGFR gene carrying the mutant is detected at 2-times normal copy number, one interpretation is a homogenous population of tumor cells, each cell carrying a mutant in the EGFR and KRAS genes, but in which the KRAS gene is duplicated.

[00197] In response to chemotherapy, a dominant tumor form can eventually give way through Darwinian selection to cancer cells carrying mutants that render the cancer unresponsive to the therapy regimen. Appearance of these resistance mutants can be delayed through methods of this invention. In one embodiment of this method, a subject is subjected to one or more

pulsed therapy cycles, each pulsed therapy cycle comprising a first period during which a drug is administered at a first amount and a second cycle during which the drug is administered at a second, reduced amount. The first period can be characterized by a tumor burden detected above a first clinical level. The second period can be characterized by a tumor burden detected below a second clinical level. First and second clinical levels can be different in different pulsed therapy cycles. For example, the first clinical level can be lower in succeeding cycles. A plurality of cycles can include at least 2, 3, 4, 5, 6, 7, 8 or more cycles. For example, the BRAF mutant V600E may be detected in polynucleotides of a disease cell at an amount indicating a tumor burden of 5% in cfDNA. Chemotherapy can commence with dabrafenib. Subsequent testing can show that the amount of the BRAF mutant in the cfDNA falls below 0.5% or to undetectable levels. At this point, dabrafenib therapy can stop or be significantly curtailed. Further subsequent testing may find that DNA bearing the BRAF mutation has risen to 2.5% of polynucleotides in cfDNA. At this point, dabrafenib therapy can be re-started, *e.g.*, at the same level as the initial treatment. Subsequent testing may find that DNA bearing the BRAF mutation has decreased to 0.5% of polynucleotides in cfDNA. Again, dabrafenib therapy can be stopped or reduced. The cycle can be repeated a number of times.

[00198] A therapeutic intervention can also be changed upon detection of the rise of a mutant form resistant to an original drug. For example, cancers with the EGFR mutation L858R respond to therapy with erlotinib. However, cancers with the EGFR mutation T790M are resistant to erlotinib. However, they are responsive to ruxolitinib. A method of this invention involves monitoring changes in tumor profile and changing a therapeutic intervention when a genetic variant associated with drug resistance rises to a predetermined clinical level.

[00199] Methods disclosed in this invention can comprise a method of detecting disease cell heterogeneity from a sample comprising polynucleotides from somatic cells and disease cells, the method comprising: a) quantifying polynucleotides in the sample bearing a sequence variant at each of a plurality of genetic loci; b) determining CNV at each of the plurality of genetic loci; different relative amounts of disease molecules at a locus, wherein the CNV indicates a genetic dose of a locus in the disease cell polynucleotides; c) determining a relative measure of quantity of polynucleotides bearing a sequence variant at a locus per genetic dose at the locus for each of a plurality of the loci; and d) comparing the relative measures at each of the plurality of loci,

wherein different relative measures indicates tumor heterogeneity. In the methods disclosed herein, the genetic dose can be determined on a total molecule basis. For example, if there are 1X total molecules at a first locus, and 1.2X molecules mapped to a second locus, then the genetic dose is 1.2. Variants at this locus can be divided by 1.2. In some aspects, the method disclosed herein can be used to detect any disease cell heterogeneity, *e.g.*, tumor cell heterogeneity. The methods can be used to detect disease cell heterogeneity from a sample comprising any types of polynucleotides, *e.g.*, cfDNA, genomic DNA, cDNA, or ctDNA. In the methods, the quantifying can comprise, for example, determining the number or relative amount of the polynucleotides. Determining CNV can comprise mapping and normalizing different relative amounts of total molecules to a locus.

[00200] In another aspect, in response to chemotherapy, a dominant tumor form can eventually give way through Darwinian selection to cancer cells carrying mutants that render the cancer unresponsive to the therapy regimen. Appearance of these resistance mutants can be delayed through methods disclosed throughout. The methods disclosed herein can comprise a method comprising: a) subjecting a subject to one or more pulsed therapy cycles, each pulsed therapy cycle comprising (i) a first period during which a drug is administered at a first amount and (ii) a second period during which the drug is administered at a second, reduced amount; wherein (A) the first period is characterized by a tumor burden detected above a first clinical level; and (B) the second period is characterized by a tumor burden detected below a second clinical level.

[00201] **K. <u>Sequence Variant Detection</u>**

[00202] Systems and methods disclosed herein can be used to detect sequence variants, *e.g.*, SNVs. For example, a sequence variant can be detected from consensus sequences from multiple sequence reads, for example, from at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at

least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, at least 100, at least 200, at least 300, at least 400, at least 500, at least 600, at least 700, at least 800, at least 900, at least 1000, at least 2000, at least 3000, at least 4000, at least 5000, at least 6000, at least 7000, at least 8000, at least 9000, at least 10000 or more sequence reads. A consensus sequence can be from sequence reads of a single strand polynucleotide. A consensus sequence can also be from sequence reads of one strand of a double-stranded polynucleotide (*e.g.*, pairing reads). In an exemplary method, pairing reads allows one to identify with increased confidence the existence of a sequence variant in a molecule. For example, if both strands of a Pair include the same variant, one can be reasonably sure that the variant existed in the original molecule, as the chance that the same variant is introduced into both strands during amplification/sequencing is rare. In contrast, if only one strand of a Pair includes the sequence variant, this is more likely to be an artifact. Similarly, the confidence that a Singlet bearing a sequence variant existed in the original molecule is less than the confidence if the variant exists in a Duplex, as there is higher probability that the variant can be introduced once than twice during amplification/sequencing.

[00203] Other methods of copy number variation detection and the sequence variant detection are described in PCT/US2013/058061, which is entirely incorporated herein by reference.

[00204] Sequence reads can be collapsed to generate a consensus sequence, which can be mapped to a reference sequence to identify genetic variants, such as CNV or SNV. As an alternative, the sequence reads are mapped prior to or even without mapping. In such a case, the sequence reads can be individually mapped to the reference to identify a CNV or SNV.

[00205] **FIG. 3** shows a reference sequence encoding a genetic Locus A. The polynucleotides in FIG. 3 may be Y-shaped or have other shapes, such as hairpin.

[00206] In some cases, an SNV or multiple-nucleotide variant (MNV) can be determined across multiple sequence reads at a given locus (e.g., nucleotide base) by aligning sequence reads that correspond to that locus. Next, a plurality of sequential nucleotide bases from at least a

subset of the sequence reads are mapped to the reference to a SNV or MNV in a polynucleotide molecule or portion thereof that corresponds to the reads. The plurality of sequential nucleotide bases can span an actual, inferred or suspected location of the SNV or MNV. The plurality of sequential nucleotide bases can span at least 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide bases.

[00207] L. Detecting/Quantifying Nucleic Acids

[00208] The methods described throughout can be used to tag nucleic acids fragments, such as deoxyribonucleic acid (DNA), at extremely high efficiency. This efficient tagging allows a person to efficiently and accurately detect rare DNA in heterogenous populations of original DNA fragments (such as in cfDNA). A rare polynucleotide (e.g., rare DNA) can be a polynucleotide that comprises a genetic variant occurring in a population of polynucleotides at a frequency of less than 10%, 5%, 4%, 3%, 2%, 1%, or 0.1%. A rare DNA can be a polynucleotide with a detectable property at a concentration less than 50%, 25%, 10%, 5%, 1%, or 0.1%

[00209] Tagging can occur in a single reaction. In some cases, two or more reactions can be performed and pooled together. Tagging each original DNA fragments in a single reaction can result in tagging such that greater than 50% (*e.g.*, 60%, 70%, 80%, 90%, 95%, or 99%) of the original DNA fragments are tagged at both ends with tags that comprise molecular barcodes, thereby providing tagged DNA fragments. Tagging can also result in greater than 30%, 35%, 40%, 45%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the original DNA fragments tagged at both ends with tags that comprise molecular barcodes. Tagging can also result in 100% of the original DNA fragments tagged at both ends with tags that comprise molecular barcodes. Tagging can also result in single end tagging.

[00210] Tagging can also occur by using an excess amount of tags as compared to the original DNA fragments. For example, the excess can be at least 5-fold excess. In other cases, the excess can be at least 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more fold excess. Tagging can comprise attachment to blunt ends or sticky ends. Tagging can also be

performed by hybridization PCR. Tagging can also be performed in low reaction volumes, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 pico- and/or microliters.

[00211] The method can also include performing high fidelity amplification on the tagged DNA fragments. Any high fidelity DNA polymerases can be used. For example, the polymerase may be KAPA HiFi DNA polymerase or Phusion DNA polymerase.

[00212] Further, the method can comprise selectively enriching a subset of the tagged DNA fragments. For example, selective enrichment can be performed by hybridization or amplification techniques. The selective enrichment can be performed using a solid support (*e.g.*, beads). The solid support (*e.g.*, beads) can comprise probes (*e.g.*, oligonucleotides specifically hybridizing to certain sequences. For example, the probes can hybridize with certain genomic regions, *e.g.*, genes. In some cases, the genomic regions, *e.g.*, genes, can be regions associated with diseases, *e.g.*, cancer. After enrichment, the selected fragmented can be attached any sequencing adaptor disclosed in this invention. For example, a sequence adaptor can comprise a flow cell sequence, a sample barcode, or both. In another example, a sequence adaptor can be a hairpin shaped adaptor and/or comprises a sample barcode. Further, the resulting fragments can be amplified and sequenced. In some cases, the adaptor does not comprise a sequencing primer region.

[00213] The method can include sequencing one or both strands of the DNA fragments. In one case, both strands of the DNA fragment are independently sequenced. The tagged, amplified, and/or selectively enriched DNA fragments are sequenced to obtain sequence reads that comprise sequence information of the molecular barcodes and at least a portion of the original DNA fragments.

[00214] The method can include reducing or tracking redundancy (as described above) in the sequence reads to determine consensus reads that are representative of single-strands of the original DNA fragments. For example, to reduce or track redundancy, the method can include comparing sequence reads having the same or similar molecular barcodes and the same or

similar end of fragment sequences. The method can comprise performing a phylogentic analysis on the sequence reads having the same or similar molecular barcodes. The molecular barcodes can have a barcode with varying edit distances (including any edit distances as described throughout), for example, an edit distance of up to 3. The end of the fragment sequences can include fragment sequences having an edit distance with varying distances (including any edit distances as described throughout), for example, an edit distance of up to 3.

[00215] The method can comprise binning the sequence reads according to the molecular barcodes and sequence information. For example, binning the sequence reads according to the molecular barcodes and sequence information can be performed from at least one end of each of the original DNA fragments to create bins of single stranded reads. The method can further comprise in each bin, determining a sequence of a given original DNA fragment among the original DNA fragments by analyzing sequence reads.

[00216] In some cases, sequence reads in each bin can be collapsed to a consensus sequence and subsequently mapped to a genome. As an alternative, sequence reads can be mapped to a genome prior to binning and subsequently collapsed to a consensus sequence.

[00217] The method can also comprise sorting sequence reads into paired reads and unpaired reads. After sorting, the number of paired reads and unpaired reads that map to each of one or more genetic loci can be quantified.

[00218] The method can include quantifying the consensus reads to detect and/or quantify the rare DNA, which are described throughout. The method can comprise detecting and/or quantifying the rare DNA by comparing a number of times each base occurs at each position of a genome represented by the tagged, amplified, and/or enriched DNA fragments.

[00219] The method can comprise tagging the original DNA fragments in a single reaction using a library of tags. The library can include at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 50, at least 100, at least 500, at least 1000, at least 5000, at least 10000, or any number of tags as disclosed throughout. For example, the library of tags can include at least 8 tags. The library of tags can include 8 tags (which can generate 64 different possible combinations). The method can be conducted such

that a high percentage of fragments, *e.g.*, greater than 50% (or any percentages as described throughout) are tagged at both ends, wherein each of the tags comprises a molecular barcode.

[00220] M. Processing and/or Analyzing Nucleic Acids

[00221] The methods described throughout can be used for processing and/or analyzing a nucleic acid sample of a subject. The method can comprising exposing polynucleotide fragments of the nucleic acid sample to a plurality of polynucleotide molecules to yield tagged polynucleotide fragments. The plurality of polynucleotide molecules that can be used are described throughout the application.

[00222] For example, the plurality of polynucleotide molecules can be each less than or equal to 40 nucleic acid bases in length and have distinct barcode sequences with respect to at least 4 nucleic acid bases and an edit distance of at least 1, wherein each of the distinct barcode sequences is within 20 nucleic acid bases from a terminal end of a respective one of the plurality of polynucleotide molecules, and wherein the plurality of polynucleotide molecules are not sequencing adaptors.

[00223] The tagged polynucleotide fragments can be subjected to nucleic acid amplification reactions under conditions that yield amplified polynucleotide fragments as amplification products of the tagged polynucleotide fragments. After amplification, the nucleotide sequence of the amplified tagged polynucleotide fragments is determined. In some cases, the nucleotide sequences of the amplified tagged polynucleotide fragments are determined without the use of polymerase chain reaction (PCR).

[00224] The method can comprise analyzing the nucleotide sequences with a programmed computer processor to identify one or more genetic variants in the nucleotide sample of the subject. Any genetic alterations can be identified, including but not limited to, base change(s), insertion(s), repeat(s), deletion(s), copy number variation(s) , epigenetic modification(s), nucleosome binding site(s), copy number change(s) due to origin(s) of replication, and transversion(s). Other genetic alterations can include, but are not limited to, one or more tumor associated genetic alterations.

[00225] The subject of the methods can be suspected of having a disease. For example, the subject can be suspected of having cancer. The method can comprise collecting a nucleic acid sample from a subject. The nucleic acid sample can be collected from blood, plasma, serum,

urine, saliva, mucosal excretions, sputum, stool, cerebral spinal fluid, skin, hair, sweat, and/or tears. The nucleic acid sample can be a cell-free nucleic acid sample. In some cases, the nucleic acid sample is collected from no more than 100 nanograms (ng) of double-stranded polynucleotide molecules of the subject.

[00226] The polynucleotide fragments can comprise double-stranded polynucleotide molecules. In some cases, the plurality of polynucleotide molecules are coupled to the polynucleotide fragments via blunt end ligation, sticky end ligation, molecular inversion probes, polymerase chain reaction (PCR), ligation-based PCR, multiplex PCR, single strand ligation, or single strand circularization.

[00227] The method as described herein results in high efficiency tagging of nucleic acids. For example, exposing the polynucleotide fragments of the nucleic acid sample to the plurality of polynucleotide molecules yields the tagged polynucleotide fragments with a conversion efficiency of at least 30%, *e.g.*, of at least 50% (*e.g.*, 60%, 70%, 80%, 90%, 95%, or 99%). Conversion efficiency of at least 30%, 35%, 40%, 45%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% can be achieved.

[00228] The method can result in a tagged polynucleotide fragment that share common polynucleotide molecules. For example, any of at least 5%, 6%, 7%, 8%, 9%, 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% of the tagged polynucleotide fragments share a common polynucleotide molecule. The method can comprise generating the polynucleotide fragments from the nucleic acid sample.

[00229] In some cases, the subjecting of the method comprises amplifying the tagged polynucleotide fragments in the presence primers corresponding to a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4,

CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1. Additionally, any combination of these genes can be amplified. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or all 54 of these genes can be amplified.

[00230] The methods described herein can comprise generating a plurality of sequence reads from a plurality of polynucleotide molecules. The plurality of polynucleotide molecules can cover genomic loci of a target genome. For example, the genomic loci can correspond to a plurality of genes as listed above. Further, the genomic loci can be any combination of these genes. Any given genomic locus can comprise at least two nucleic acid bases. Any given genomic locus can also comprise a plurality of nucleic acid bases, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more nucleic acid bases.

[00231] The method can comprise grouping with a computer processor the plurality of sequence reads into families. Each of the family can comprises sequence reads from one of the template polynucleotides. Each family can comprise sequence reads from only one of the template polynucleotides. For each of the family, the sequence reads can be merged to generate a consensus sequence. The grouping can comprise classifying the plurality of sequence reads into families by identifying (i) distinct molecular barcodes coupled to the plurality of polynucleotide molecules and (ii) similarities between the plurality of sequence reads, wherein each family includes a plurality of nucleic acid sequences that are associated with a distinct combination of molecular barcodes and similar or identical sequence reads.

[00232] Once merged, a consensus sequence can be called at a given genomic locus among the genomic loci. At any given genomic loci, any of the following can be determined: i) genetic variants among the calls; ii) frequency of a genetic alteration among the calls; iii) total number of calls; and iv) total number of alterations among the calls. The calling can comprise calling at least one nucleic acid base at the given genomic locus. The calling can also comprise calling a plurality of nucleic acid bases at the given genomic locus. In some cases, the calling can comprise phylogenetic analysis, voting (*e.g.*, biased voting), weighing, assigning a probability to

each read at the locus in a family, or calling the base with the highest probability. The consensus sequence can be generated by evaluating a quantitative measure or a statistical significance level for each of the sequence reads. If a quantitative measure is performed, the method can comprise use of a binomial distribution, exponential distribution, beta distribution, or empirical distribution. However, frequency of the base at the particular location can also be used for calling, for example, if 51% or more of the reads is a "A" at the location, then the base may be called an "A" at that particular location. The method can further comprise mapping a consensus sequence to a target genome.

[00233] The method can further comprising performing consensus calling at an additional genomic locus among the genomic loci. The method can comprise determining a variation in copy number at one of the given genomic locus and additional genomic locus based on counts at the given genomic locus and additional genomic locus.

[00234] The methods described herein can comprise providing template polynucleotide molecules and a library of adaptor polynucleotide molecules in a reaction vessel. The adaptor polynucleotide molecules can have from 2 to 1,000 different barcode sequences and in some cases are not sequencing adaptors. Other variations of adaptor polynucleotide molecules are described throughout, which can also be used in the methods.

[00235] The polynucleotide molecules of the adaptors can have the same sample tag. The adaptor polynucleotide molecules can be coupled to both ends of the template polynucleotide molecules. The method can comprise coupling the adaptor polynucleotide molecules to the template polynucleotide molecules at an efficiency of at least 30%, *e.g.*, of at least 50% (*e.g.*, 60%, 70%, 80%, 90%, 95%, or 99%), thereby tagging each template polynucleotide with a tagging combination that is among 4 to 1,000,000 different tagging combinations, to produce tagged polynucleotide molecules. In some cases, the reaction can occur in a single reaction vessel. Coupling efficiency can also be at least 30%, 35%, 40%, 45%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. Tagging can be non-unique tagging.

[00236] The tagged polynucleotide molecules can then be subject to an amplification reaction under conditions that will yield amplified polynucleotide molecules as amplification products of the tagged polynucleotide molecules. The template polynucleotide molecules can be double-stranded. Further, the template polynucleotide molecules can be blunt ended. In some cases, the amplification reaction comprises non-specifically amplifying the tagged polynucleotide molecules. The amplification reaction can also comprises using a priming site to amplify each of the tagged polynucleotide molecules. The priming site can be a primer, *e.g.*, a universal primer. The priming site can also be a nick.

[00237] The method can also comprise sequencing the amplified polynucleotide molecules. The sequencing can comprise (i) subjecting the amplified polynucleotide molecules to an additional amplification reaction under conditions that yield additional amplified polynucleotide molecules as amplification products of the amplified polynucleotide molecules, and/or (ii) sequencing the additional amplified polynucleotide molecules. The additional amplification can be performed in the presence of primers comprising flow cells sequences, which will produce polynucleotide molecules that are capable of binding to a flow cell. The additional amplification can also be performed in the presence of primers comprising sequences for hairpin shaped adaptors. The hairpin shaped adaptors can be attached to both ends of a polynucleotide fragment to generate a circular molecule, which can be sequenced multiple times. The method can further comprise identifying genetic variants upon sequencing the amplified polynucleotide molecules.

[00238] The method can further comprising separating polynucleotide molecules comprising one or more given sequences from the amplified polynucleotide molecules, to produce enriched polynucleotide molecules. The method can also comprise amplifying the enriched polynucleotide molecules with primers comprising the flow cell sequences. This amplification with primers comprising flow cell sequences will produce polynucleotide molecules that are capable of binding to a flow cell. The amplification can also be performed in the presence of primers comprising sequences for hairpin shaped adaptors. The hairpin shaped adaptors can be attached to both ends of a polynucleotide fragment to generate a circular molecule, which can be sequenced multiple times.

[00239] Flow cell sequences or hairpin shaped adaptors can be added by non-amplification methods such as through ligation of such sequences. Other techniques such as hybridization methods can be used, *e.g.*, nucleotide overhangs.

[00240] The method can be performed without aliquoting the tagged polynucleotide molecules. For example, once the tagged polynucleotide molecule is made, the amplification and sequencing can occur in the same tube without any further preparation.

[00241] The methods described herein can be useful in detecting single nucleotide variations (SNV), copy number variations (CNV), insertions, deletions, and/or rearrangements. In some cases, the SNVs, CNVs, insertions, deletions, and/or rearrangements, can be associated with disease, for example, cancer.

[00242] **N. Monitoring a Patient's Status**

[00243] Methods disclosed herein can also be used to monitor a patient's disease status. The disease of a subject can be monitored over time to determine a progression of the disease (e.g., regression). Markers indicative of the disease can be monitored in a biological sample of the subject, such as a cell-free DNA sample.

[00244] For example, monitoring a subject's cancer status can comprise (a) determining an amount of one or more SNVs or copy numbers of a plurality of genes (e.g., in an exon), (b) repeating such determination at different points in time, and (c) determining if there is a difference in the number of SNVs, level of SNVs, number or level of genomic rearrangements, or copy numbers between (a) and (b). The genes can be selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1. The genes can be selected from any 5, 10, 15, 20, 30, 40, 50, or all of the genes in this group.

[00245] O. Sensitivity and Specificity

[00246] Methods disclosed herein can be used to detect cancer polynucleotides in a sample, and cancer in a subject, with high measures of agreement, *e.g.*, high sensitivity and/or specificity. For example, such methods can detect cancer polynucleotides (e.g., rare DNA) in a sample at a concentration that is less than 5%, 1%, 0.5%, 0.1%, 0.05%, or 0.01%, at a specificity of at least 99%, 99.9%, 99.99%, 99.999%, 99.9999%, or 99.99999%. Such polynucleotides may be indicative of cancer or other disease. Further, such methods can detect cancer polynucleotides in a sample with a positive predictive value of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9%, 99.99%, 99.999%, or 99.9999%.

[00247] Subjects identified as positive in a test that are in reality positive are referred as true positives (TP). Subjects identified as positive in a test that are in reality negative are referred as false positives (FP). Subjects identified as negative in a test that are in reality negative are referred as true negatives (TN). Subjects identified as negative in a test that are in reality positive are referred as false negatives (FN). Sensitivity is the percentage of actual positives identified in a test as positive. This includes, for example, instances in which one should have found a cancer genetic variant and did. (Sensitivity =TP/(TP+FN).) Specificity is the percentage of actual negatives identified in a test as negative. This includes, for example, instances in which one should have found no cancer genetic variant and did not. Specificity can be calculated using the following equation: Specificity = TN/(TN+FP). Positive predictive value (PPV) can be measured by the percentage of subjects who test positive that are true positives. PPV can be calculated using the following equation: PPV= TP/(TP+FP). Positive predictive value can be increased by increasing sensitivity (*e.g.*, chance of an actual positive being detected) and/or specificity (*e.g.*, chance of not mistaking an actual negative for a positive).

[00248] Low conversion rates of polynucleotides into adaptor-tagged polynucleotides can compromise sensitivity as it decreases the chance of converting, and therefore detecting, rare polynucleotide targets. Noise in a test can compromise specificity as it increases the number of false positives detected in a test. Both low conversion rate and noise compromise positive predictive value as they decrease the percentage of true positives and increase the percentage of false positives.

[00249] The methods disclosed herein can achieve high levels of agreement, *e.g.*, sensitivity and specificity, leading to high positive predictive values. Methods of increasing sensitivity include high efficiency conversion of polynucleotides into adaptor-tagged polynucleotides in a sample. Methods of increasing specificity include reducing sequencing errors, for example, by molecular tracking.

[00250] Methods of the present disclosure can be used to detect genetic variation in non-uniquely tagged initial starting genetic material (e.g., rare DNA) at a concentration that is less than 5%, 1%, 0.5%, 0.1%, 0.05%, or 0.01%, at a specificity of at least 99%, 99.9%, 99.99%, 99.999%, 99.9999%, or 99.99999%. In some aspects, the methods can further comprise converting polynucleotides in the initial starting material at an efficiency of at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. Sequence reads of tagged polynucleotides can be subsequently tracked to generate consensus sequences for polynucleotides with an error rate of no more than 2%, 1%, 0.1%, or 0.01%.

[00251] **2. <u>Pooling Methods</u>**

[00252] Disclosed herein are methods of detecting copy number variation and/or sequence variants at one or more genetic loci in a test sample. One embodiment is shown in **FIG. 8**. Typically, detecting copy number variation involves determining a quantitative measure (*e.g.*, an absolute or relative number) of polynucleotides mapping to a genetic locus of interest in a genome of a test sample, and comparing that number to a quantitative measure of polynucleotides mapping to that locus in a control sample. In certain methods, the quantitative measure is determined by comparing the number of molecules in the test sample that map to a locus of interest with a number of molecules in the test sample mapping to a reference sequence, *e.g.*, a sequence expected to be present at wild type ploidy number. In some examples, the reference sequence is HG19, build 37, or build 38. The comparison could involve, for example, determining a ratio. Then, this measure is compared with a similar measure determined in a control sample. So, for example, if a test sample has a ratio of 1.5:1 for locus of interest versus reference locus, and a control sample has a ratio of 1:1 for the same loci, one may conclude that the test sample exhibits polyploidy at the locus of interest.

[00253] When the test sample and the control sample are analyzed separately, the work flow can introduce distortions between final numbers in the control and test samples.

[00254] In one method disclosed herein (*e.g.*, flow chart 800), polynucleotides are provided from a test and a control sample (802). Polynucleotides in a test sample and those in a control sample are tagged with tags that identify the polynucleotides as originating from the test or control sample (a source tag). (804.) The tag can be, for example, a polynucleotide sequence or barcode that unambiguously identifies the source.

[00255] The polynucleotides in each of the control and test samples also can be tagged with identifier tags that will be carried by all amplification progeny of a polynucleotide. Information from start and end sequences of a polynucleotide and identifier tags can identify sequence reads from polynucleotides amplified from an original parent molecule. Each molecule can be uniquely tagged compared with other molecules in the sample. Alternatively, each molecule need not be uniquely tagged compared with other molecules in the sample. That is, the number of different identifier sequences can be fewer than that the number of molecules in sample. By combining identifier information with start/stop sequence information, the probability of confusing two molecules having the same start/stop sequence is significantly diminished.

[00256] Number of different identifiers used to tag a nucleic acid (*e.g.*, cfDNA) can dependent on the number of different haploid genome equivalents. Different identifiers can be used to tag at least 2, least 10, least 100, least 200, least 300, least 400, least 500, least 600, least 700, least 800, least 900, least 1,000, least 2,000, least 3,000, least 4,000, least 5,000, least 6,000, least 7,000, least 8,000, least 9,000, least 10,000 or more different haploid genome equivalents. Accordingly, the number of different identifiers used to tag a nucleic acid sample, *e.g.*, cell-free DNA from 500 to 10,000 different haploid genome equivalents and be between any of 1, 2, 3, 4 and 5 and no more than 100, 90, 80, 70, 60, 50, 40 or 30. For example, the number of different identifier used to tag a nucleic acid sample from 500 to 10,000 different haploid genome equivalents can be 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or less.

[00257] Polynucleotides can be tagged by ligation of adaptors comprising the tags or identifiers before amplification. Ligation can be performed using an enzyme, *e.g.*, a ligase. For example, tagging can be performed using a DNA ligase. The DNA ligase can be a T4 DNA ligase, *E. coli* DNA ligase, and/or mammalian ligase. The mammalian ligase can be DNA ligase I, DNA ligase III, or DNA ligase IV. The ligase may also be a thermostable ligase. Tags can be ligated to a blunt-end of a polynucleotide (blunt-end ligation). Alternatively, tags can be ligated to a sticky end of a polynucleotide (sticky-end ligation). The polynucleotides can be tagged by blunt end ligation using adaptors (*e.g.*, adaptors having forked ends). High efficiency of ligation can be achieved using high excess of adaptors (*e.g.*, more than 1.5X, more than 2X, more than 3X, more than 4X, more than 5X, more than 6X, more than 7X, more than 8X, more than 9X, more than 10X, more than 11X, more than 12X, more than 13X, more than 14X, more than 15X, more than 20X, more than 25X, more than 30X, more than 35X, more than 40X, more than 45X, more than 50X, more than 55X, more than 60X, more than 65X, more than 70X, more than 75X, more than 80X, more than 85X, more than 90X, more than 95X, or more than 100).

[00258] Once tagged with tags that identify source of the polynucleotides, polynucleotides from different sources (*e.g.*, different samples) can be pooled. After pooling, polynucleotides from different sources (*e.g.*, different samples) can be distinguished by any measurement using the tags, including any process of quantitative measurement. For example, as shown in (806) (**FIG. 8**), polynucleotides from the control sample and the test sample can be pooled. The pooled molecules can be subject to the sequencing (808) and bioinformatic work flow. Both will be subject to the same variations in the process and, therefore, any differential bias is reduced. Because molecules originating from control and test samples are differently tagged, they can be distinguished in any process of quantitative measurement.

[00259] The relative amount of control and test sample pooled can be varied. The amount of control sample can be same as the amount of test sample. The amount of control sample can also be larger than the amount of test sample. Alternatively, the amount of control sample can be smaller than the amount of test sample. The smaller the relative amount of one sample to the total, the fewer identifying tags needed in the original tagging process. A number can be selected to reduce to acceptable levels the probability that two parent molecules having the same start/end sequences will bear the same identifying tag. This probability can be less than 10%,

less than 1%, less than 0.1% or less than 0.01%. The probability can be less than 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1%.

[00260] Methods disclosed herein can also comprise grouping sequence reads. For example, bioinformatic workflow can include grouping sequence reads produced from progeny of a single parent molecule, as shown in (810) (**FIG. 8**). This can involve any of the redundancy reduction methods described herein. Molecules sourced from test and control samples can be differentiated based on source tags they carry (812). Molecules mapping to a target locus are quantified for both test-sourced and control-sourced molecules (812). This can include the normalization methods discussed herein, *e.g.*, in which numbers at a target locus are normalized against numbers at a reference locus.

[00261] Normalized (or raw) quantities at a target locus from test and control samples are compared to determine presence of copy number variation (814).

[00262] **3. <u>Computer Control Systems</u>**

[00263] The present disclosure provides computer control systems that are programmed to implement methods of the disclosure. **FIG. 6** shows a computer system 1501 that is programmed or otherwise configured to implement the methods of the present disclosure. The computer system 1501 can regulate various aspects sample preparation, sequencing and/or analysis. In some examples, the computer system 1501 is configured to perform sample preparation and sample analysis, including nucleic acid sequencing. The computer system 1501 can be an electronic device of a user or a computer system that is remotely located with respect to the electronic device. The electronic device can be a mobile electronic device.

[00264] The computer system 1501 includes a central processing unit (CPU, also "processor" and "computer processor" herein) 1505, which can be a single core or multi core processor, or a plurality of processors for parallel processing. The computer system 1501 also includes memory or memory location 1510 (*e.g.*, random-access memory, read-only memory, flash memory), electronic storage unit 1515 (*e.g.*, hard disk), communication interface 1520 (*e.g.*, network adapter) for communicating with one or more other systems, and peripheral devices 1525, such as cache, other memory, data storage and/or electronic display adapters. The memory 1510, storage unit 1515, interface 1520 and peripheral devices 1525 are in

communication with the CPU 1505 through a communication bus (solid lines), such as a motherboard. The storage unit 1515 can be a data storage unit (or data repository) for storing data. The computer system 1501 can be operatively coupled to a computer network ("network") 1530 with the aid of the communication interface 1520. The network 1530 can be the Internet, an internet and/or extranet, or an intranet and/or extranet that is in communication with the Internet. The network 1530 in some cases is a telecommunication and/or data network. The network 1530 can include one or more computer servers, which can enable distributed computing, such as cloud computing. The network 1530, in some cases with the aid of the computer system 1501, can implement a peer-to-peer network, which may enable devices coupled to the computer system 1501 to behave as a client or a server.

[00265] The CPU 1505 can execute a sequence of machine-readable instructions, which can be embodied in a program or software. The instructions may be stored in a memory location, such as the memory 1510. The instructions can be directed to the CPU 1505, which can subsequently program or otherwise configure the CPU 1505 to implement methods of the present disclosure. Examples of operations performed by the CPU 1505 can include fetch, decode, execute, and writeback.

[00266] The CPU 1505 can be part of a circuit, such as an integrated circuit. One or more other components of the system 1501 can be included in the circuit. In some cases, the circuit is an application specific integrated circuit (ASIC).

[00267] The storage unit 1515 can store files, such as drivers, libraries and saved programs. The storage unit 1515 can store user data, *e.g.*, user preferences and user programs. The computer system 1501 in some cases can include one or more additional data storage units that are external to the computer system 1501, such as located on a remote server that is in communication with the computer system 1501 through an intranet or the Internet.

[00268] The computer system 1501 can communicate with one or more remote computer systems through the network 1530. For instance, the computer system 1501 can communicate with a remote computer system of a user (*e.g.*, an operator). Examples of remote computer systems include personal computers (*e.g.*, portable PC), slate or tablet PC's (*e.g.*, Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (*e.g.*, Apple® iPhone, Android-enabled

device, Blackberry®), or personal digital assistants. The user can access the computer system 1501 via the network 1530.

[00269] Methods as described herein can be implemented by way of machine (*e.g.*, computer processor) executable code stored on an electronic storage location of the computer system 1501, such as, for example, on the memory 1510 or electronic storage unit 1515. The machine executable or machine readable code can be provided in the form of software. During use, the code can be executed by the processor 1505. In some cases, the code can be retrieved from the storage unit 1515 and stored on the memory 1510 for ready access by the processor 1505. In some situations, the electronic storage unit 1515 can be precluded, and machine-executable instructions are stored on memory 1510.

[00270] The code can be pre-compiled and configured for use with a machine have a processer adapted to execute the code, or can be compiled during runtime. The code can be supplied in a programming language that can be selected to enable the code to execute in a pre-compiled or as-compiled fashion.

[00271] Aspects of the systems and methods provided herein, such as the computer system 1501, can be embodied in programming. Various aspects of the technology may be thought of as "products" or "articles of manufacture" typically in the form of machine (or processor) executable code and/or associated data that is carried on or embodied in a type of machine readable medium. Machine-executable code can be stored on an electronic storage unit, such memory (*e.g.*, read-only memory, random-access memory, flash memory) or a hard disk. "Storage" type media can include any or all of the tangible memory of the computers, processors or the like, or associated modules thereof, such as various semiconductor memories, tape drives, disk drives and the like, which may provide non-transitory storage at any time for the software programming. All or portions of the software may at times be communicated through the Internet or various other telecommunication networks. Such communications, for example, may enable loading of the software from one computer or processor into another, for example, from a management server or host computer into the computer platform of an application server. Thus, another type of media that may bear the software elements includes optical, electrical and electromagnetic waves, such as used across physical interfaces between local devices, through wired and optical landline networks and over various air-links. The physical elements that carry

such waves, such as wired or wireless links, optical links or the like, also may be considered as media bearing the software. As used herein, unless restricted to non-transitory, tangible "storage" media, terms such as computer or machine "readable medium" refer to any medium that participates in providing instructions to a processor for execution.

[00272] Hence, a machine readable medium, such as computer-executable code, may take many forms, including but not limited to, a tangible storage medium, a carrier wave medium or physical transmission medium. Non-volatile storage media include, for example, optical or magnetic disks, such as any of the storage devices in any computer(s) or the like, such as may be used to implement the databases, etc. shown in the drawings. Volatile storage media include dynamic memory, such as main memory of such a computer platform. Tangible transmission media include coaxial cables; copper wire and fiber optics, including the wires that comprise a bus within a computer system. Carrier-wave transmission media may take the form of electric or electromagnetic signals, or acoustic or light waves such as those generated during radio frequency (RF) and infrared (IR) data communications. Common forms of computer-readable media therefore include for example: a floppy disk, a flexible disk, hard disk, magnetic tape, any other magnetic medium, a CD-ROM, DVD or DVD-ROM, any other optical medium, punch cards paper tape, any other physical storage medium with patterns of holes, a RAM, a ROM, a PROM and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave transporting data or instructions, cables or links transporting such a carrier wave, or any other medium from which a computer may read programming code and/or data. Many of these forms of computer readable media may be involved in carrying one or more sequences of one or more instructions to a processor for execution.

[00273] The computer system 1501 can include or be in communication with an electronic display 1535 that comprises a user interface (UI) 1540. The UI can allow a user to set various conditions for the methods described herein, for example, PCR or sequencing conditions. Examples of UI's include, without limitation, a graphical user interface (GUI) and web-based user interface.

[00274] Methods and systems of the present disclosure can be implemented by way of one or more algorithms. An algorithm can be implemented by way of software upon execution by the

central processing unit 1505. The algorithm can, for example, process the reads to generate a consequence sequence.

[00275] **FIG. 7** schematically illustrates another system for analyzing a sample comprising nucleic acids from a subject. The system includes a sequencer, bioinformatic software and internet connection for report analysis by, for example, a hand held device or a desktop computer

[00276] Disclosed herein is a system for analyzing a target nucleic acid molecule of a subject, comprising: a communication interface that receives nucleic acid sequence reads for a plurality of polynucleotide molecules that cover genomic loci of a target genome; computer memory that stores the nucleic acid sequence reads for the plurality of polynucleotide molecules received by the communication interface; and a computer processor operatively coupled to the communication interface and the memory and programmed to (i) group the plurality of sequence reads into families, wherein each family comprises sequence reads from one of the template polynucleotides, (ii) for each of the families, merge sequence reads to generate a consensus sequence, (iii) call the consensus sequence at a given genomic locus among the genomic loci, and (iv) detect at the given genomic locus any of genetic variants among the calls, frequency of a genetic alteration among the calls, total number of calls; and total number of alterations among the calls, wherein the genomic loci correspond to a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1. The different variations of each component of the system are described throughout the disclosure within the methods and compositions. These individual components and variations thereof, are also applicable in this system.

[00277] **4. Kits**

[00278] Kits comprising the compositions as described herein. The kits can be useful in performing the methods as described herein. Disclosed herein is a kit comprising a plurality of

oligonucleotide probes that selectively hybridize to least 5, 6, 7, 8, 9, 10, 20, 30, 40 or all genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1. The number genes to which the oligonucleotide probes can selectively hybridize can vary. For example, the number of genes can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or 54. The kit can include a container that includes the plurality of oligonucleotide probes and instructions for performing any of the methods described herein.

[00279] The oligonucleotide probes can selectively hybridize to exon regions of the genes, *e.g.*, of the at least 5 genes. In some cases, the oligonucleotide probes can selectively hybridize to at least 30 exons of the genes, *e.g.*, of the at least 5 genes. In some cases, the multiple probes can selectively hybridize to each of the at least 30 exons. The probes that hybridize to each exon can have sequences that overlap with at least 1 other probe. In some embodiments, the oligoprobes can selectively hybridize to non-coding regions of genes disclosed herein, for example, intronic regions of the genes. The oligoprobes can also selectively hybridize to regions of genes comprising both exonic and intronic regions of the genes disclosed herein.

[00280] Any number of exons can be targeted by the oligonucleotide probes. For example, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, , 295, 300, 400, 500, 600, 700, 800, 900, 1,000, or more, exons can be targeted.

[00281] The kit can comprise at least 4, 5, 6, 7, or 8 different library adaptors having distinct molecular barcodes and identical sample barcodes. The library adaptors may not be sequencing

adaptors. For example, the library adaptors do not include flow cell sequences or sequences that permit the formation of hairpin loops for sequencing. The different variations and combinations of molecular barcodes and sample barcodes are described throughout, and are applicable to the kit. Further, in some cases, the adaptors are not sequencing adaptors. Additionally, the adaptors provided with the kit can also comprise sequencing adaptors. A sequencing adaptor can comprise a sequence hybridizing to one or more sequencing primers. A sequencing adaptor can further comprise a sequence hybridizing to a solid support, *e.g.*, a flow cell sequence. For example, a sequencing adaptor can be a flow cell adaptor. The sequencing adaptors can be attached to one or both ends of a polynucleotide fragment. In some cases, the kit can comprise at least 8 different library adaptors having distinct molecular barcodes and identical sample barcodes. The library adaptors may not be sequencing adaptors. The kit can further include a sequencing adaptor having a first sequence that selectively hybridizes to the library adaptors and a second sequence that selectively hybridizes to a flow cell sequence. In another example, a sequencing adaptor can be hairpin shaped. For example, the hairpin shaped adaptor can comprise a complementary double stranded portion and a loop portion, where the double stranded portion can be attached (*e.g.*, ligated) to a double-stranded polynucleotide. Hairpin shaped sequencing adaptors can be attached to both ends of a polynucleotide fragment to generate a circular molecule, which can be sequenced multiple times. A sequencing adaptor can be up to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, or more bases from end to end. The sequencing adaptor can comprise 20-30, 20-40, 30-50, 30-60, 40-60, 40-70, 50-60, 50-70, bases from end to end. In a particular example, the sequencing adaptor can comprise 20-30 bases from end to end. In another example, the sequencing adaptor can comprise 50-60 bases from end to end. A sequencing adaptor can comprise one or more barcodes. For example, a sequencing adaptor can comprise a sample barcode. The sample barcode can comprise a pre-determined sequence. The sample barcodes can be used to identify the source of the polynucleotides. The sample barcode can be at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,

21, 22, 23, 24, 25, or more (or any length as described throughout) nucleic acid bases, *e.g.*, at least 8 bases. The barcode can be contiguous or non-contiguous sequences, as described above.

[00282] The library adaptors can be blunt ended and Y-shaped and can be less than or equal to 40 nucleic acid bases in length. Other variations of the can be found throughout and are applicable to the kit.

EXAMPLES

[00283] **Example 1. Methods for copy number variation detection.**

[00284] Blood collection

[00285] 10-30 mL Blood samples are collected at room temperature. The samples are centrifuged to remove cells. Plasma is collected after centrifugation.

[00286] cfDNA extraction

[00287] The sample is subjected to proteinase K digestion. DNA is precipitated with isopropanol. DNA is captured on a DNA purification column (*e.g.*, a QIAamp DNA Blood Mini Kit) and eluted in 100 µl solution. DNAs below 500 bp are selected with Ampure SPRI magnetic bead capture (PEG/salt). The resulting production is suspended in 30 µl H_2O. Size distribution is checked (major peak = 166 nucleotides; minor peak = 330 nucleotides) and quantified. 5 ng of extracted DNA contain approximately 1700 haploid genome equivalents ("HGE"). The general correlation between the amount of DNA and HGE is as follow: 3 pg DNA = 1 HGE; 3 ng DNA = 1K HGE; 3 µg DNA = 1M HGE; 10 pg DNA = 3 HE; 10 ng DNA = 3K HGE; 10 µg DNA = 3M HGE.

[00288] "Single Molecule" library prep

[00289] High-efficiency DNA tagging (>80%) is performed by blunt-end repair and ligation with 8 different octomers (*i.e.*, 64 combinations) with overloaded hairpin adaptors. 2.5 ng DNA (*i.e.* approximately 800 HGE) is used as the starting material. Each hairpin adaptor comprises a random sequence on its non-complementary portion. Both ends of each DNA fragment are attached with hairpin adaptors. Each tagged fragment can be identified by the random sequence on the hairpin adaptors and a 10 p endogenous sequence on the fragment.

[00290] Tagged DNA is amplified by 10 cycles of PCR to produce about 1-7 µg DNAs that contain approximately 500 copies of each of the 800 HGE in the starting material.

[00291] Buffer optimization, polymerase optimization and cycle reduction may be performed to optimize the PCR reactions. Amplification bias, *e.g.*, non-specific bias, GC bias, and/or size bias are also reduced by optimization. Noise(s) (*e.g.*, polymerase-introduced errors) are reduced by using high-fidelity polymerases.

[00292] The Library may be prepared using Verniata or Sequenom methods.

[00293] Sequences may be enriched as follow: DNAs with regions of interest (ROI) are captured using biotin-labeled bead with probe to ROIs. The ROIs are amplified with 12 cycles of PCR to generate a 2000 times amplification. The resulting DNA is then denatured and diluted to 8 pM and loaded into an Illumina sequencer.

[00294] Massively parallel sequencing

[00295] 0.1 to 1% of the sample (approximately 100pg) are used for sequencing.

[00296] Digital bioinformatics

[00297] Sequence reads are grouped into families, with about 10 sequence reads in each family. Families are collapsed into consensus sequences by voting (*e.g.*, biased voting) each position in a family. A base is called for consensus sequence if 8 or 9 members agree. A base is not called for consensus sequence if no more than 60% of the members agree.

[00298] The resulting consensus sequences are mapped to a reference genome. Each base in a consensus sequence is covered by about 3000 different families. A quality score for each sequence is calculated and sequences are filtered based on the their quality scores.

[00299] Sequence variation is detected by counting distribution of bases at each locus. If 98% of the reads have the same base (homozygous) and 2% have a different base, the locus is likely to have a sequence variant, presumably from cancer DNA.

[00300] CNV is detected by counting the total number of sequences (bases) mapping to a locus and comparing with a control locus. To increase CNV detection, CNV analysis is performed specific regions, including regions on ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET,SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A,

BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, or NTRK1 genes.

[00301] Example 2. Method for Correcting Base Calling by Determining the Total Number Unseen Molecules in a Sample

[00302] After fragments are amplified and the sequences of amplified fragments are read and aligned, the fragments are subjected to base calling. Variations in the number of amplified fragments and unseen amplified fragments can introduce errors in base calling. These variations are corrected by calculating the number of unseen amplified fragments.

[00303] When base calling for locus A (an arbitrary locus), it is first assumed that there are N amplified fragments. The sequence readouts can come from two types of fragments: double-strand fragments and single-strand fragments. The following is a theoretical example of calculating the total number of unseen molecules in a sample.

[00304] N is the total number of molecules in the sample.
Assuming 1000 is the number of duplexes detected.
Assuming 500 is the number of single-stranded molecule detected.
P is the probability of seeing a strand.
Q is the probability of not detecting a strand.

[00305] Since Q = 1 -P.
1000 = NP(2).
500 = N2PQ.
1000 / P(2) = N.
500÷2 PQ = N.
1000 / P(2) = 500÷2PQ.
1000 * 2 PQ = 500 P(2).
2000 PQ = 500 P(2).
2000 Q = 500 P.
2000 (1-P) = 500P
2000-2000 P = 500P.
2000 = 500P +2000 P.
2000 = 2500 P.
2000÷2500 = P.
0.8 = P.
1000/ P(2) = N.
1000÷0.64 = N.
1562 = N.
Number of unseen fragments = 62.

[00306] Example 3. Identification of genetic variants in cancer-associated somatic variants in a patient.

[00307] An assay is used to analyze a panel of genes to identify genetic variants in cancer-associated somatic variants with high sensitivity.

[00308] Cell-free DNA is extracted from plasma of a patient and amplified by PCR. Genetic variants are analyzed by massively parallel sequencing of the amplified target genes. For one set of genes, all exons are sequenced as such sequencing coverage had shown to have clinically utility (Table 1). For another set of genes, sequencing coverage included those exons with a previously reported somatic mutation (Table 2). The minimum detectable mutant allele (limit of detection) is dependent on the patient's sample cell-free DNA concentration, which varied from less than 10 to over 1,000 genomic equivalents per mL of peripheral blood. Amplification may not be detected in samples with lower amounts of cell-free DNA and/or low-level gene copy amplification. Certain sample or variant characteristics resulted in reduced analytic sensitivity, such as low sample quality or improper collection.

[00309] The percentage of genetic variants found in cell-free DNA circulating in blood is related to the unique tumor biology of this patient. Factors that affected the amount/percentages of detected genetic variants in circulating cell-free DNA in blood include tumor growth, turn-over, size, heterogeneity, vascularization, disease progression or treatment. Table 3 annotates the percentage, or allele frequency, of altered circulating cell-free DNA (% cfDNA) detected in this patient. Some of the detected genetic variants are listed in descending order by % cfDNA.

[00310] Genetic variants are detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genetic variants are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatment. "Minor Alterations" are defined as those alterations detected at less than 10% the allele frequency of "Major Alterations". The detected allele frequencies of these alterations (Table 3) and associated treatments for this patient are annotated.

[00311] All genes listed in Tables 1 and 2 are analyzed as part of the Guardant360™ test. Amplification is not detected for *ERBB2*, *EGFR*, or *MET* in the circulating cell-free DNA isolated from this patient's blood specimen.

[00312] Patient test results comprising the genetic variants are listed in Table 4.

Table 1. Genes in which all exons are sequenced

GENES IN WHICH ALL EXONS ARE SEQUENCED			
ALK	< 0.1%	APC	< 0.1%
AR	< 0.1%	BRAF	< 0.1%
CDKN2A	< 0.1%	EGFR	< 0.1%
ERBB2	< 0.1%	FBXW7	< 0.1%
KRAS	< 0.1%	MET	< 0.1%
MYC	< 0.1%	NOTCH1	< 0.1%
NRAS	< 0.1%	PIK3CA	< 0.1%
PTEN	< 0.1%	PROC	< 0.1%
RB1	< 0.1%	TP53	< 0.1%

LOD: Limit of Detection. The minimum detectable mutant allele frequency for this specimen in which 80% of somatic variants is detected.

Table 2. Genes in which exons with a previously reported somatic mutation are sequenced

GENES IN WHICH EXONS WITH A PREVIOUSLY REPORTED SOMATIC MUTATION ARE SEQUENCED			
ABL1	< 0.1%	AKT1	< 0.1%
ATM	< 0.1%	CDH1	< 0.1%
CSF1R	< 0.1%	CTNNB1	< 0.1%
ERBB4	< 0.1%	EZH2	< 0.1%
FGFR1	< 0.1%	FGFR2	< 0.1%
FGFR3	< 0.1%	FLT3	< 0.1%
GNA11	< 0.1%	GNAQ	< 0.1%
GNAS	< 0.1%	HNF1A	< 0.1%
HRAS	< 0.1%	IDH1	< 0.1%
IDH2	< 0.1%	JAK2	< 0.1%
JAK3	< 0.1%	KDR	< 0.1%
KIT	< 0.1%	MLH1	< 0.1%
MPL	< 0.1%	NPM1	< 0.1%
PDGFRA	< 0.1%	PTPN11	< 0.1%
RET	< 0.1%	SMAD4	< 0.1%
SMARCB1	< 0.1%	SMO	< 0.1%
SRC	< 0.1%	STK11	< 0.1%
TERT	< 0.1%	VHL	< 0.1%

LOD: Limit of Detection. The minimum detectable mutant allele frequency for this specimen in which 80% of somatic variants is detected.

Table 3. Allele frequency of altered circulating cell-free DNA detected in this patient

Gene	cfDNA with alterations (%)	cfDNA without alterations (%)
BRAF V600E	8.9	91.1
NRAS Q61K	6.2	93.8
JAK V617F	1.5	98.6

Table 4. Genomic alterations detected in selected genes

Detected: 51 Genomic Alterations							
Gene	**Chromo-some**	**Position**	**Mutation (nt)**	**Mutation (AA)**	**Percentage**	**Cosmic ID**	**DBSNP ID**
KRAS	12	25368462	C>T		100.0%		rs4362222
ALK	2	29416572	T>C	I1461V	100.0%		rs1670283
ALK	2	29444095	C>T		100.0%		rs1569156
ALK	2	29543663	T>C	Q500Q	100.0%		rs2293564
ALK	2	29940529	A>T	P234P	100.0%		rs2246745
APC	5	112176756	T>A	V1822D	100.0%		rs459552
CDKN2A	9	21968199	C>G		100.0%	COSM14251	rs11515
FGFR3	4	1807894	G>A	T651T	100.0%		rs7688609
NOTCH1	9	139410424	A>G		100.0%		rs3125006
PDGFRA	4	55141055	A>G	P567P	100.0%		rs1873778
HRAS	11	534242	A>G	H27H	100.0%	COSM249860	rs12628
EGFR	7	55214348	C>T	N158N	99.9%	COSM42978	rs2072454
TP53	17	7579472	G>C	P72R	99.8%		rs1042522
APC	5	112162854	T>C	Y486Y	55.0%		rs2229992
APC	5	112177171	G>A	P1960P	53.8%		rs465899
EGFR	7	55266417	T>C	T903T	53.6%		rs1140475
APC	5	112176325	G>A	G1678G	53.2%		rs42427
APC	5	112176559	T>G	S1756S	53.0%		rs866006
EGFR	7	55229255	G>A	R521K	53.0%		
MET	7	116397572	A>G	Q648Q	52.7%		
APC	5	112175770	G>A	T1493T	52.7%		rs41115
EGFR	7	55249063	G>A	Q787Q	52.6%		rs1050171
NOTCH1	9	139411714	T>C		52.4%		rs11145767
EGFR	7	55238874	T>A	T629T	52.0%		rs2227984
ERBB2	17	37879588	A>G	I655V	51.6%		rs1136201
NOTCH1	9	139397707	G>A	D1698D	51.3%	COSM33747	rs10521
ALK	2	30143499	G>C	L9L	51.0%		rs4358080
APC	5	112164561	G>A	A545A	51.0%		rs351771
FLT3	13	28610183	A>G		50.8%		rs2491231
NOTCH1	9	139418260	A>G	N104N	50.5%		rs4489420
ALK	2	29444076	G>T		50.4%		rs1534545
PIK3CA	3	178917005	A>G		50.3%		rs3729674
NOTCH1	9	139412197	G>A		50.2%		rs9411208
ALK	2	29455267	A>G	G845G	50.0%	COSM148825	rs2256740
KIT	4	55593464	A>C	M541L	49.9%	COSM28026	

NOTCH1	9	139391636	G>A	D2185D	48.9%		rs2229974
PDGFRA	4	55152040	C>T	V824V	48.9%	COSM22413	rs2228230
ALK	2	29416481	T>C	K1491R	48.9%	COSM1130802	rs1881420
ALK	2	29445458	G>T	G1125G	48.6%		rs3795850
NOTCH1	9	139410177	T>C		48.5%		rs3124603
RET	10	43613843	G>T	L769L	48.2%		rs1800861
EGFR	7	55214443	G>A		48.0%		rs7801956
ALK	2	29416366	G>C	D1529E	47.2%		rs1881421
EGFR	7	55238087	C>T		45.5%		rs10258429
RET	10	43615633	C>G	S904S	44.8%		rs1800863
BRAF	7	140453136	A>T	V600E	8.9%	COSM476	
NRAS	1	115256530	G>T	Q61K	6.2%	COSM580	rs121913254
JAK2	9	5073770	G>T	V617F	1.5%	COSM12600	rs77375493

[00313] Example 4. Determining patient-specific limits of detection for genes analyzed by Guardant360™ assays.

[00314] Using the method of Example 3, Genetic alterations in cell-free DNA of a patient are detected. The sequence reads of these genes include exon and/or intron sequences.

[00315] Limits of detection of the test are shown in Table 5. The limits of detection values are dependent on cell-free DNA concentration and sequencing coverage for each gene.

Table 5. Limits of Detection of selected genes in a patient using Guardant

Complete Exon and Partial Intron Coverage					
APC	0.1%	AR *	0.2%	ARID1A	
BRAF *	0.1%	BRCA1		BRCA2	
CCND1 *		CCND2 *		CCNE1 *	
CDK4 *		CDK6 *		CDKN2A	0.1%
CDKN2B		EGFR *	< 0.1%	ERBB2 *	0.1%
FGFR1 *	< 0.1%	FGFR2 *	0.1%	HRAS	0.1%
KIT *	0.1%	KRAS *	0.1%	MET *	0.1%
MYC *	0.1%	NF1		NRAS	0.1%
PDGFRA *	0.1%	PIK3CA*	0.1%	PTEN	0.1%
RAF1 *		TP53	0.1%		
Exons Covered with Reported Somatic Mutations					
AKT1	0.1%	ALK	< 0.1%	ARAF	
ATM	0.1%	CDH1	0.1%	CTNNB1	0.1%
ESR1		EZH2	0.1%	FBXW7	0.1%
FGFR3	0.1%	GATA3		GNA11	0.1%
GNAQ	0.1%	GNAS	0.1%	HNF1A	0.1%

IDH1	0.1%	IDH2	0.1%	JAK2	0.1%
JAK3	0.1%	MAP2K1		MAP2K2	
MLH1	0.1%	MPL	0.2%	NFE2L2	
NOTCH1	0.1%	NPM1	0.1%	PTPN11	0.1%
RET	0.1%	RHEB		RHOA	
RIT1		ROS1		SMAD4	0.1%
SMO	0.1%	SRC	< 0.1%	STK11	0.2%
TERT	0.1%	VHL	0.2%		
Fusions					
ALK	< 0.1%	RET	0.1%	ROS1	
NTRK1					

LOD: Limit of Detection. The minimum detectable mutant allele frequency for this specimen in which 80% of somatic variants is detected. * indicates CNV genes.

[00316] Example 5. Correcting Sequence Errors Comparing Watson and Crick Sequences

[00317] Double-stranded cell-free DNA is isolated from the plasma of a patient. The cell-free DNA fragments are tagged using 16 different bubble-containing adaptors, each of which comprises a distinctive barcode. The bubble-containing adaptors are attached to both ends of each cell-free DNA fragment by ligation. After ligation, each of the cell-free DNA fragment can be distinctly identified by the sequence of the distinct barcodes and two 20 bp endogenous sequences at each end of the cell-free DNA fragment.

[00318] The tagged cell-free DNA fragments are amplified by PCR. The amplified fragments are enriched using beads comprising oligonucleotide probes that specifically bind to a group of cancer-associated genes. Therefore, cell-free DNA fragments from the group of cancer-associated genes are selectively enriched.

[00319] Sequencing adaptors, each of which comprises a sequencing primer binding site, a sample barcode, and a cell-flow sequence, are attached to the enriched DNA molecules. The resulting molecules are amplified by PCR.

[00320] Both strands of the amplified fragments are sequenced. Because each bubble-containing adaptor comprises a non-complementary portion (*e.g.*, the bubble), the sequence of the one strand of the bubble-containing adaptor is different from the sequence of the other strand (complement). Therefore, the sequence reads of amplicons derived from the Watson strand of an

original cell-free DNA can be distinguished from amplicons from the Crick strand of the original cell-free DNA by the attached bubble-containing adaptor sequences.

[00321] The sequence reads from a strand of an original cell-free DNA fragment are compared to the sequence reads from the other strand of the original cell-free DNA fragment. If a variant occurs in only the sequence reads from one strand, but not other strand, of the original cell-free DNA fragment, this variant will be identified as an error (*e.g.*, resulted from PCR and/or amplification), rather than a true genetic variant.

[00322] The sequence reads are grouped into families. Errors in the sequence reads are corrected. The consensus sequence of each family is generated by collapsing.

[00323] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION FEE- 37 CFR 1.17(F) (GROUP I)	1462	1	400	400
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**400**

Electronic Acknowledgement Receipt

EFS ID:	38225290
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	07-JAN-2020
Filing Date:	
Time Stamp:	14:13:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$400
RAM confirmation Number	E202017E14553607
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00262

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	2020-01-07_GH0004US-CON3_Pet1_53.pdf	71399 4d01d7a826fb5320ef28ef2a3bc8a37ce1f395a1	no	2
Warnings:					
Information:					
2		2020-01-07_GH0004US-CON3_SpecAsFiled.pdf	627713 84130b6952b9ecf9e40a852d9eb62385f5d066ad	yes	91

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	91	91
Claims	86	90
Specification	1	85

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30273 3b73bd8bd64fc48aa1ed1bfa9fd013e881395b65	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	729385		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/672,267

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2720

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/672,267	01/07/2020		2720	42534-708.304	30	2

CONFIRMATION NO. 3448

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

FILING RECEIPT

OC000000113841649

Date Mailed: 01/10/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA;
Stetanie Ann Ward Mortimer, Moraao.Hjji, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Assignment For Published Patent Application

GUARDANT HEALTH, INC., Redwood City, CA
GUARDANT HEALTH, INC., Redwood City, CA

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/601,168 10/14/2019 *
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013
(*)Data provided by applicant is not consistent with PTO records.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/09/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/672,267**

Projected Publication Date: 04/16/2020

Non-Publication Request: No

Early Publication Request: No

Title

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/672,267	Filing Date 01/07/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	01/22/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LDRC
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/EVA V GILLIS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: To be assigned Examiner: To be assigned

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESUBMISSION OF PRELIMINARY AMENDMENT

Sir:

Applicant filed a reply to a Notice of Incomplete Application on January 7, 2020, which included submission of a previously omitted specification. To avoid any doubt as to which claims are currently pending, Applicant respectfully requests consideration of the above-referenced application in view of the following amendments and remarks that were previously submitted on December 6, 2019:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1-30. (Cancelled).

31. (New): A method for preparing a population of cell-free nucleic acid molecules obtained from a bodily fluid sample of a subject for sequencing, the method comprising:

(a) attaching molecular barcodes from a set of molecular barcodes to a plurality of cell-free nucleic acid molecules from the population to produce tagged parent polynucleotides,

wherein attaching comprises ligating a molecular barcode from the set of molecular barcodes to both ends of a molecule of the cell-free nucleic acid molecules,

wherein ligating comprises using more than a 30X molar excess of molecular barcodes as compared to the cell-free nucleic acid molecules, and

wherein at least 20% of the cell-free nucleic acid molecules from the population of cell-free nucleic acid molecules are attached to molecular barcodes;

(b) amplifying a plurality of the tagged parent polynucleotides to generate amplified progeny polynucleotides; and

(c) selectively enriching a subset of the amplified progeny polynucleotides for a plurality of genomic regions of interest.

32. (New): The method of claim 31, wherein the bodily fluid sample is selected from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, and tears.

33. (New): The method of claim 31, wherein the population comprises 1 nanogram (ng) to 100 ng of cell-free nucleic acid molecules.

34. (New): The method of claim 31, wherein the subject has cancer or is suspected of having cancer.
35. (New): The method of claim 31, wherein the cell-free nucleic acid molecules are selected from the group consisting of double-stranded deoxyribonucleic acid (DNA), single-stranded DNA, ribonucleic acid (RNA), cDNA, and any combination of these.
36. (New): The method of claim 31, wherein the molecular barcodes are ligated to the cell-free nucleic acid molecules by blunt-end ligation or sticky-end ligation.
37. (New): The method of claim 31, wherein the molecular barcodes of the set of molecular barcodes have 2 to 100,000 different molecular barcode sequences that are from 5 to 20 nucleotides in length.
38. (New): The method of claim 31, wherein ligating comprises using more than a 100X molar excess of molecular barcodes as compared to the cell-free nucleic acid molecules.
39. (New): The method of claim 31, wherein at least 40% of the cell-free nucleic acid molecules from the population of cell-free nucleic acid molecules are attached to molecular barcodes.
40. (New): The method of claim 31, wherein the genomic regions of interest comprise sequences from one or more genes selected from the group consisting of:
ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.
41. (New): The method of claim 31, where selectively enriching the subset of amplified progeny polynucleotides for a plurality of genomic regions of interest comprises using a set of probes that hybridize to the plurality of genomic regions of interest.
42. (New): The method of claim 41, wherein the plurality of genomic regions of interest comprises exon sequences.
43. (New): The method of claim 31, wherein molecular barcodes of the set of molecular barcodes are part of adapters.

44. (New): The method of claim 43, wherein the adapters are Y-shaped adapters.
45. (New): The method of claim 31, further comprising attaching sample identifiers to a plurality of the cell-free nucleic acid molecules in the population or the enriched amplified progeny polynucleotides.
46. (New): The method of claim 31, further comprising amplifying a plurality of enriched amplified progeny polynucleotides.
47. (New): A method for generating a cell-free deoxyribonucleic acid (cfDNA) sequencing library from a blood sample of a subject to conduct cancer testing, the method comprising:
    (a) performing a ligation reaction using more than a 30X molar excess of adapters comprising molecular barcodes as compared to cfDNA molecules in a population of cfDNA molecules obtained from the blood sample to produce tagged parent polynucleotides,
        wherein the molecular barcodes are members of a set of molecular barcodes comprising between 2 to 1,000 different molecular barcode sequences,
        wherein each end of a tagged parent polynucleotide has ligated thereon a respective molecular barcode from among the set of molecular barcodes, and
        wherein the efficiency of the ligation is more than 20%;
    (b) amplifying a plurality of the tagged parent polynucleotides to generate amplified progeny polynucleotides;
    (c) selectively enriching the amplified progeny polynucleotides for a plurality of cancer-associated genomic regions of interest; and
    (d) amplifying a subset of enriched amplified progeny polynucleotides, thereby generating the cell-free nucleic acid sequencing library.
48. (New): The method of claim 47, wherein the cfDNA molecules are double-stranded.
49. (New): The method of claim 47, wherein the population of cfDNA molecules is between 1 ng and 100 ng.
50. (New): The method of claim 47, wherein the ligation reaction is blunt-end ligation or sticky-end ligation.
51. (New): The method of claim 47, wherein the ligation reaction has a ligation efficiency of more than 30%.

52. (New): The method of claim 47, wherein the ligation reaction has a ligation efficiency of more than 50%.
53. (New): The method of claim 47, wherein the ligation reaction comprises using more than an 80X molar excess of adaptors as compared to the cfDNA molecules.
54. (New): The method of claim 47, wherein the ligation reaction comprises using more than a 100X molar excess of adapters as compared to the cfDNA molecules.
55. (New): The method of claim 47, wherein the ligation reaction has a ligation efficiency of more than 40% and comprises using more than a 60X molar excess of adaptors as compared to the cfDNA molecules.
56. (New): The method of claim 47, wherein the molecular barcodes in the set of molecular barcodes comprise 5 to 100 different molecular barcode sequences that are from 5 to 20 nucleotides in length.
57. (New): The method of claim 47, wherein the cancer-associated genomic regions of interest comprise sequences from one or more genes selected from the group consisting of: ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.
58. (New): The method of claim 47, where selectively enriching the subset of amplified progeny polynucleotides for a plurality of genomic regions of interest comprises using a set of probes that hybridize to the plurality of genomic regions of interest.
59. (New): The method of claim 57, wherein the cancer-associated genomic regions of interest comprise exon sequences.
60. (New): The method of claim 47, further comprising attaching sample identifiers to a plurality of the cell-free nucleic acid molecules in the population or the enriched amplified progeny polynucleotides.

REMARKS

Claims 1-30 were previously pending, but are hereby cancelled without disclaimer or prejudice. Claims 31-60 are newly added. Support for the new claims may be found throughout the application as filed. No new matter is added by these amendments. Thus, claims 31-60 are now pending and ready for examination.

CONCLUSION

Applicant believes that the present application is now in condition for examination and respectfully requests that the Examiner expedite the prosecution of this application to allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: January 22, 2020 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

Electronic Acknowledgement Receipt

EFS ID:	38372823
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	22-JAN-2020
Filing Date:	07-JAN-2020
Time Stamp:	21:15:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2020-01-22_GH0004US-CON3_PA_resubmit.pdf	117681 1c522d7b0d3a4d6cec7dca299b5d772b3d233cdd	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
Warnings:			
Information:			
	Total Files Size (in bytes):	117681	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 01/23/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
BENZION, GARY	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/23/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/672,267	**Applicant(s)** TALASAZ et al.	
	Examiner TERRI S JOHNSON	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 01 November 2019 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to TERRI JOHNSON at (571)272 -2991. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/TERRI S JOHNSON/ Paralegal Specialist, OPET	

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 03/03/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
03/03/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Office Action Summary	Application No. 16/672,267	Applicant(s) TALASAZ et al.	
	Examiner KENNETH R HORLICK	Art Unit 1637	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 31-60 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 31-60 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 11/1/19 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date See Continuation Sheet.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Continuation of Attachment(s) 2) Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date: 12/6/19; 12/6/19; 12/6/19; 12/6/19; 12/6/19; 12/6/19; 12/6/19; 12/6/19

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

NON-PRIOR ART REJECTIONS

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ619 (CCPA 1970); In re Thorington, 418 F.2d 528, 163 USPQ644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(l) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-l.jsp.

3. Claims 31-60 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 9,902,992. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims and the patented claims are related as genus-species. That is, the steps of the instant claims are included within the steps of the patent claims.

4. Claims 31-60 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-21 of U.S. Patent No. 9,920,366. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims and the patented claim are related as genus-species. That is, the steps of the instant claims are included within the steps of the patented claim.

5. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-60 of copending Application No. 16/601,168 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims and the copending claims are related as genus-species. That is, the steps of the instant claims are included within the steps of the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

6. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-60 of copending Application No. 16/714,579 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims and the copending claims are related as obvious species-genus. That is, the 'more than a 30X molar excess' of the instant claims is a clearly suggested species within the genus 'at least a 10X molar excess' of the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

PRIOR ART REJECTION

7. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

8. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 31-60 are rejected under 35 U.S.C. 103 as being unpatentable over Schmitt et al. (US 9,752,188; effective filing date 3/20/12) in view of Deciu et al. (US 2013/0288244; effective filing date 3/14/13), and further in view of Sacko et al. (US 2010/0264331).

These claims are drawn to methods comprising: ligating barcodes to cell-free nucleic acid molecules, using more than a 30X molar excess of barcodes relative to cell-free nucleic acid molecules, wherein at least 20% of said molecules are attached to barcodes; amplifying tagged molecules; and selectively enriching tagged molecules for genomic regions of interest.

Schmitt et al. discloses a method comprising: tagging DNA molecules with a set of tags comprising barcodes; and selectively enriching (amplifying) for tagged strands that map to a region of interest. See columns 5-30, especially column 20, line 39 to column 21, line 25.

Schmitt et al. does not disclose wherein more than a 30X molar excess of adapters/barcodes is used such that at least 20% of molecules are tagged, nor wherein the DNA is cell-free DNA.

Deciu et al. discloses the desirability to optimize ligation of adaptors to both ends of a polynucleotide (see paragraph [1152]).

Sacko et al. discloses detecting cell-free DNA from blood of cancer patients because it comprises DNA having microsatellite mutations and instabilities, which are useful in diagnostics (see paragraph 0005).

One of ordinary skill in the art would have been motivated to modify the method of Schmitt et al. by using more than a 30X molar excess of adapters/barcodes such that at least 20% of nucleic acid molecules are tagged because this would have merely involved routine optimization of known-important reaction parameters, which as well established in U.S. patent practice does not support unobviousness (see M.P.E.P. 2144.05). This is supported by Deciu et al., which discloses the desirability to optimize ligation of adaptors to both ends of a polynucleotide in paragraph [1152]. Ligation reactions were textbook-level subject matter for which the important parameters, such as enzyme and polynucleotide component concentrations, were unarguably known. It is submitted that the further limitations of the dependent claims also fall within the category of routine optimization of known-important reaction parameters. The skilled artisan would have been motivated to modify the method of Schmitt et al. by using cell-free DNA because Sacko et al. disclosed that cell-free DNA may contain somatic genetic variants associated with cancers, and is thus useful in diagnostics. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the application was filed to carry out the claimed methods.

CONCLUSION

9. No claims are free of the prior art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENNETH R HORLICK whose telephone number is (571)272-0784. The examiner can normally be reached on Mon. - Thurs. 8:30 - 6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

02/27/20

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Notice of References Cited	Application/Control No. 16/672,267	Applicant(s)/Patent Under Reexamination TALASAZ et al.	
	Examiner KENNETH R HORLICK	Art Unit 1637	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20100264331-A1	10-2010	Sacko; Mory	G01N21/6428	250/459.1
*	B	US-20130288244-A1	10-2013	DECIU; Cosmin	G16B20/00	435/6.11
	C					
	D					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
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	O					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor name search	02/27/2020	KH
updated parent searches in USPAT and PGPUB	02/27/2020	KH
reviewed parent applications and references therein	02/27/2020	KH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	1	NAWROZ, et al. Microsatellite alterations in serum DNA of head and neck cancer patients. Nat Med. 1996 Sep;2 (9):1035-7.	
	2	NEWMAN, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nat Med. 2014 May;20(5):548-54. doi: 10.1038/nm.3519. Epub 2014 Apr 6.	
	3	NG, S.B., et al., "Targeted capture and massively parallel sequencing of 12 human exomes," Nature 2009, 461(7261), 272-276	
	4	NIELSEN, R. et al. "Genotype and SNP calling from next-generation sequencing data" Nature Reviews Genetics (2011) 12(6):443-451	
	5	NORD, et al. Accurate and exact CNV identification from targeted high-throughput sequence data. BMC Genomics. 2011 Apr 12;12:184.	
	6	Notice of Allowance dated 01/31/2017 for U.S. Patent Application No. 14/712,754.	
	7	Notice of allowance dated 03/21/2014 for US Application No. 12/969,581.	
	8	Notice of allowance dated 06/15/2017 for US Application No.15/076,565.	
	9	Notice of allowance dated 06/19/2014 for US Application No. 12/969,581.	
	10	Notice of allowance dated 08/01/2017 for US Application No. 15/492,659	
	11	Notice of allowance dated 08/04/2017 for US Application No.15/467,570	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	12	Notice of allowance dated 08/22/2014 for US Application No. 12/969,581.	
	13	Notice of allowance dated 08/29/2017 for US Application No. 15/492,659	
	14	Notice of allowance dated 09/11/2017 for US Application No. 15/076,565	
	15	Notice of allowance dated 10/03/2017 for US Application No. 15/076,565.	
	16	Notice of allowance dated 10/25/2017 for US Application No. 14/861,989	
	17	Notice of allowance dated 12/28/2017 for US Application No. 14/861,989.	
	18	Office Action dated 02/09/2017 for U.S. Patent Application No. 15/076,565.	
	19	Office action dated 05/13/2019 for US Application No. 15/669,779.	
	20	Office action dated 05/20/2016 for US Application No. 14/855,301.	
	21	Office action dated 05/31/2016 for US Application No. 14/712,754.	
	22	Office action dated 06/01/2017 for US Application No. 15/467,570	

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	23	Office action dated 06/03/2016 for US Application No. 14/861,989.	
	24	Office action dated 06/12/2017 for US Application No. 15/492,659.	
	25	Office action dated 07/18/2017 for US Application No. 14/861,989	
	26	Office Action dated 07/30/2019 for U.S. Application No. 16/283,635.	
	27	Office action dated 08/06/2019 for US Application No. 14/855,301.	
	28	Office action dated 10/03/2013 for US Application No. 12/969,581.	
	29	Office Action dated 10/12/2016 for U.S. Patent Application No. 14/712,754.	
	30	Office action dated 10/20/2017 for US Application No. 14/425,189.	
	31	Office Action dated 11/21/2016 for U.S. Patent Application No. 14/855,301.	
	32	Office action dated 12/04/2015 for US Application No. 14/712,754.	
	33	Office action dated 12/07/2017 for US Application No. 14/855,301	

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	34	Office Action dated 12/09/2016 for U.S. Patent Application No. 14/861,989.	
	35	Office action dated 12/21/2018 for US Application No. 15/978,848.	
	36	OGINO, et al. Quantification of PCR bias caused by a single nucleotide polymorphism in SMN gene dosage analysis. J Mol Diagn. 2002 Nov;4(4):185-90.	
	37	Opposition Brief dated August 7, 2018 for Japanese Opposition No. 2018-700659 to JP Patent 6275145	X
	38	Opposition Decision dated January 15, 2019 for Japanese Opposition No. 2018-700659 to JP Patent 6275145	☒
	39	Opposition Form and Statement to EP2893040 filed October 2, 2019 by Foundation Medicine Inc.	☐
	40	Opposition Form and Statement to EP2893040 filed October 2, 2019 by Grunecker Patent-und Rechtsanwalte PartG mbB	☐
	41	Opposition Form and Statement to EP2893040 filed October 2, 2019 by Personal Genome Diagnostics, Inc.	☐
	42	Opposition Form and Statement to EP2893040 filed October 2, 2019 by Strawman Limited	☐
	43	Opposition Form and Statement to EP3087204 filed November 14, 2018	☐
	44	Pacific Biosciences. Template Preparation and Sequencing Guide. Publication date: 2014-10-14. Pacific Biosciences website http://www.pacificbiosciences.com/support/pubmap/documentation.html.	☐

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	45	PAN, et al. Loss of heterozygosity patterns provide fingerprints for genetic heterogeneity in multistep cancer progression of tobacco smoke-induced non-small cell lung cancer. Cancer Res. 2005 Mar 1;65(5):1664-9.	☐
	46	PARK, et al. Discovery of common Asian copy number variants using integrated high-resolution array CGH and massively parallel DNA sequencing. Nat Genet. 2010 May;42(5):400-5. doi: 10.1038/ng.555. Epub 2010 Apr 4.	☐
	47	PARKINSON, N.J. et al., "Preparation of high-quality next-generation sequencing libraries from picogram quantities of target DNA," Genome Res. 2012, 22(1), 125-133	☐
	48	PEL, J. et al. "Duplex proximity sequencing (pro-seq): A method to improve DNA sequencing accuracy without the cost of molecular barcoding redundancy" bioRxiv (2017) https://doi.org/10.1101/163444	☐
	49	PERAKIS, S. et al. "Advances in Circulating Tumor DNA Analysis" Adv Clin Chem (2017) pp 1-81	☐
	50	PIHLAK, et al. Rapid genome sequencing with short universal tiling probes. Nature Biotechnology, 26: 676-684 (2008).	☐

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CERTIFICATION STATEMENT

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Examiner Name	
Attorney Docket Number	42534-708.304

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	1	Guardant Health vs. FMI Invalidity Exhibit C-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	2	Guardant Health vs. FMI Invalidity Exhibit C-4, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	3	Guardant Health vs. FMI Invalidity Exhibit C-5, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	4	Guardant Health vs. FMI Invalidity Exhibit D-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	5	Guardant Health vs. FMI Invalidity Exhibit D-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	6	Guardant Health vs. FMI Invalidity Exhibit D-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	7	Guardant Health vs. FMI Invalidity Exhibit D-5, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	8	Guardant Health vs. FMI Second Amended Complaint dated March 6, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	9	Guardant Health vs. FMI Suppl Invalidity References dated February 15, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	10	Guardant Health vs. FMI Supplemental Invalidity Contentions dated March 29, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	11	Guardant Health vs. PGDx Amended Answer to Second Amended Complaint dated April 30, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	

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	12	Guardant Health vs. PGDx Invalidity Claim Chart A, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	13	Guardant Health vs. PGDx Invalidity Claim Chart B, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	14	Guardant Health vs. PGDx Invalidity Claim Chart C, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	15	Guardant Health vs. PGDx Invalidity Claim Chart D, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	16	Guardant Health vs. PGDx Invalidity Claim Chart E, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	17	Guardant Health vs. PGDx Invalidity Claim Chart F, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
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	36	HIATT, et al. Single molecule molecular inversion probes for targeted, high-accuracy detection of low-frequency variation. Genome Res. 2013 May;23(5):843-54. doi: 10.1101/gr.147686.112. Epub 2013 Feb 4.	
	37	HIBI, et al. Molecular detection of genetic alterations in the serum of colorectal cancer patients. Cancer Res. 1998 Apr 1;58(7):1405-7.	
	38	HiSeq 2000 User Guide (2010)	
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	45	HUG, et al. Measurement of the number of molecules of a single mRNA species in a complex mRNA preparation. J Theor Biol. 2003 Apr 21;221(4):615-24.
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	50	Illumina "Preparing Samples for Paired-End Sequencing (2008)

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
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Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

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	1	2013159035	WO	A2	2013-10-24	Mitchell et al.		
	2	2013173394	WO	A2	2013-11-21	Wang et al.		
	3	2013181170	WO	A1	2013-12-05	OTWINOWSKI et al.	Entire Document	

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	4	2013188471	WO	A2	2013-12-19	Faham et al.		
	5	2013190441	WO	A2	2013-12-27	CHIU et al.	Entire Document	
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	9	2014039556	WO	A1	2014-03-13	TALASAZ et al.	Entire Document	
	10	2014093330	WO	A1	2014-06-19	Raymond et al.		
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	12	2014149134	WO	A2	2014-09-25	TALASAZ et al.	Entire Document	
	13	2014151117	WO	A1	2014-09-25	Diehn et al.	Entire Document	
	14	2014152990	WO	A1	2014-09-25	SPENCE et al.		

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	15	2015159293	WO	A2	2015-10-22	DOR et al.	Entire Document	
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	38	Guardant Health vs. FMI 1st Amended Answer to Second Amended Complaint dated May 6, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	39	Guardant Health vs. FMI Invalidity Contentions dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	40	Guardant Health vs. FMI Invalidity Exhibit A-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	41	Guardant Health vs. FMI Invalidity Exhibit A-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	42	Guardant Health vs. FMI Invalidity Exhibit A-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	43	Guardant Health vs. FMI Invalidity Exhibit A-8, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	44	Guardant Health vs. FMI Invalidity Exhibit B-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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	49	Guardant Health vs. FMI Invalidity Exhibit C-11, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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Art Unit	
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/672,267	01/07/2020	435	1637	42534-708.304

APPLICANTS
GUARDANT HEALTH, INC., Redwood City, CA;

INVENTORS
AmirAli TALASAZ, Atherton, CA;
Stetanie Ann Ward Mortimer, Moraao.Hjji, CA;

**** CONTINUING DATA ***************************

This application is a CON of 16/601,168 10/14/2019 *
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
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Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ☑ No Verified and Acknowledged /KENNETH R HORLICK/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2019-11-01
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

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	1	INGOLIA, et al. Genome-wide analysis in vivo of translation with nucleotide resolution using ribosome profiling. Science. 2009 Apr 10;324(5924):218-23. Epub 2009 Feb 12.	
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	Attorney Docket Number	42534-708.304

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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	Filing Date	2019-11-01
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-12-06
Name/Print	Timothy A. Hott	Registration Number	67740

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304

CONFIRMATION NO. 3448

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

PUBLICATION NOTICE

OC000000116286435

Title:METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Publication No.US-2020-0115746-A1
Publication Date:04/16/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/672,267	Filing Date 01/07/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/07/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
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This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): ELTOUKHY et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: 1637 Examiner: Kenneth R. HORLICK

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Sir:

This paper is in response to the Office Action mailed on March 3, 2020. The shortened statutory period for reply expires June 3, 2020, therefore, this response is timely filed. Applicants respectfully request reconsideration of the above-referenced application in view of the following remarks:

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. – 60. (Cancelled).

61. (New): A method, comprising:

(a) providing a population of cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) tagging a plurality of the cfDNA molecules in the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein the duplex tags are attached at both ends of a molecule of the cfDNA molecules;

(c) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and

(e) reducing and/or tracking redundancy in the set of sequence reads to generate a plurality of consensus sequences representative of original cfDNA molecules from among the tagged parent polynucleotides, wherein the plurality of consensus sequences are generated from (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides or (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides.

62. (New): The method of claim 61, wherein the sample is obtained from a subject having cancer.

63. (New): The method of claim 61, wherein the plurality of cfDNA molecules comprises 1 nanogram (ng) to 100 ng of cfDNA molecules.

64. (New): The method of claim 61, wherein the molecular barcodes are ligated to the cfDNA molecules using more than a 10X molar excess of duplex tags as compared to the cfDNA molecules.

65. (New): The method of claim 64, wherein at least 20% of the cfDNA molecules from the sample are tagged with the duplex tags.

66. (New): The method of claim 61, wherein tagging comprises non-uniquely tagging the plurality of the cfDNA molecules with the set of duplex tags comprising molecular barcodes from the set of molecular barcodes, wherein the cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 and fewer than a number of cfDNA molecules that map to the mappable base position

67. (New): The method of claim 61, wherein the molecular barcodes in the set of molecular barcodes have predetermined sequences.

68. (New): The method of claim 61, wherein the molecular barcodes in the set of molecular barcodes have 5 to 10,000 different molecular barcode sequences and are 5 to 20 base pairs in length.

69. (New): The method of claim 61, further comprising enriching the amplified progeny polynucleotides for target regions of interest prior to sequencing.

70. (New): The method of claim 69, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1,

CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

71. (New): The method of claim 61, further comprising amplifying a plurality of the enriched progeny polynucleotides prior to sequencing.

72. (New): The method of claim 61, wherein the molecular barcodes are part of sequencing adapters.

73. (New): The method of claim 72, wherein the adapter is a Y-shaped adapter.

74. (New): The method of claim 61, wherein reducing and/or tracking redundancy in the set of sequence reads comprises mapping a plurality of the sequence reads to a reference sequence.

75. (New): The method of claim 61, further comprising:

(f) determining quantitative measures of at least two of (i) paired reads, (ii) unpaired reads, (iii) read depth of the paired reads and (iv) read depth of the unpaired reads.

76. (New): The method of claim 75, further comprising:

(g) estimating with a programmed computer processor a quantitative measure of total cfDNA molecules based on said quantitative measures of at least two of (i) paired reads, (ii) unpaired reads, (iii) read depth of the paired reads and (iv) read depth of the unpaired reads.

77. (New): The method of claim 76, wherein (f) comprises determining quantitative measures of paired reads and unpaired reads, and wherein in (g), the quantitative measure of total cfDNA molecules is determined based on the quantitative measures of paired reads and unpaired reads.

78. (New): A method, comprising:

(a) providing a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) non-uniquely tagging a plurality of the double-stranded cfDNA molecules in the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce non-uniquely tagged parent polynucleotides,

wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at

least 2 and fewer than a number of double-stranded cfDNA molecules that map to the mappable base position;

(c) amplifying a plurality of the non-uniquely tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads;

(e) reducing and/or tracking redundancy in the set of sequence reads;

(f) sorting sequence reads into paired reads and unpaired reads, wherein (i) a paired read corresponds to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides, and (ii) an unpaired read corresponds to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides; and

(g) determining quantitative measures of at least two of (i) paired reads, (ii) unpaired reads, (iii) read depth of the paired reads and (iv) read depth of the unpaired reads; and

79. (New): The method of claim 78, wherein the sample is blood, plasma, or serum.

80. (New): The method of claim 78, wherein the plurality of double-stranded cfDNA molecules comprises 1 nanogram (ng) to 100 ng of double-stranded cfDNA molecules.

81. (New): The method of claim 78, wherein the tagging comprises ligating the molecular barcodes to double-stranded cfDNA molecules.

82. (New): The method of claim 78, wherein the molecular barcodes in the set have 2 to 10,000 different molecular barcode sequences.

83. (New): The method of claim 78, wherein the molecular barcodes in the set have 5 to 10,000 different molecular barcode sequences and are 5 to 20 base pairs in length.

84. (New): The method of claim 78, further comprising enriching the amplified progeny polynucleotides for target regions of interest prior to sequencing.

85. (New): The method of claim 84, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN,

RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

86. (New): The method of claim 78, further comprising amplifying a plurality of the enriched progeny polynucleotides prior to sequencing.

87. (New): The method of claim 78, wherein reducing and/or tracking redundancy in the set of sequence reads comprises collapsing a plurality of the sequence reads to generate consensus sequences representative of original double-stranded cfDNA molecules from among the non-uniquely tagged parent polynucleotides.

88. (New): The method of claim 87, further comprising mapping a plurality of the sequence reads and/or consensus sequences to a reference sequence.

89. (New): The method of claim 78, further comprising:

(h) estimating with a programmed computer processor a quantitative measure of total double-stranded polynucleotide molecules based on said quantitative measures of at least two of (i) paired reads, (ii) unpaired reads, (iii) read depth of the paired reads and (iv) read depth of the unpaired reads.

90. (New): The method of claim 89, wherein (g) comprises determining quantitative measures of paired reads and unpaired reads, and wherein in (h), the quantitative measure of total double-stranded cfDNA molecules is determined based on the quantitative measures of paired reads and unpaired reads.

REMARKS

Claims 31-60 were pending prior to entry of the above-referenced claim amendments, but are hereby cancelled without disclaimer or prejudice. Claims 61-90 have been newly added, support for which may be found throughout the application as published, for example, at least at paragraphs [0061], [0113], [0117], [0133], [0171], [0199], [0208], [0236], [0261]. No new matter is added by these amendments. Accordingly, claims 61-90 are now pending and set for examination.

I. Nonstatutory Double Patenting Rejection

Claims 31-60 were rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-33 of U.S. Patent No. 9,902,992. Claims 31-60 were rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-21 of U.S. Patent No. 9,920,366. Claims 31-60 were provisionally rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 31-60 of copending Application No. 16/601,168. Claims 31-60 were provisionally rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 31-60 of copending Application No. 16/714,579.

Without conceding in the basis of the rejections, Applicant has cancelled claims 31-60. Accordingly, the nonstatutory double patenting rejections to claims 31-60 are moot in view of the cancellation of these claims.

II. Prior Art Rejection— 35 U.S.C. §103

Claims 31-60 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Schmitt et al. (U.S. 9,752,188) in view of Deciu et al. (U.S. 2013/0288244) and further in view of Sacko et al. (U.S. 2010/0264331).

Without conceding in the basis of the rejection, Applicant has cancelled claims 31-60. Accordingly, the 35 U.S.C. §103 rejection to claims 31-60 is moot in view of the cancellation of these claims.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or cancelled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

This paper fully addresses the rejections raised in the Office Action mailed February 18, 2020. Applicant believes that the present application is now in condition for allowance and respectfully requests that the Examiner expedite the prosecution of this application to allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. 708.304/GH0004US-CON3).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: May 7, 2020 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

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505 Penobscot Drive
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	1637
Filing Date:	November 1, 2019	Examiner:	Kenneth R. HORLICK
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $240.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON3).

Respectfully submitted,

Dated: May 7, 2020

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
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PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	1	CLARK, T.A. et al. "Analytical Validation of a Hybrid Capture Based Next-Generation Sequencing Clinical Assay for Genomic Profiling of Cell-Free Circulating Tumor DNA," J. Mol. Diagnostics (2018) 20(5):686-702	
	2	PAWELETZ, C.P. et al. "Bias-corrected targeted next-generation sequencing for rapid, multiplexed detection of actionable alterations in cell-free DNA from advanced lung cancer patients" Clin Canc Res (2016) 22(4):915-922	
	3	PHALLEN, J. et al. "Direct detection of early-stage cancers using circulating tumor DNA" Sci Trans Med (2017) Vol. 9, Issue 403, eaan2415DOI: 10.1126/scitranslmed.aan2415	
	4	SHIROGUCHI, et al. Digital RNA sequencing minimizes sequence-dependent bias and amplification noise with optimized single-molecule barcodes. Proc Natl Acad Sci U S A. 2012 Supplemental Information (8 pages)	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-05-07
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	39383196
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	07-MAY-2020
Filing Date:	07-JAN-2020
Time Stamp:	17:45:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$240
RAM confirmation Number	E202057H46091604
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00408

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2020-05-07_GH0004US-CON3_OA1Response.pdf	124425 ba0c243b0b65892b5d4822369509cd337ab8e88c	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	8

Warnings:

Information:

2	Transmittal Letter	2020-05-07_GH0004US-CON3_IDSTrans.pdf	144796 111b20283b108f4801b9e5fb26ec3891473298fa	no	4

Warnings:

Information:

3	Information Disclosure Statement (IDS) Form (SB08)	2020-05-07_GH0004US-CON3_SB08.pdf	1053645 abd8dffa53d95337bae7fb70cbfb7a89da97b8eb	no	4

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

4	Non Patent Literature	CLARK_JMolDiag_2018_686-702pdf.pdf	3158287 a0919e0ddb3ec5f7ca0f3bb3ae016a43ad3b2eae	no	17

Warnings:

Information:

5	Non Patent Literature	PAWELETZ_ClinCancRes_2017_915-922.pdf	464079 c369c3784c7b07ce8e0a55ee7d5c9373f45dbcfa	no	16
Warnings:					
Information:					
6	Non Patent Literature	Phallen_SciTranslMed_2017.pdf	2398204 aaf91fd1b3e2177ce9a1fc5427081c5a67d4cce6	no	13
Warnings:					
Information:					
7	Non Patent Literature	SHIROGUCHI_PNAS_2012_SupplInfo.pdf	667103 3563ff1f6c63079ada69be1a2ffaca1ba5cb9bef	no	8
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30410 51263f95333b2101e2138a15f27a3a2dffe9f813	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	8040949	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	10287631	B2	2019-05-14	Salk et al.	Entire Document
	2	10370713	B2	2019-08-06	Salk et al.	Entire Document
	3	10385393	B2	2019-08-20	Salk et al.	Entire Document
	4	10388403	B2	2019-08-20	Rava et al.	Entire Document
	5	10604804	B2	2020-03-31	Salk et al.	Entire Document

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20190271040	A1	2019-09-05	Salk et al.	Entire Document

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	2	20190292597	A1	2019-09-26	Salk et al.	Entire Document
	3	20190338358	A1	2019-11-07	Salk et al.	Entire Document
	4	20190352714	A1	2019-11-21	Salk et al.	Entire Document

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	KAMPS-HUGHES, N. et al. "ERASE-Seq: Leveraging replicate measurements to enhance ultralow frequency variant detection in NGS data"PLOS One (2018)	
	2	LENNON, N.J. et al. "Technological considerations for genome-guided diagnosis and management of cancer" Gen Med (2016) 8:112	
	3	MISHRA, S. et al. "Different Facets of Copy Number Changes: Permanent, Transient, and Adaptive" Mol Cell Biol (2016) 36(7):1050-1063	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	4	MOENCH, S. "Genomic Profiling Using Guardant 360 Cell-Free DNA-Based Assay vs Tumor-Based Genotyping Assays in Advanced NSCLC, CANCER THERAPY ADVISOR (Feb. 28, 2019), https://www.cancertherapyadvisor.com/home/news/conferencecoverage/american-association-for-cancer-research-aacr/aacr-2019/genomic-profiling-using-guardant-360-cell-free-dna-based assay-vs-tumor-based-genotyping-assays-in-advanced-nsclc/ (lastaccessed Nov. 30, 2019)
	5	NEWMAN, A. et al. "Integrated digital error suppression for improved detection of circulating tumor DNA" Nature Biotech (2016) 34(5):547-555
	6	ODEGAARD, J.I. et al. "Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies" Clin Canc Res (2018) 24(15):3539-3549
	7	OU, SHI et al. "Liquid Biopsy to Identify Actionable Genomic Alterations" Am Soc Clin Onc (2018) 978
	8	SATHIRAPONGSASUTI, J.F. et al. "Exome sequencing-based copy-number variation and loss of heterozygosity detection: ExomeCNV" BioInformatics (2011) 27(19):2648-2654
	9	TRAPNELL, C. et al. "How to map billions of short reads onto genomes" Nature Biotech (2009) 27(5):455-457
	10	VAN LOO, P. et al. "Allele-specific copy number analysis of tumors" PNAS (2010) 107(39):16910-16915
	11	WANG, T.T. et al. "High efficiency error suppression for accurate detection of low-frequency variants" NAR (2019) 47 (15):

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-06-03
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	39613340
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	03-JUN-2020
Filing Date:	07-JAN-2020
Time Stamp:	13:37:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$240
RAM confirmation Number	E202063D37212543
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00418

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2020-06-03_GH0004US-CON3_IDSTrans.pdf	144204 e06eb1dbd3f3fe56163527ccbbc8a0b14dc03975	no	4
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	2020-06-03_GH0004US-CON3_SB08.pdf	1054672 42c31603c56b61e7ffe8d384a20438630eca37e4	no	5
Warnings:					
Information:					
3	Non Patent Literature	KAMPS-HUGHES_PLOSOne_2018.pdf	5707894 ea4d5cf7239d69ce8d4cdfae92b25404809533e1	no	18
Warnings:					
Information:					
4	Non Patent Literature	LENNON_GenMed_2016_112.pdf	689512 67e86d14248058462070 40bcbbef63ab7e600b00	no	10
Warnings:					
Information:					
5	Non Patent Literature	MISHRA_MCB_2016_1050-1063.pdf	1216913 5f63e365b9b13c1c13c502d1372bc57258b43782	no	14
Warnings:					
Information:					
6	Non Patent Literature	MOENCH_CancTherAdv_2019.pdf	640654 cbedcb9c9350ebc56dce20b0e103f70bf26863c3	no	3
Warnings:					
Information:					

7	Non Patent Literature	NEWMAN_NatMed_2014_547-555.pdf	1377423 69ec2aa88500b798bf011f81a5bfe5b8de41be93	no	9
Warnings:					
Information:					
8	Non Patent Literature	ODEGAARD_ClinCancRes_2018_3539-3549.pdf	1062206 cb51a9f4833c005db46554e71fa08573f616a364	no	11
Warnings:					
Information:					
9	Non Patent Literature	OU_ACSO_2018_978-997.pdf	664167 dde74d5088588343da8b04ede4fcf58466ae171e	no	20
Warnings:					
Information:					
10	Non Patent Literature	Sathirapongsasuti_BioInformatics_2011.pdf	484289 78ff01d10aa50d956f5f7a931c727355df943f9e	no	7
Warnings:					
Information:					
11	Non Patent Literature	TRAPNELL_NatBiotech_2009_455-457.pdf	183342 8d9e4daf2d810f2b71651c6febd734337a82b52a	no	3
Warnings:					
Information:					
12	Non Patent Literature	VAN_LOO_PNAS_2010_16910-16915.pdf	2450725 77581bb7574de0bfab9474778d4b67be852c428a	no	6
Warnings:					
Information:					
13	Non Patent Literature	WANG_NAR_2019.pdf	735593 e5227ff4b8dcb4d907196ad89e55c94d3b43e356	no	11
Warnings:					
Information:					

14	Fee Worksheet (SB06)	fee-info.pdf	30410 496f0ef13035176d1488eae55026c234d12f21d8	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	16442004

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	1637
Filing Date:	November 1, 2019	Examiner:	Kenneth R. HORLICK
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $240.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON3).

Respectfully submitted,

Dated: June 3, 2020

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 07/14/2020
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/14/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Office Action Summary	Application No. 16/672,267	Applicant(s) TALASAZ et al.	
	Examiner KENNETH R HORLICK	Art Unit 1637	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 05/07/20.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 61-90 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 61-90 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 5/7/20;6/3/20.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

NEW GROUNDS OF OBJECTION AND REJECTION NECESSITATED BY THE AMENDMENT

2. Claim 66 is objected to because of the following informality: it lacks a period at the end. Correction is required.

3. The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71, 73, and 78-90 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

A) Claims 71 and 86 are indefinite because 'the enriched progeny polynucleotides' lacks proper antecedent basis. Correction is required.

B) Claim 73 is indefinite because 'the adapter' lacks proper antecedent basis. Correction is required.

C) Claims 78-90 are confusing because independent claim 78 lacks a period at the end, and it is unclear if intended text is missing at the end. Correction is required.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

5. Claims 61-90 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 2 of U.S. Patent No. 9,920,366. Although the claims at issue are not identical, they are not patentably distinct from each other because the patented claim and the instant claims are related as species-genus. That is, the steps of the instant claims, including analysis of paired reads and unpaired reads, are included in the steps of the patented claim.

6. Claims 61-90 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31, 33-41, 47-49, 51, 57-59, and 61-71 of copending Application No. 16/601,168 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the copending claims and the instant claims are related as species-genus. That is, the steps of the instant claims, including analysis of paired reads and unpaired reads, are included in the steps of the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

7. Claims 61-90 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 54-73 of copending Application No. 15/892,178 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the copending claims and the instant claims are related as species-genus. That is, the steps of the instant claims, including analysis of paired reads and unpaired reads, are included in the steps of the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

CONCLUSION

8. Claims 61-90 are free of the prior art, but are rejected for other reasons. No claims are allowable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENNETH R HORLICK whose telephone number is (571)272-0784. The examiner can normally be reached on Mon. - Thurs. 8:30 - 6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

07/08/20

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor name search	02/27/2020	KH
updated parent searches in USPAT and PGPUB	02/27/2020	KH
reviewed parent applications and references therein	02/27/2020	KH
updated in USPAT and PGPUB	07/08/2020	KH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

/K.R.H/	1	CLARK, T.A. et al. "Analytical Validation of a Hybrid Capture Based Next-Generation Sequencing Clinical Assay for Genomic Profiling of Cell-Free Circulating Tumor DNA," J. Mol. Diagnostics (2018) 20(5):686-702
/K.R.H/	2	PAWELETZ, C.P. et al. "Bias-corrected targeted next-generation sequencing for rapid, multiplexed detection of actionable alterations in cell-free DNA from advanced lung cancer patients" Clin Canc Res (2016) 22(4):915-922
/K.R.H/	3	PHALLEN, J. et al. "Direct detection of early-stage cancers using circulating tumor DNA" Sci Trans Med (2017) Vol. 9, Issue 403, eaan2415DOI: 10.1126/scitranslmed.aan2415
/K.R.H/	4	SHIROGUCHI, et al. Digital RNA sequencing minimizes sequence-dependent bias and amplification noise with optimized single-molecule barcodes. Proc Natl Acad Sci U S A. 2012 Supplemental Information (8 pages)

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	07/06/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-05-07
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	10287631	B2	2019-05-14	Salk et al.	Entire Document
/K.R.H/	2	10370713	B2	2019-08-06	Salk et al.	Entire Document
/K.R.H/	3	10385393	B2	2019-08-20	Salk et al.	Entire Document
/K.R.H/	4	10388403	B2	2019-08-20	Rava et al.	Entire Document
/K.R.H/	5	10604804	B2	2020-03-31	Salk et al.	Entire Document

If you wish to add additional U.S. Patent citation information please click the Add button. Add

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	20190271040	A1	2019-09-05	Salk et al.	Entire Document

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

/K.R.H/	2	20190292597	A1	2019-09-26	Salk et al.	Entire Document	
/K.R.H/	3	20190338358	A1	2019-11-07	Salk et al.	Entire Document	
/K.R.H/	4	20190352714	A1	2019-11-21	Salk et al.	Entire Document	

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/K.R.H/	1	KAMPS-HUGHES, N. et al. "ERASE-Seq: Leveraging replicate measurements to enhance ultralow frequency variant detection in NGS data"PLOS One (2018)	
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/K.R.H/	3	MISHRA, S. et al. "Different Facets of Copy Number Changes: Permanent, Transient, and Adaptive" Mol Cell Biol (2016) 36(7):1050-1063	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

/K.R.H/	4	MOENCH, S. "Genomic Profiling Using Guardant 360 Cell-Free DNA-Based Assay vs Tumor-Based Genotyping Assays in Advanced NSCLC, CANCER THERAPY ADVISOR (Feb. 28, 2019), https://www.cancertherapyadvisor.com/home/news/conferencecoverage/american-association-for-cancer-research-aacr/aacr-2019/genomic-profiling-using-guardant-360-cell-free-dna-based assay-vs-tumor-based-genotyping-assays-in-advanced-nsclc/ (lastaccessed Nov. 30, 2019)
/K.R.H/	5	NEWMAN, A. et al. "Integrated digital error suppression for improved detection of circulating tumor DNA" Nature Biotech (2016) 34(5):547-555
/K.R.H/	6	ODEGAARD, J.I. et al. "Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies" Clin Canc Res (2018) 24(15):3539-3549
/K.R.H/	7	OU, SHI et al. "Liquid Biopsy to Identify Actionable Genomic Alterations" Am Soc Clin Onc (2018) 978
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/K.R.H/	9	TRAPNELL, C. et al. "How to map billions of short reads onto genomes" Nature Biotech (2009) 27(5):455-457
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/K.R.H/	11	WANG, T.T. et al. "High efficiency error suppression for accurate detection of low-frequency variants" NAR (2019) 47 (15):

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EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	07/06/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-06-03
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): ELTOUKHY et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: 1637 Examiner: Kenneth R. HORLICK

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Sir:

This communication is in response to the Final Office Action mailed on July 14, 2020. The shortened statutory period for reply expires October 14, 2020, therefore, this response is timely filed. Applicant respectfully requests reconsideration of the above-referenced application in view of the following remarks:

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. – 60. (Cancelled).

61. (Currently Amended): A method, comprising:

(a) providing a population of cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) tagging a plurality of the cfDNA molecules [[in]] of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein [[the]] duplex tags from the set of duplex tags are attached at both ends of a molecule of the plurality of the cfDNA molecules;

(c) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and

(e) reducing [[and/]]or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes to generate a plurality of consensus sequences representative of original cfDNA molecules from among the tagged parent polynucleotides, wherein the plurality of consensus sequences [[are]] is generated from (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides, or (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides.

62. (Currently Amended): The method of claim 61, wherein the population of cfDNA molecules is obtained or derived from a sample ~~is obtained~~ from a subject having cancer.

63. (Currently Amended): The method of claim 61, wherein the plurality of cfDNA molecules comprises between 1 nanogram (ng) [[to]] and 100 ng of cfDNA molecules.

64. (Currently Amended): The method of claim 61, wherein the ~~molecular barcodes~~ duplex tags are ligated to the plurality of the cfDNA molecules using more than a 10X ~~molar~~ excess of duplex tags as compared to the population of cfDNA molecules.

65. (Currently Amended): The method of claim 64, wherein at least 20% of the cfDNA molecules [[from]] of the population ~~sample~~ are tagged with the duplex tags.

66. (Currently Amended): The method of claim 61, wherein the tagging comprises non-uniquely tagging the plurality of the cfDNA molecules with the set of duplex tags comprising molecular barcodes from the set of molecular barcodes, wherein the cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 [[and]] to fewer than a number of the cfDNA molecules that map to the mappable base position.

67. (Currently Amended): The method of claim 61, wherein the molecular barcodes [[in]] of the set of molecular barcodes have pre-determined sequences.

68. (Currently Amended): The method of claim 61, wherein the molecular barcodes [[in]] of the set of molecular barcodes have between 5 [[to]] and 10,000 different molecular barcode sequences and [[are]] have a length of between 5 [[to]] and 20 base pairs ~~in length~~.

69. (Currently Amended): The method of claim 61, further comprising enriching a plurality of the amplified progeny polynucleotides for target regions of interest prior to the sequencing to produce enriched progeny polynucleotides.

70. (Previously Presented): The method of claim 69, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1,

BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

71. (Currently Amended): The method of claim 69 [[61]], further comprising amplifying a plurality of the enriched progeny polynucleotides prior to the sequencing.

72. (Currently Amended): The method of claim 61, wherein the ~~molecular barcodes~~ duplex tags of the set of duplex tags are part of sequencing adapters.

73. (Currently Amended): The method of claim 72, wherein the sequencing adapters [[is a]] are Y-shaped adapters.

74. (Currently Amended): The method of claim 61, wherein the reducing [[and/]]or tracking redundancy in the set of sequence reads comprises mapping a plurality of the sequence reads to a reference sequence.

75. (Currently Amended): The method of claim 61, further comprising:

(f) determining quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads at one or more loci of a reference sequence.

76. (Currently Amended): The method of claim 75, further comprising:

(g) estimating with a programmed computer processor a quantitative measure of tagged parent polynucleotides ~~total cfDNA molecules~~ based at least in part on [[said]] the quantitative measures of the at least two of (i) the paired reads, (ii) the unpaired reads, (iii) the read depth of the paired reads, and (iv) the read depth of the unpaired reads at each of the one or more loci.

77. (Currently Amended): The method of claim 76, wherein (f) comprises determining quantitative measures of the paired reads and the unpaired reads, and wherein in (g), the quantitative measures of the tagged parent polynucleotides ~~total cfDNA molecules~~ is determined based at least in part on the quantitative measures of the paired reads and the unpaired reads.

78. (Currently Amended): A method, comprising:

(a) providing a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) non-uniquely tagging a plurality of the double-stranded cfDNA molecules [[in]] of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce non-uniquely tagged parent polynucleotides,

wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 [[and]] to fewer than a number of the double-stranded cfDNA molecules that map to the mappable base position;

(c) amplifying a plurality of the non-uniquely tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads;

(e) reducing [[and/]]or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes;

(f) sorting the set of sequence reads into paired reads and unpaired reads, wherein (i) a paired read corresponds to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides, and (ii) an unpaired read corresponds to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides; and

(g) determining, at one or more loci of a reference sequence, quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads. [[; and]]

79. (Currently Amended): The method of claim 78, wherein the population of double-stranded cfDNA molecules is obtained or derived from a sample from a subject having cancer~~is blood, plasma, or serum~~.

80. (Currently Amended): The method of claim 78, wherein the plurality of double-stranded cfDNA molecules comprises between 1 nanogram (ng) [[to]] and 100 ng of double-stranded cfDNA molecules.

81. (Currently Amended): The method of claim 78, wherein the non-uniquely tagging comprises ligating the ~~molecular barcodes~~ duplex tags to the plurality of the double-stranded cfDNA molecules.

82. (Currently Amended): The method of claim 78, wherein the molecular barcodes [[in]] of the set of molecular barcodes have between 2 [[to]] and 10,000 different molecular barcode sequences.

83. (Currently Amended): The method of claim 78, wherein the molecular barcodes [[in]] of the set of molecular barcodes have between 5 [[to]] and 10,000 different molecular barcode sequences and [[are]] have a length of between 5 [[to]] and 20 base pairs ~~in length~~.

84. (Currently Amended): The method of claim 78, further comprising enriching a plurality of the amplified progeny polynucleotides for target regions of interest prior to the sequencing to produce enriched progeny polynucleotides.

85. (Previously Presented): The method of claim 84, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

86. (Currently Amended): The method of claim 84 [[78]], further comprising amplifying a plurality of the enriched progeny polynucleotides prior to the sequencing.

87. (Currently Amended): The method of claim 78, wherein reducing [[and/]]or tracking redundancy in the set of sequence reads comprises collapsing a plurality of the sequence reads to generate consensus sequences representative of original double-stranded cfDNA molecules from among the non-uniquely tagged parent polynucleotides.

88. (Currently Amended): The method of claim 87, further comprising mapping a plurality of the set of sequence reads and/or the consensus sequences to a reference sequence.

89. (Currently Amended): The method of claim 78, further comprising:

(h) estimating with a programmed computer processor a quantitative measure of non-uniquely tagged parent polynucleotides ~~total double-stranded polynucleotide molecules~~ based at least in part on [[said]] the quantitative measures of the at least two of (i) the paired reads, (ii) the unpaired reads, (iii) the read depth of the paired reads, and (iv) the read depth of the unpaired reads at each of the one or more loci.

90. (Currently Amended): The method of claim 89, wherein (g) comprises determining quantitative measures of the paired reads and the unpaired reads, and wherein in (h), the quantitative measure of the non-uniquely tagged parent polynucleotides ~~total double-stranded cfDNA molecules~~ is determined based at least in part on the quantitative measures of the paired reads and the unpaired reads.

REMARKS

Claims 61-90 were pending prior to entry of the above-referenced claim amendments. Claims 61-69, 71-84, and 86-90 are amended herein to correct minor formalities including antecedent basis. Support for these amendments can be found throughout the specification as filed, for example, at least at paragraphs [0061] and [0206]. No new matter is being introduced by any of these claim amendments.

I. Claim Objection

Claim 66 was objected to because of the following informality: it lacks a period at the end. Applicant has amended claim 66 herein to address the error. No new matter is being introduced.

II. Rejection under 35 U.S.C. §112 (b)

Claims 71, 73, and 78-90 were rejected under 35 U.S.C. §112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Without conceding in the basis of the rejection and solely to advance prosecution, Applicant has amended claims 69, 71, 84, and 86 herein to provide proper antecedent basis for "the enriched progeny polynucleotides." Further, Applicant has amended claim 73 herein to provide proper antecedent basis for "the adapter." Further, Applicant has amended claim 78 herein to add a period at the end and remove unintended text.

Accordingly, Applicant respectfully requests that this rejection be withdrawn.

III. Nonstatutory Double Patenting Rejection

Claims 61-90 were rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claim 2 of U.S. Patent No. 9,920,366. Claims 61-90 were provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 31, 33-41, 47-49, 51, 57-59, and 61-71 of copending Application No. 16/601,168, and over claims 54-73 of copending Application No. 15/892,178.

Without conceding in the basis of the rejection and solely to advance prosecution, Applicant submits herewith a terminal disclaimer over U.S. Patent No. 9,920,366, Application No. 16/601,168, and Application No. 15/892,178.

Accordingly, Applicant respectfully requests that this rejection be withdrawn.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or cancelled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

This paper fully addresses the rejections raised in the Office Action mailed July 14, 2020. Applicant believes that the present application is now in condition for allowance and respectfully requests that the Examiner expedite the prosecution of this application to allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: August 5, 2020 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

Electronic Acknowledgement Receipt

EFS ID:	40206256
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	05-AUG-2020
Filing Date:	07-JAN-2020
Time Stamp:	19:02:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2020-08-05_GH004US-CON3_FOAResponse.pdf	138645 b6632872490b2f12aaaa77e460955e55ed41ad99	yes	9

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	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	7
	Applicant Arguments/Remarks Made in an Amendment	8	9
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	16672267
Filing Date	07-Jan-2020
First Named Inventor	AmirAli TALASAZ
Attorney Docket Number	42534-708.304
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
GUARDANT HEALTH, INC.	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16601168 filed on 10/14/2019

15892178 filed on 02/08/2018

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

9920366

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

( ) Small Entity

( ) Micro Entity

(●) Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

(●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 67740

( ) A sole inventor

( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

( ) A joint inventor; all of whom are signing this request

Signature	/Timothy A. Hott/ 00454

Name	Timothy A. Hott

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16672267

Filing Date: 07-Jan-2020

Applicant/Patent under Reexamination: TALASAZ

Electronic Terminal Disclaimer filed on August 5, 2020

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	40206281
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	05-AUG-2020
Filing Date:	07-JAN-2020
Time Stamp:	19:07:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	E202085J07020236
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00459

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	37082 4e5dbf9580ca8629cf436cdbeb976144655ed20e	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30267 90e9e906149b744a4d404268a895adf2c60f1968	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	67349		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/672,267	Filing Date 01/07/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/05/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARISSA R BLYTHER/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

115823 7590 08/25/2020
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER
HORLICK, KENNETH R

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/25/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	11/25/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

115823 7590 08/25/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	11/25/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
HORLICK, KENNETH R	1637	435-006120

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 08/25/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/25/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/672,267	Applicant(s) TALASAZ et al.	
	Examiner KENNETH R HORLICK	Art Unit 1637	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the response filed 08/05/20.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 61-90 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

EXAMINER'S COMMENTS

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. The terminal disclaimer filed on 08/05/20 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **US '366 or any patent issuing from US applications '168 or '178** has been reviewed and is accepted. The terminal disclaimer has been recorded.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENNETH R HORLICK whose telephone number is (571)272-0784. The examiner can normally be reached on Mon. - Thurs. 8:30 - 6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

08/17/20

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor name search	02/27/2020	KH
updated parent searches in USPAT and PGPUB	02/27/2020	KH
reviewed parent applications and references therein	02/27/2020	KH
updated in USPAT and PGPUB	07/08/2020	KH
updated in USPAT and PGPUB	08/17/2020	KH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
NONE	NONE	08/17/2020	KH

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

CPC								
Symbol							**Type**	**Version**
C12Q	/	1	/	6869			F	2013-01-01
C12Q	/	1	/	6886			I	2013-01-01
G16B	/	15	/	00			A	2019-02-01
C12Q	/	2600	/	158			A	2013-01-01
C12Q	/	2535	/	122			A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	17 August 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200817

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12P	/	19	/	34

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	6.12

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					
435	91.2					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 30	
/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637 (Primary Examiner) 17 August 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	61	10	70	19	79	28	88								
2	62	11	71	20	80	29	89								
3	63	12	72	21	81	30	90								
4	64	13	73	22	82										
5	65	14	74	23	83										
6	66	15	75	24	84										
7	67	16	76	25	85										
8	68	17	77	26	86										
9	69	18	78	27	87										

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637 (Primary Examiner)	17 August 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20200817

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/03/2020	07/14/2020	08/17/2020						
	31	✓	-							
	32	✓	-							
	33	✓	-							
	34	✓	-							
	35	✓	-							
	36	✓	-							
	37	✓	-							
	38	✓	-							
	39	✓	-							
	40	✓	-							
	41	✓	-							
	42	✓	-							
	43	✓	-							
	44	✓	-							
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	59	✓	-							
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3	63		✓	=						
4	64		✓	=						
5	65		✓	=						
6	66		✓	=						
7	67		✓	=						
8	68		✓	=						
9	69		✓	=						
10	70		✓	=						
11	71		✓	=						
12	72		✓	=						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

CLAIM		DATE								
Final	Original	03/03/2020	07/14/2020	08/17/2020						
13	73		✓	=						
14	74		✓	=						
15	75		✓	=						
16	76		✓	=						
17	77		✓	=						
18	78		✓	=						
19	79		✓	=						
20	80		✓	=						
21	81		✓	=						
22	82		✓	=						
23	83		✓	=						
24	84		✓	=						
25	85		✓	=						
26	86		✓	=						
27	87		✓	=						
28	88		✓	=						
29	89		✓	=						
30	90		✓	=						

OK TO ENTER: /K.R.H/

/K.R.H/ (08/17/2020)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): ELTOUKHY et al.	Confirmation No.: 3448
Serial Number: 16/672,267	Customer No.: 115823
Filing Date: November 1, 2019	Group Art Unit: 1637
Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Examiner: Kenneth R. HORLICK

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Sir:

This communication is in response to the Final Office Action mailed on July 14, 2020. The shortened statutory period for reply expires October 14, 2020, therefore, this response is timely filed. Applicant respectfully requests reconsideration of the above-referenced application in view of the following remarks:

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 3448

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/672,267	01/07/2020 RULE	435	1637	42534-708.304

APPLICANTS

GUARDANT HEALTH, INC., Redwood City, CA;

INVENTORS

AmirAli TALASAZ, Atherton, CA;
Stetanie Ann Ward Mortimer, Moraao.Hjji, CA;

**** CONTINUING DATA ***************************

This application is a CON of 16/601,168 10/14/2019 *
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013
(*)Data provided by applicant is not consistent with PTO records.

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

01/09/2020

Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ☑ No Verified and Acknowledged /KENNETH R HORLICK/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	11	30	2

ADDRESS

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304
UNITED STATES

TITLE

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

FILING FEE RECEIVED		
2720	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	1	Guardant Health, Inc. Response to Notices of Opposition in EP2893040 filed May 29, 2020.
	2	IPR2019-00634, Final Written Decision of U.S. Patent 9,840,743, dated August 18, 2020
	3	IPR2019-00652, Final Written Decision of U.S. Patent 9,834,822, dated August 18, 2020

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-08-27
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	40405909
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	27-AUG-2020
Filing Date:	07-JAN-2020
Time Stamp:	18:47:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$240
RAM confirmation Number	E20208QI47466059
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00482

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2020-08-27_GH0004US-CON3_IDSTrans.pdf	144355 4afd26cd8e24cf52bc3185901efd73e6b30e412d	no	4
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	2020-08-27_GH0004US-CON3_SB08.pdf	1053381 1cee2b49b51cc77d3e7d45c6c7795a8a511cad39	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Information Disclosure Statement (IDS) Form (SB08)	2020-08-27_GH0004US-CON3_SB08A.pdf	1053248 789fb0c99e9efb3e3b76f900f0ad4e24a0dd4602	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Fee Worksheet (SB06)	fee-info.pdf	30410 558157611bb053953d31eed7869e86ed40f9903a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2281394		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	1637
Filing Date:	November 1, 2019	Examiner:	Kenneth R. HORLICK
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☐ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☒ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: 15/892,178

Information Disclosure Statement(s) filed on: 8/19/20 and 8/26/20

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $240.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON3).

Respectfully submitted,

Dated: August 27, 2020

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

	1	EPO Preliminary Opinion, dated August 25, 2020, in EP2893040	
	2	LO, DENNIS Interview with Professor Dennis Lo, Qiagen News (2002)	
	3	Opponents Reply dated August 20, 2020 to Proprietor's Observation in EP2893040.	
	4	Opposition Form and Statement to EP3470533 filed August 6, 2020 by Foundation Medicine Inc.	
	5	US Provisional Appl. No. 61/625,623 filed 04/17/2012.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-08-27
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 09/09/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
09/09/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

CORRECTED ***Notice of Allowability***	**Application No.** 16/672,267	**Applicant(s)** TALASAZ et al.	
	Examiner KENNETH R HORLICK	**Art Unit** 1637	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the submission of 08/27/20.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 61-90 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 8/27/20; 8/27/20.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

/K.R.H/	1	EPO Preliminary Opinion, dated August 25, 2020, in EP2893040	
/K.R.H/	2	LO, DENNIS Interview with Professor Dennis Lo, Qiagen News (2002)	
/K.R.H/	3	Opponents Reply dated August 20, 2020 to Proprietor's Observation in EP2893040.	
/K.R.H/	4	Opposition Form and Statement to EP3470533 filed August 6, 2020 by Foundation Medicine Inc.	
/K.R.H/	5	US Provisional Appl. No. 61/625,623 filed 04/17/2012.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	09/03/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
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First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-08-27
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

/K.R.H/	1	Guardant Health, Inc. Response to Notices of Opposition in EP2893040 filed May 29, 2020.
/K.R.H/	2	IPR2019-00634, Final Written Decision of U.S. Patent 9,840,743, dated August 18, 2020
/K.R.H/	3	IPR2019-00652, Final Written Decision of U.S. Patent 9,834,822, dated August 18, 2020

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	09/03/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-08-27
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/672,267	01/07/2020	1637	2720	42534-708.304	30	2

CONFIRMATION NO. 3448

CORRECTED FILING RECEIPT

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000119825347

Date Mailed: 09/14/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA;
Stetanie Ann Ward Mortimer, Moraao.Hjji, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Assignment For Published Patent Application

GUARDANT HEALTH, INC., Redwood City, CA
GUARDANT HEALTH, INC., Redwood City, CA

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/601,168 10/14/2019
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/09/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/672,267**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): TALASAZ et al.	Confirmation No.: 3448
Serial Number: 16/672,267	Customer No.: 115823
Filing Date: January 7, 2020	Group Art Unit: 1637
Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Examiner: Kenneth R. HORLICK

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

Sir:

Applicants respectfully request the Commissioner issue a Corrected Filing Receipt in the above-captioned applications. Applicants submit herewith the following:

1. Request for Correction in a Patent Application Relating to Inventorship or an Inventor name, or order of names, other than in a Reissue Application (37 CFR 1.48) to add Helmy Eltoukhy as an inventor
2. A Corrected Application Data Sheet adding Helmy Eltoukhy
3. Declaration signed by Helmy Eltoukhy
4. Required fees under 37 CFR 1.17

Applicants also respectfully request the Commissioner correct the following obvious errors in the Filing Receipt.

Please correct Stefanie Ann Ward Mortimer's information as follows:

Stefanie Ann Ward Mortimer, Morgan Hill, CA

Please delete the "Assignment for Published Patent Application" information as that information is not included on any of the submitted Application Data Sheets.

This information was correct on the Application Data Sheet as filed. A marked copy of the Filing Receipt is submitted herewith.

The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,

GUARDANT HEALTH, INC.

Date: September 15, 2020

By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/672,267	01/07/2020	1637	2720	42534-708.304	30	2

CONFIRMATION NO. 3448

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650 Page Mill Road
Palo Alto, CA 94304

OC000000119825547

Date Mailed: 09/14/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA; ~~Morgan Hill~~
~~Stefanie~~ ~~Stetanie~~ Ann Ward Mortimer, ~~Moraga, Hjji,~~ CA;
~~Helmy Eltoukhy, Atherton, CA~~

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Assignment For Published Patent Application

~~GUARDANT HEALTH, INC., Redwood City, CA~~
~~GUARDANT HEALTH, INC., Redwood City, CA~~

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/601,168 10/14/2019
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	AmirAli		TALASAZ	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Atherton	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	State/Province	CA
Postal Code	94063	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stefanie	Ann Ward	MORTIMER	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Morgan Hill	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2000 Willow Springs Road		
Address 2			
City	Morgan Hill	State/Province	CA
Postal Code	95037	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Helmy		ELTOUKHY	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

City	Atherton	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	State/Province	CA
Postal Code	94063	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	115823		
Email Address	patents@guardanthealth.com	Add Email	Remove Email
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		
Attorney Docket Number	42534-708.304	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	11	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	15823		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16601168	2019-10-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
6601168	Continuation of	15892178	2018-02-08
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15892178	Continuation of	14861989	2015-09-22	9920366	2018-03-20

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
4861989	Continuation of	0 PCTUS2014072383	2014-12-24

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2014072383	Claims benefit of provisional	61948509	2014-03-05
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2014072383	Claims benefit of provisional	61921456	2013-12-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[j] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(◉) Assignee ( ) Legal Representative under 35 U.S.C. 117 ( ) Joint Inventor

( ) Person to whom the inventor is obligated to assign. ( ) Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	GUARDANT HEALTH, INC.		
Mailing Address Information For Applicant:			
Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	**State/Province**	CA
Country	US	Postal Code	94063
Phone Number		Fax Number	
Email Address	patents@guardanthealth.com		

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

CORRECTED APPLICATION DATA SHEET

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Timothy A. Hott/			Date (YYYY-MM-DD)	2020-09-15
First Name	Timothy	Last Name	Hott	Registration Number	67740

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-708.304
	Application Number	
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Doc Code: R48.REQ
Document Description: Request under Rule 48 correcting inventorship

PTO/AIA/40 (04-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

Application Number	16/672,267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Practitioner Docket Number	42534-708.304

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby **requests that the inventorship be corrected or changed, or that the name of the inventor or a joint inventor, or the order of the names of joint inventors, be changed,** in the above-identified application. **Note**: 37 CFR 1.48 applies to any request to correct inventorship filed on or after September 16, 2012, regardless of the application filing date. **Do not submit this form after payment of the issue fee or if the application has been patented.** See 37 CFR 1.324 for correction of inventorship in a patent.

Please check the applicable box(es) below.

For a nonprovisional application:

☒ 1. This request is to correct or change the inventorship in a **nonprovisional** application (**under 37 CFR 1.48(a)**) and includes:

☒ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the Manual of Patent Examining Procedure (MPEP) section 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☒ The processing fee set forth in 37 CFR 1.17(i). $ 140.00

☒ An inventor is being added. An inventor's oath or declaration by any actual inventor who has not yet executed an oath or declaration is required (see 37 CFR 1.48(b)). See MPEP 602.01(a) for information about an inventor's oath or declaration for an application filed on/after September 16, 2012 (*e.g.*, form **PTO/AIA/01**). For information about an inventor's oath or declaration for an application filed before September 16, 2012 (*e.g.*, form **PTO/SB/01**), see MPEP 602.01(b).

☒ This request is being filed after the first Office action on the merits has been given or mailed (see 37 CFR 1.48(c) and 1.17(d)). Check one of the following:

☐ This request to correct or change the inventorship is due solely to the cancellation of claims in the application.

OR

☒ The fee set forth in 37 CFR 1.17(d) is due (in addition to the fee set forth in 37 CFR 1.17(i)). $ 600.00

PTO/AIA/40 (04-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

☐ 2. This request is to correct or update the name of the inventor or a joint inventor, or the order of names of joint inventors, in a **nonprovisional** application (**under 37 CFR 1.48(f)**) and includes:

☐ An application data sheet in accordance with 37 CFR 1.76(c) identifying the complete inventive entity, including the corrected or updated name of the inventor, or the new order of names shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the MPEP 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☐ The processing fee set forth in 37 CFR 1.17(i). $ _____

For a provisional application:

☐ This request is to change or correct the inventorship, or correct or update the name of the inventor or a joint inventor, in a **provisional** application (**under 37 CFR 1.48(d)**) and includes:

☐ **Attached hereto** is a document that is signed by a party set forth in 37 CFR 1.33(b) and identifies each inventor by his or her legal name, in the preferred order. Note: the document may be an application data sheet in accordance with 37 CFR 1.76(c) that identifies the changes with markings (underlining for insertions, strikethrough for deletions).

☐ The processing fee set forth in 37 CFR 1.17(q). $ _____

Fee Payment Information:

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

■ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 602231.

■ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ Applicant*

■ attorney or agent of record
Registration number 67740

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Timothy A. Hott/

Typed or printed name Timothy A. Hott/

Date September 15, 2020

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

■ ** Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/861,989

filed on September 22, 2015.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

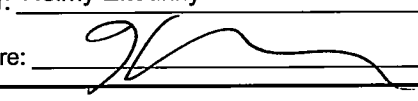
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Helmy Eltoukhy Date (Optional): 11/10/15

Signature: 

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/672,267	09/15/2020 05:00:42 PM ET	42534-708.304

Title of Invention

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	3448	FILED BY	Michelle Chan
PATENT CENTER #	60081877	FILING DATE	01/07/2020
CUSTOMER #	115823	FIRST NAMED INVENTOR	AmirAli TALASAZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Tim Hott

Documents

TOTAL DOCUMENTS: 4

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2020-09-15_GH0004US-CON3_ReqCorrFR.pdf	3	Request under Rule 48 correcting inventorship	184 KB
2020-09-15_GH0004US-CON3_CorrADS.pdf	8	Application Data Sheet	783 KB
Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
2020-09-15_GH0004US-CON3_R48_CorrInv.pdf	3	Request under Rule 48 correcting inventorship	199 KB
2020-09-15_GH0004US-CON3_EltoukhyDec.pdf	1	Oath or Declaration filed	64 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2020-09-15_GH0004US-CON3_ReqCorrFR.pdf	DAA2A92F9D53F04C31B29726052325B9874547A5B1B5DB3BD2E6BD3D536F67F57DB48EE24E0C9F5A123B3C583F83A9EEBEA169CCE1588F2919297081007E61E7
2020-09-15_GH0004US-CON3_CorrADS.pdf	7636ECE699A46A2E6DACB6BB9C00699BBEC63090DA88683B2F2F14A9318A28A58DBB19839E873997DF1283A7C16CBB77294097C68FC49D25EF1B601DDFE2BCC0
2020-09-15_GH0004US-CON3_R48_CorrInv.pdf	D04ED0870E55D891CD8B2F8A81BDD3722CD08FDA12DFD38C6131F230000E55C9EAAEF1085DFF37B622E1279DE632E91D55BAD4B909420061DF33D2FCD3346A98
2020-09-15_GH0004US-CON3_EltoukhyDec.pdf	B4BFD44F8CF35A2703381B21704D3C22B05045A79BA646E5AFEFE3E9C9542CE94574EFD4ED7BE2FF641A9B819A216B22995C63E19115E494C1F66F222FCCADAE

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/672,267	09/15/2020 05:00:42 PM ET	42534-708.304

Title of Invention

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	3448	FILED BY	Michelle Chan
PATENT CENTER #	60081877	AUTHORIZED BY	Tim Holt
CUSTOMER #	115823	FILING DATE	01/07/2020
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	AmirAli TALASAZ

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 602231	E20209EH01177614	Michelle Chan

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	140.00	1	140.00
1819	CORRECTION OF INVENTORSHIP AFTER FIRST ACTION ON MERITS	600.00	1	600.00
			TOTAL AMOUNT:	$740.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d)

and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/672,267	01/07/2020	1637	2720	42534-708.304	30	2

CONFIRMATION NO. 3448

UPDATED FILING RECEIPT

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000119988907

Date Mailed: 09/18/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA;
Stetanie Ann Ward Mortimer, Moraao.Hjji, CA;
Helmy Eltoukhy, Atherton, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/601,168 10/14/2019
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304

CONFIRMATION NO. 3448

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000119988908

Date Mailed: 09/18/2020

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 09/15/2020.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/rmohamed/

Document Description: Application Data Sheet to update/correct info
Doc Code: ADS.CORR

CORRECTED ADS FORM

Application Number	16672267
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Inventor Information

****If no data is shown, no data has been corrected****

	Data of Record	Updated Data
Order Number	1	
Name	AmirAli TALASAZ	
Residence Information		
Residency	us-residency	
City	Atherton	
State	CA	
Country of Residence	US	
Mailing Address of Inventor		
Address 1	505 Penobscot Drive	
Address 2		
City,State/Province, Postal Code	Redwood City CA 94063	
Country	US	

	Data of Record	Updated Data
Order Number	2	
Name	Stetanie Ann Ward Mortimer	
Residence Information		
Residency	us-residency	
City	~~Moraao.Hjji~~	Morgan Hill
State	CA	
Country of Residence	US	
Mailing Address of Inventor		
Address 1		
Address 2		
City,State/Province, Postal Code		
Country		

	Data of Record	Updated Data
Order Number	3	
Name	Helmy Eltoukhy	

Residence Information

Residency	us-residency	
City	Atherton	
State	CA	
Country of Residence	US	

Mailing Address of Inventor

Address 1		
Address 2		
City,State/Province, Postal Code		
Country		

Application Information

	Data of Record	Updated Data
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	
Attorney Docket Number	42534-708.304	
Entity Type	Regular Undiscounted	

Domestic Benefit/National Stage Information

****If no data is shown, no data has been corrected****

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121,365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S. C. 119(e) or 120, and 37 CFR 1.78(a).

		Data of Record	Updated Data
	Prior Application Status		
	Application Number		
	Continuity Type		
	Prior Application Number		
	Filing Date (YYYY-MM-DD)		
	Patent Number		
	Issue Date (YYYY-MM-DD)		

Foreign Priority Information

****If no data is shown, no data has been corrected****

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

		Data of Record	Updated Data
	Application Number		
	Country		
	Filing Date		
	Access Code		

Applicant Information

****If no data is shown, no data has been corrected****
Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

	Data of Record	Updated Data
Applicant Type		

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is		
Name of the Deceased or Legally Incapacitated Inventor		
Applicant is an Organization		
Name		
Organization Name		
Address 1		
Address 2		
City,State/Province,Postal Code		
Country		
Phone Number		
Fax Number		
Email Address		

Assignee Information including Non-Applicant Assignee Information

****If no data is shown, no data has been corrected****
Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office

	Data of Record	Updated Data
Order		
Applicant is an Organization		
Name		

Organization Name		

Mailing Address

Address 1		
Address 2		
City,State/Province,Postal Code		
Country		
Phone Number		
Fax Number		
Email Address		

Signature

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Timothy A. Hott/	Registration Number	67740
First Name	Timothy A.	Last Name	Hott

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**140**

Electronic Acknowledgement Receipt

EFS ID:	40606539
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	18-SEP-2020
Filing Date:	07-JAN-2020
Time Stamp:	19:26:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$140
RAM confirmation Number	E20209HJ26072773
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00538

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet to update/ correct info	CorrectedADS.pdf	80378 4129cd735df3fba92304a0545bf80a666a48c1e3	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30321 d7d215134b53883540fe73a6fa4e6adea319c6e4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	110699		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46575

Refund Accounting Date:09/21/2020

Effective Date	Sale Item Reference Number	Refund Total
09/18/2020	16672267	$140.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20209KA23200935	1830	PROCESSING FEE, EXCEPT PROV. APPLS.	$140.00	DA	602231

United States Patent and Trademark Office
Office of the Chief Financial Officer

Document Code:WFEE

User :C46575

Sale Adjustment Accounting Date:09/21/2020

Effective Date	Sale Accounting Date	Sale Item Reference Number
09/18/2020	09/21/2020	16672267

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20209KA23200935	1830	PROCESSING FEE, EXCEPT PROV. APPLS.	$140.00	DA

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/672,267	01/07/2020	1637	2720	42534-708.304	30	2

CONFIRMATION NO. 3448

CORRECTED FILING RECEIPT

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000120048008

Date Mailed: 09/22/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

AmirAli TALASAZ, Atherton, CA;
Stetanie Ann Ward Mortimer, Morgan Hill, CA;
Helmy Eltoukhy, Atherton, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/601,168 10/14/2019
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013

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Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 09/21/2020
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/672,267**
Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
Title

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
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CONFIRMATION NO. 3448

CORRECTED FILING RECEIPT

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000120115378

Date Mailed: 09/24/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA;
Stefanie Ann Ward Mortimer, Morgan Hill, CA;
Helmy Eltoukhy, Atherton, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/601,168 10/14/2019 PAT 10801063
which is a CON of 15/892,178 02/08/2018
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 09/21/2020
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/672,267**
Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
Title

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
16672267	07-Jan-2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION :

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1637	006120	KENNETH HORLICK

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1000	$0	$1000	25-Nov-2020	$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
115823 Wilson Sonsini Goodrich & Rosati / Guardant Health 650 Page Mill Road Palo Alto CA 94304 UNITED STATES 650-493-9300 Patents@guardanthealth.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☐ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency, or credit any overpayment, to Deposit Account Number _____ . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. Timothy A. Hott
2.
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
GUARDANT HEALTH, INC.	Redwood City	CALIFORNIA	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Timothy A. Hott/	**Date**	09-25-2020
Name	Timothy A Hott	**Registration Number**	67740

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	40671006
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	25-SEP-2020
Filing Date:	07-JAN-2020
Time Stamp:	13:49:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E20209OD49390762
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00554

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Web85b.pdf	46194 bab8c2cf7ed1a87e9a2b1d4a2ae01228f848ae03	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31872 b453e3b8c8db9136047df194fac77ba797a81977	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	78066		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 10/07/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
10/07/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/672,267	01/07/2020	TALASAZ et al.	42534-708.304

	EXAMINER	
Wilson Sonsini Goodrich & Rosati / Guardant Health **650 Page Mill Road** **Palo Alto, CA 94304**	KENNETH R HORLICK	
	ART UNIT	**PAPER**
	1637	20201001

DATE MAILED: _____

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

See corrected IDS of 06/03/20 with information added for item 11.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	10287631	B2	2019-05-14	Salk et al.	Entire Document
/K.R.H/	2	10370713	B2	2019-08-06	Salk et al.	Entire Document
/K.R.H/	3	10385393	B2	2019-08-20	Salk et al.	Entire Document
/K.R.H/	4	10388403	B2	2019-08-20	Rava et al.	Entire Document
/K.R.H/	5	10604804	B2	2020-03-31	Salk et al.	Entire Document

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	20190271040	A1	2019-09-05	Salk et al.	Entire Document

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

/K.R.H/	2	20190292597	A1	2019-09-26	Salk et al.	Entire Document	
/K.R.H/	3	20190338358	A1	2019-11-07	Salk et al.	Entire Document	
/K.R.H/	4	20190352714	A1	2019-11-21	Salk et al.	Entire Document	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/K.R.H/	1	KAMPS-HUGHES, N. et al. "ERASE-Seq: Leveraging replicate measurements to enhance ultralow frequency variant detection in NGS data"PLOS One (2018)	
/K.R.H/	2	LENNON, N.J. et al. "Technological considerations for genome-guided diagnosis and management of cancer" Gen Med (2016) 8:112	
/K.R.H/	3	MISHRA, S. et al. "Different Facets of Copy Number Changes: Permanent, Transient, and Adaptive" Mol Cell Biol (2016) 36(7):1050-1063	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

/K.R.H/	4	MOENCH, S. "Genomic Profiling Using Guardant 360 Cell-Free DNA-Based Assay vs Tumor-Based Genotyping Assays in Advanced NSCLC, CANCER THERAPY ADVISOR (Feb. 28, 2019), https://www.cancertherapyadvisor.com/home/news/conferencecoverage/american-association-for-cancer-research-aacr/aacr-2019/genomic-profiling-using-guardant-360-cell-free-dna-based assay-vs-tumor-based-genotyping-assays-in-advanced-nsclc/ (lastaccessed Nov. 30, 2019)
/K.R.H/	5	NEWMAN, A. et al. "Integrated digital error suppression for improved detection of circulating tumor DNA" Nature Biotech (2016) 34(5):547-555
/K.R.H/	6	ODEGAARD, J.I. et al. "Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies" Clin Canc Res (2018) 24(15):3539-3549
/K.R.H/	7	OU, SHI et al. "Liquid Biopsy to Identify Actionable Genomic Alterations" Am Soc Clin Onc (2018) 978
/K.R.H/	8	SATHIRAPONGSASUTI, J.F. et al. "Exome sequencing-based copy-number variation and loss of heterozygosity detection: ExomeCNV" BioInformatics (2011) 27(19):2648-2654
/K.R.H/	9	TRAPNELL, C. et al. "How to map billions of short reads onto genomes" Nature Biotech (2009) 27(5):455-457
/K.R.H/	10	VAN LOO, P. et al. "Allele-specific copy number analysis of tumors" PNAS (2010) 107(39):16910-16915
/K.R.H/	11	WANG, T.T. et al. "High efficiency error suppression for accurate detection of low-frequency variants" NAR (2019) 47 (15): e87

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	10/01/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-06-03
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	11/17/2020	10837054	42534-708.304	3448

115823 7590 10/28/2020

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

AmirAli TALASAZ, Atherton, CA;
GUARDANT HEALTH, INC., Redwood City, CA;
Stefanie Ann Ward Mortimer, Morgan Hill, CA;
Helmy Eltoukhy, Atherton, CA;

Doc Code: QPIDS.REQ
Document Description: QuickPath Information Disclosure Statement

PTO/SB/09 (09-18)

CERTIFICATION AND REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM

Non-Provisional Application Number: 16/672,267	Filing Date: 2020-01-07
First Named Inventor: AmirAli TALASAZ	Title of Invention: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE-IDENTIFIED APPLICATION.

1. Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee.
2. Check the box next to the appropriate selection:

   ☑ Each item of information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(1).

   OR

   ☐ No item of information contained in the IDS was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the IDS was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(2).

   OR

   ☐ See attached certification statement in compliance with 37 CFR 1.97(e).
3. Please charge the IDS fee set forth in 37 CFR 1.17(p) to Deposit Account No. 602231.
4. A Petition to Withdraw from Issue After Payment of the Issue Fee (37 CFR 1.313(c)(2)), including the petition fee set forth in 37 CFR 1.17(h), is submitted herewith as a **Web-based ePetition**. **WARNING:** Do not submit the petition as a follow-on paper via EFS-Web. Submit the petition as a Web-based ePetition by signing on to EFS-Web as a registered user, selecting the radio button next to "Existing application/patent," and then selecting the radio button next to "ePetition (for automatic processing and immediate grant, if all petitions requirements are met)." Failure to use the Web-based ePetition interface will result in automatic entry of the RCE.
5. A request for continued examination (RCE) under 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.
6. The RCE will be treated as a "conditional" RCE. In the event the examiner determines that any item of information contained in the IDS necessitates the reopening of prosecution in the application, the undersigned understands that (i) the RCE will be processed and treated as an RCE under 37 CFR 1.114 and therefore (ii) the IDS fee under 37 CFR 1.17(p) will be returned in accordance with 37 CFR 1.97(b)(4). In the event that no item of information in the IDS necessitates reopening prosecution, the undersigned understands that the RCE will not be processed and the RCE fee under 37 CFR 1.17(e) will be returned.
7. This certification and request is being filed as a **Web-based ePetition** and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE.

Signature /Timothy A. Hott/	Date 2020-11-09
Name (Print/Typed) Timothy A. Hott	Practitioner Registration Number (If applicable) 67740

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below.**

☑ *Total of 1 forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	1637
Filing Date:	November 1, 2019	Examiner:	Kenneth R. HORLICK
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $260.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☐ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☒ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: 15/892,178

Information Disclosure Statement(s) filed on: 11/9/2020

AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $260.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON3).

Respectfully submitted,

Dated: November 9, 2020

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20130096011	A1	2013-04-18	Rava et al.	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2012148477	WO	A1	2012-11-01	FODOR et al.	Entire Document	

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

	1	JIANG et al. "Basics in Bioinformatics Lecture Notes of the Graduate Summer School on Bioinformatics of China" Springer Heidelberg New York Dordrecht London (2013)	
	2	Opposition Form and Statement to EP3378952 filed November 4, 2020 by Dirk Buhler	
	3	Opposition Form and Statement to EP3378952 filed November 5, 2020 by Foundation Medicine Inc.	
	4	Opposition Form and Statement to EP3378952 filed November 5, 2020 by Grunecker	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-11-09
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
RCE- 1ST REQUEST	1801	1	1360	1360
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1500**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Decision Date : November 9, 2020

In re Application of :

AmirAli TALASAZ

DECISION ON PETITION

UNDER CFR 1.313(c)(2)

Application No : 16672267

Filed : 07-Jan-2020

Attorney Docket No : 42534-708.304

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed November 9, 2020, to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1637 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt

EFS ID:	41076867
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	09-NOV-2020
Filing Date:	07-JAN-2020
Time Stamp:	20:13:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1500
RAM confirmation Number	E2020A9K13205725
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00577

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition automatically granted by EFS	petition-request.pdf	31544 73afdf4912931fd85b4554a68ceabf35a75d915b	no	2
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	2020-11-09_GH0004US-CON3_RCE.pdf	1364274 f7eb7fab18d9fcae70620d93b0e1325e61ea1063	no	3
Warnings:					
Information:					
3	Quick Path Information Disclosure Statement	2020-11-09_GH0004US-CON3_QPIDS.pdf	196111 3ad368a0e7485005e33fb35f07742525c99cf9f7	no	2
Warnings:					
Information:					
4	Transmittal Letter	2020-11-09_GH0004US-CON3_IDSTrans.pdf	144879 34f4c4733972275de5beba580f8acfe83400d9d0	no	4
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	2020-11-09_GH0004US-CON3_SB08.pdf	1053470 60148842a0ee78143a0258842d8e8a32336c67a4	no	4
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	31917 edde5c6186236255d1cdc6c0ba28c275d10a0dda	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	2822195

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web	PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)**
Application Number	16672267
Filing Date	07-Jan-2020
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	KENNETH HORLICK
Attorney Docket Number	42534-708.304
Title	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:
(1) Petition fee; and
(2) One of the following reasons:
(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Petition Fee

- ◯ Small Entity
- ◯ Micro Entity
- ◉ Regular Undiscounted

Reason for withdrawal from issue

◯ One or more claims are unpatentable ◉ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ◯ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).
RCE request,submission, and fee. ☐ I certify, in accordance with 37 CFR 1.4(d)(4) that : The RCE request ,submission, and fee have already been filed in the above-identified application on ☒ Are attached.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ◯ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ◯ A sole inventor ◯ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ◯ A joint inventor; all of whom are signing this e-petition

Signature	/Timothy A. Hott/
Name	Timothy A. Hott
Registration Number	67740

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 11/27/2020

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER
HORLICK, KENNETH R

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
11/27/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

CORRECTED ***Notice of Allowability***	**Application No.** 16/672,267	**Applicant(s)** TALASAZ et al.	
	Examiner KENNETH R HORLICK	**Art Unit** 1637	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the submission of 11/09/20.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 61-90 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/9/20.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	20130096011	A1	2013-04-18	Rava et al.	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/K.R.H/	1	2012148477	WO	A1	2012-11-01	FODOR et al.	Entire Document	

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

/K.R.H/	1	JIANG et al. "Basics in Bioinformatics Lecture Notes of the Graduate Summer School on Bioinformatics of China" Springer Heidelberg New York Dordrecht London (2013)	
/K.R.H/	2	Opposition Form and Statement to EP3378952 filed November 4, 2020 by Dirk Buhler	
/K.R.H/	3	Opposition Form and Statement to EP3378952 filed November 5, 2020 by Foundation Medicine Inc.	
/K.R.H/	4	Opposition Form and Statement to EP3378952 filed November 5, 2020 by Grunecker	

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	11/23/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

X That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

X The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

X A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-11-09
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46472

Refund Accounting Date:12/01/2020

Effective Date	Sale Item Reference Number	Refund Total
11/09/2020	16672267	$1,360.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I2020B1728435021	1801	RCE- 1ST REQUEST	$1,360.00	DA	602231

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46472

Sale Adjustment Accounting Date:12/01/2020

Effective Date	Sale Accounting Date	Sale Item Reference Number
11/09/2020	12/01/2020	16672267

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I2020B1728435021	1801	RCE- 1ST REQUEST	$1,360.00	DA

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/05/2021	10883141	42534-708.304	3448

115823 7590 12/16/2020

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

AmirAli TALASAZ, Atherton, CA;
GUARDANT HEALTH, INC., Redwood City, CA;
Stefanie Ann Ward Mortimer, Morgan Hill, CA;
Helmy Eltoukhy, Atherton, CA;

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/672,267	Filing Date 01/07/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/22/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MONIQUE BENJAMIN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16/672,267	Filing Date	2020-01-07	Docket Number (if applicable)	42534-708.304	Art Unit	1637
First Named Inventor	AmirAli TALASAZ			Examiner Name	Kenneth R. HORLICK		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 602231

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-12-22
Name	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): ELTOUKHY et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: 1637 Examiner: Kenneth R. HORLICK

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION ACCOMPANYING A REQUEST FOR CONTINUED EXAMINATION

Sir:

Applicant respectfully requests consideration of the above-referenced application in view of the following remarks:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 8 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. – 60. (Cancelled).

61. (Currently amended): A method, comprising:

(a) providing a population of cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) tagging a plurality of the cfDNA molecules of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein duplex tags from the set of duplex tags are attached at both ends of a molecule of the plurality of the cfDNA molecules;

(c) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and

(e) reducing or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes to generate a plurality of consensus sequences representative of original cfDNA molecules from among the tagged parent polynucleotides, wherein the plurality of consensus sequences is generated from (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides, and [[or]] (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides.

62. (Previously Presented): The method of claim 61, wherein the population of cfDNA molecules is obtained or derived from a sample from a subject having cancer.

63. (Previously Presented): The method of claim 61, wherein the plurality of cfDNA molecules comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules.

64. (Previously Presented): The method of claim 61, wherein the duplex tags are ligated to the plurality of the cfDNA molecules using more than a 10X excess of duplex tags as compared to the population of cfDNA molecules.

65. (Previously Presented): The method of claim 64, wherein at least 20% of the cfDNA molecules of the population are tagged with the duplex tags.

66. (Previously Presented): The method of claim 61, wherein the tagging comprises non-uniquely tagging the plurality of the cfDNA molecules with the set of duplex tags comprising molecular barcodes from the set of molecular barcodes, wherein the cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the cfDNA molecules that map to the mappable base position.

67. (Previously Presented): The method of claim 61, wherein the molecular barcodes of the set of molecular barcodes have pre-determined sequences.

68. (Previously Presented): The method of claim 61, wherein the molecular barcodes of the set of molecular barcodes have between 5 and 10,000 different molecular barcode sequences and have a length of between 5 and 20 base pairs.

69. (Previously Presented): The method of claim 61, further comprising enriching a plurality of the amplified progeny polynucleotides for target regions of interest prior to the sequencing to produce enriched progeny polynucleotides.

70. (Previously Presented): The method of claim 69, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1,

BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

71. (Previously Presented): The method of claim 69, further comprising amplifying a plurality of the enriched progeny polynucleotides prior to the sequencing.

72. (Previously Presented): The method of claim 61, wherein the duplex tags of the set of duplex tags are part of sequencing adapters.

73. (Previously Presented): The method of claim 72, wherein the sequencing adapters are Y-shaped adapters.

74. (Previously Presented): The method of claim 61, wherein the reducing or tracking redundancy in the set of sequence reads comprises mapping a plurality of the sequence reads to a reference sequence.

75. (Previously Presented): The method of claim 61, further comprising:

(f) determining quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads at one or more loci of a reference sequence.

76. (Previously Presented): The method of claim 75, further comprising:

(g) estimating with a programmed computer processor a quantitative measure of tagged parent polynucleotides based at least in part on the quantitative measures of the at least two of (i) the paired reads, (ii) the unpaired reads, (iii) the read depth of the paired reads, and (iv) the read depth of the unpaired reads at each of the one or more loci.

77. (Previously Presented): The method of claim 76, wherein (f) comprises determining quantitative measures of the paired reads and the unpaired reads, and wherein in (g), the quantitative measures of the tagged parent polynucleotides is determined based at least in part on the quantitative measures of the paired reads and the unpaired reads.

78. (Previously Presented): A method, comprising:

(a) providing a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) non-uniquely tagging a plurality of the double-stranded cfDNA molecules of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce non-uniquely tagged parent polynucleotides,

wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the double-stranded cfDNA molecules that map to the mappable base position;

(c) amplifying a plurality of the non-uniquely tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads;

(e) reducing or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes;

(f) sorting the set of sequence reads into paired reads and unpaired reads, wherein (i) a paired read corresponds to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides, and (ii) an unpaired read corresponds to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides; and

(g) determining, at one or more loci of a reference sequence, quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads.

79. (Previously Presented): The method of claim 78, wherein the population of double-stranded cfDNA molecules is obtained or derived from a sample from a subject having cancer.

80. (Previously Presented): The method of claim 78, wherein the plurality of double-stranded cfDNA molecules comprises between 1 nanogram (ng) and 100 ng of double-stranded cfDNA molecules.

81. (Previously Presented): The method of claim 78, wherein the non-uniquely tagging comprises ligating the duplex tags to the plurality of the double-stranded cfDNA molecules.

82. (Previously Presented): The method of claim 78, wherein the molecular barcodes of the set of molecular barcodes have between 2 and 10,000 different molecular barcode sequences.

83. (Previously Presented): The method of claim 78, wherein the molecular barcodes of the set of molecular barcodes have between 5 and 10,000 different molecular barcode sequences and have a length of between 5 and 20 base pairs.

84. (Previously Presented): The method of claim 78, further comprising enriching a plurality of the amplified progeny polynucleotides for target regions of interest prior to the sequencing to produce enriched progeny polynucleotides.

85. (Previously Presented): The method of claim 84, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

86. (Previously Presented): The method of claim 84, further comprising amplifying a plurality of the enriched progeny polynucleotides prior to the sequencing.

87. (Previously Presented): The method of claim 78, wherein reducing or tracking redundancy in the set of sequence reads comprises collapsing a plurality of the sequence reads to generate consensus sequences representative of original double-stranded cfDNA molecules from among the non-uniquely tagged parent polynucleotides.

88. (Previously Presented): The method of claim 87, further comprising mapping a plurality of the set of sequence reads and/or the consensus sequences to a reference sequence.

89. (Previously Presented): The method of claim 78, further comprising:

(h) estimating with a programmed computer processor a quantitative measure of non-uniquely tagged parent polynucleotides based at least in part on the quantitative measures of the

at least two of (i) the paired reads, (ii) the unpaired reads, (iii) the read depth of the paired reads, and (iv) the read depth of the unpaired reads at each of the one or more loci.

90. (Previously Presented): The method of claim 89, wherein (g) comprises determining quantitative measures of the paired reads and the unpaired reads, and wherein in (h), the quantitative measure of the non-uniquely tagged parent polynucleotides is determined based at least in part on the quantitative measures of the paired reads and the unpaired reads.

REMARKS

Claims 61-90 were pending prior to entry of the above-referenced claim amendments. Claim 61 is amended herein to better define the claimed subject matter. No new matter is being introduced by any of these claim amendments.

The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: December 22, 2020 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	1637
Filing Date:	November 1, 2019	Examiner:	Kenneth R. HORLICK
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $260.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON3).

Respectfully submitted,

Dated: December 22, 2020

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
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PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	10752951	B2	2020-08-25	Salk et al.	Entire Document

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

	1	Office action dated 12/21/2020 for US Application No. 16/945,124.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-12-22
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2140**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Decision Date : December 22, 2020

In re Application of :

AmirAli TALASAZ

DECISION ON PETITION

UNDER CFR 1.313(c)(2)

Application No : 16672267

Filed : 07-Jan-2020

Attorney Docket No : 42534-708.304

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed December 22, 2020to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1637 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt

EFS ID:	41468267
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	22-DEC-2020
Filing Date:	07-JAN-2020
Time Stamp:	16:59:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$2140
RAM confirmation Number	E2020BLG59243539
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00614

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition automatically granted by EFS	petition-request.pdf	31544 f66f4f78ce1839e5569b650e98f1f916f1b50d91	no	2
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	2020-12-22_GH0004US_CON3_RCETrans.pdf	1364364 c2db1ad018cddc7b3962360a78ea2a5989039c38	no	3
Warnings:					
Information:					
3		2020-12-22_GH0004US-CON3_RCESubm.pdf	122239 bc39c6aa2e2000eabd7de57797949be12f9cde88	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	7
Applicant Arguments/Remarks Made in an Amendment	8	8

Warnings:					
Information:					
4	Transmittal Letter	2020-12-22_GH0004US-CON3_IDSTrans.pdf	144639 0b0f040bcdff34ba3bafb66d85c2c6ffb18047dd	no	4
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	2020-12-22_GH0004US-CON3_SB08.pdf	1053161 c2b721552db82ac57848d5b700fcdadb122210cf	no	4

Warnings:					
Information:					
6	Other Reference-Patent/App/Search documents	OA_16945124_2020-12-21.PDF	408898 414662a6b17b4a9396cbf0a18467fe4dd3737928	no	10
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	32175 0516ba7e129c0118840bfe67c580924d90183f30	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3157020		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web	PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)**
Application Number	16672267
Filing Date	07-Jan-2020
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	KENNETH HORLICK
Attorney Docket Number	42534-708.304
Title	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:
(1) Petition fee; and
(2) One of the following reasons:
(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Petition Fee

- ○ Small Entity
- ○ Micro Entity
- ◉ Regular Undiscounted

Reason for withdrawal from issue

◯ One or more claims are unpatentable ◉ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ◯ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).
RCE request,submission, and fee. ☐ I certify, in accordance with 37 CFR 1.4(d)(4) that : The RCE request ,submission, and fee have already been filed in the above-identified application on ☒ Are attached.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ◯ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ◯ A sole inventor ◯ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ◯ A joint inventor; all of whom are signing this e-petition

Signature	/Timothy A. Hott/
Name	Timothy A. Hott
Registration Number	67740

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 01/11/2021

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/11/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Office Action Summary	Application No. 16/672,267	Applicant(s) TALASAZ et al.	
	Examiner KENNETH R HORLICK	Art Unit 1637	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/22/20.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 61-90 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 61-90 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 12/22/20.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/20 has been entered.

NEW GROUNDS OF REJECTION

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal

Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 61-90 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of copending Application No. 16/945,124 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the copending claims and the instant claims are related as genus-obvious species. That is, the species 'reducing or tracking redundancy' in the instant claims is clearly an obvious species within the genus 'reducing and/or tracking redundancy' in the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

4. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

Claims 61-62, 67, 69, 71-72, 74-75, 78-79, 81, 84, and 86-88 are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Salk et al. (US 10,752,951; effective filing date at least March 15, 2013; newly cited by Applicant).

It is readily apparent that the noted instant claims are substantially identical to claims 1-28 of Salk et al. Thus, the claimed methods cannot be distinguished from the patented methods of Salk et al.

6. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 63-65, 68, 70, 73, 76-77, 80, 82-83, 85, and 89-90 are rejected under 35 U.S.C. 103 as being unpatentable over Salk et al.

While the further limitations of these dependent claims are not explicitly disclosed in the claims or specification of Salk et al., they clearly merely relate to routine optimization of known-important reaction parameters, which as well established in U.S. patent practice does not support unobviousness. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Salk et al. in the manner of these claims.

ALLOWABLE SUBJECT MATTER

7. Claim 66 is free of the prior art, but is rejected for another reason. It is noted that in the Final Written Decision of IPR2019-00652, the Patent Trial and Appeal Board found, with respect to related U.S. Patent No. 9,834,822, that the Salk et al. specification (specifically in U.S. Patent No. 9,752,188) did not teach or suggest wherein 'cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number the cfDNA molecules that map to the mappable base position.'

CONCLUSION

8. No claims are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENNETH R HORLICK whose telephone number is (571)272-0784. The examiner can normally be reached on Mon. - Thurs. 8:30 - 6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available

through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

01/05/21

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor name search	02/27/2020	KH
updated parent searches in USPAT and PGPUB	02/27/2020	KH
reviewed parent applications and references therein	02/27/2020	KH
updated in USPAT and PGPUB	07/08/2020	KH
updated in USPAT and PGPUB	08/17/2020	KH
updated in USPAT and PGPUB	01/05/2021	KH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	10752951	B2	2020-08-25	Salk et al.	Entire Document

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

/K.R.H/	1	Office action dated 12/21/2020 for US Application No. 16/945,124.

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EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	01/05/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-12-22
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/672,267	Filing Date 01/07/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	07/09/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: 1637 Examiner: Kenneth R. HORLICK

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Dear Sir:

This communication is in response to the Non-Final Office Action mailed January 11, 2021. With the submission of a petition for a 3-month extension of time, setting the period for reply by July 11, 2021, this response is timely filed. Reconsideration of the above-referenced application is respectfully requested in view of the following amendments and remarks.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ et al.	Confirmation No.:	1052
Serial No.:	16/672,267	Art Unit:	1637
Filing Date:	November 1, 2019	Examiner:	Kenneth R. HORLICK
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS		

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $260.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $260.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0004US-CON3).

Respectfully submitted,

Dated: July 9, 2021

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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WIPO | PCT

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61/433,488	17 January 201 1 (17.01.201 1)	US
61/474,205	11 April 201 1 (11.04.201 1)	US
61/474,168	11 April 201 1 (11.04.201 1)	US

(71) Applicant *(for all designated States except US):* **LIFE TECHNOLOGIES CORPORATION** [US/US]; 5791 Van Allen Way, Carlsbad, California 92008 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only):* **HENDRICKS, Steph¬en** [US/US]; Life Technologies Corporation, 5791 Van A1-len Way, Carlsbad, California 92008 (US).

(74) Agent: **GERMAN, Roberta;** Life Technologies Corporation, 5791 Van Allen Way, Carlsbad, California 92008 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/099832 A2

(54) **Title:** ENZYMATIC LIGATION OF NUCLEIC ACIDS

(57) **Abstract:** Methods, assays, compositions and kits for the ligation of short polynucleotides are presented herein. The short polynucleotides are optionally no more than 7 nucleotides in length, and can be as short as 3 or 4 nucleotides in length. The ligation is optionally performed by CV ligase.

ENZYMATIC LIGATION OF NUCLEIC ACIDS

[0001] This application claims priority to the following U.S. provisional applications, each of which is incorporated by reference in its entirety: App. No. 61/474,205 filed April 11, 2011; App. No. 61/474,168 filed April 11, 2011; App. No. 61/433,502 filed January 17, 2011; and App. No. 61/433,488 filed January 17, 2011.

Background

[0002] DNA ligases can join polynucleotides together, for example by catalyzing the formation of a phosphodiester bond at single- or double-stranded breaks on duplex DNA. Ligases can be sensitive to the degree of hybridization between opposing nucleic acid strands in a duplex. For example, successful ligation can occur less frequently (or not at all) where a strand to be ligated to an adjacent strand is in a duplex and is not complementary to its opposing strand in the duplex. In some cases a single nucleotide mismatch between strands in a duplex can significantly impair or prevent ligation. The capacity of ligases for discrimination based on hybridization, including single nucleotide discrimination, has led to the development of ligase-mediated detection techniques *(e.g.,* Landegren, U., Bioessays, 15(11):761-765 (1993), and Barany, PNAS USA, 88(1):189-193 (1991)). Ligase-based linear signal amplification known as LDR *(i.e.,* ligase detection reaction), combined with PCR *(i.e.,* polymerase chain reaction)-based gene specific target amplification, has been proven to be a useful tool in cancer and disease gene mutation detection. PCR/LDR techniques typically rely on two properties of a DNA ligase: (i) specificity, and (ii) thermostability.

Summary

[0003] This application relates to ligation reagents and methods. Among other things, methods of and reagents for ligating nucleic acids to other nucleic acids are provided, including ligation of two polynucleotides. Either or both polynucleotides can be single-stranded or double-stranded. One or both polynucleotides can be a short oligonucleotide. In some embodiments oligonucleotides and/or polynucleotides of different lengths can be ligated to each other. The ligation can be enzymatic, and ligations can be template-

dependent or template-independent. The nucleic acids that are ligated or involved in the ligation reaction can be labeled or unlabeled and immobilized or in solution.

[0004] Some embodiments involve template-independent ligation of double-stranded or single-stranded polynucleotides (e.g., oligonucleotides). The single-stranded polynucleotides are optionally not hybridized to another polynucleotide. In some embodiments, an oligonucleotide can be hybridized to or otherwise associated with all or a portion of an overhang or other single-stranded region of a duplex nucleic acid and ligated to a free end of a strand of the duplex or to another oligonucleotide that is hybridized or otherwise associated with an overhang or other single-stranded portion of the duplex.

[0005] Some embodiments involve ligation of single-stranded polynucleotides (e.g., oligonucleotides). Optionally, the single-stranded polynucleotides are hybridized hybridized adjacent or near each other on another single polynucleotide. In some embodiments, an oligonucleotide can be hybridized to or otherwise associated with all or a portion of an overhang or other single-stranded region of a duplex nucleic acid and ligated to a free end of a strand of the duplex or to another oligonucleotide that is hybridized or otherwise associated with an overhang or other single-stranded portion of the duplex.

[0006] In some aspects, methods and reagents are provided for hybridizing or otherwise associating a first oligonucleotide and a second oligonucleotide to a third oligonucleotide or to a polynucleotide such that the termini of the first and second oligonucleotides are adjacent to or near each other. Such hybridization or association can occur sequentially, simultaneously, or substantially simultaneously. The terminus of the first oligonucleotide can be ligated to the adjacent or nearby terminus of the second oligonucleotide.

[0007] Nucleotide base mismatches between a first and/or second oligonucleotide and a third oligonucleotide or polynucleotide can affect the efficiency of ligation. For example, mismatches at the terminal position of either or both a first and second oligonucleotides can affect ligation efficiency, reducing the probability of successful ligation or precluded ligation entirely. Mismatches at other or at multiple positions can also affect ligation efficiency, reducing the probability of successful ligation or precluding ligation entirely.

[0008] Also provided are methods and reagents for performing multiple ligations sequentially, in parallel, or both sequentially and in parallel.

[0009] Optionally, one or more of the primer, probe or template is labeled. For example the probe can be labeled. Else the primer or template is labeled.

[0010] In some embodiments, methods of ligation are provided that provide information about the sequence of a nucleic acid. For example, in some aspects a ligation can be performed in the presence of multiple oligonucleotides that are at least partially complementary to a target region on a template. Oligonucleotide probes can be used that hybridize or otherwise associate with a template adjacent to or near a terminus of a primer or probe that is hybridized to or otherwise associated with a template. Multiple oligonucleotide probes, each at least partially complementary to a region of a template can be used to determine sequence information in a template-dependent manner as is known in the art. For example, oligonucleotide ligation is used to determine nucleic acid sequence information in the SOLiD System (Life Technologies-Applied Biosystems, Carlsbad, CA). According to some embodiments, sequence information is determined ligating oligonucleotide probes to an oligonucleotide primer in a template sequence-dependent manner, for example by using a SFL. The oligonucleotide probes can be a set of multiple probes having different sequences and distinguishing labels, and the primer and probes can have lengths of not more than 8, 7, 6, 5, 4, 3 or 2 nucleotides. The labels can provide information about the sequence of the probe.

[0011] In some embodiments, ligation can be performed by a "small footprint ligase" (herein "SFL") that can ligate short polynucleotides. SFLs can be used in each of the embodiments of ligations discussed above and in the remainder of this disclosure, as well as in other embodiments of ligations known to person of skill in the art. For example, in some embodiments an SFL can ligate the termini of a first oligonucleotide and a second oligonucleotide. The first oligonucleotide can be a primer and the second oligonucleotide can be a probe, each hybridizing or otherwise associating with a portion of a third oligonucleotide or a polynucleotide.

[0012] In some embodiments, the SFL can ligate oligonucleotides that are 8, 7, 6, 5, 4, 3 or 2 nucleotides in length to a polynucleotide. Ligation of such oligonucleotides can be to oligonucleotides of the same length or of different length or to a polynucleotide. For example, an oligonucleotide of 2 or 3 nucleotides in length can be ligated to an oligonucleotide of 2, 3, 4, 5, 6, 7, 8 or more nucleotides in length or to longer oligonucleotides or to a polynucleotide.

[0013] Also provided are kit comprising a small footprint ligase ("SFL") or functional variant or fragment or derivative thereof. Exemplary SFLs are identified herein, and their

sequences provided. Optionally, the kit can also include one or more oligonucleotide probes less than 12 nucleotides in length, (e.g., not more than 8, 6, 5, 4, 3 or 2 nucleotides in length). Optionally, the kit includes CV ligase and one or more oligonucleotides probes less than 6 nucleotides in length.

Brief Description of the Drawings

[0014] **Figure 1.** (A) Extended P1 covalent bead ligation substrate. Shown is a ligation substrate designed to mimic the conditions used in SOLiD™ sequencing. Figure 1(A) represents DNA covalently linked to a bead (such as a magnetic bead, e.g., of 0.1 to 1 μιη diameter). DNA on this bead was enriched by PCR using the 40 nucleotide P1 sequence. To the region GCGGATGTACGGTACAGCAG, a 20-mer complementary "primer" is annealed that has a 5' $P0_4$ which reacts with the 3Ό H group of the SOLiD probe, as well as a 3' fluorescent label for detection using capillary electrophoresis. To the overhang sequence CGAATAGA, complementary probes can hybridize to demonstrate the ligation reaction. (B) P1 covalent bead ligation substrate. Shown is a similar ligation substrate to that in Figure 1(A), however the reaction in this case will occur much closer to the bead surface. Probes are hybridized to the overhang region AGTCGGTGAT, where the underlined residues are opposite the inosine triplet of probes having the structure Dye-5' III (s)-xy-NNN 3', as described in further detail herein.

[0015] **Figure 2:** Sequences of exemplary ligases. The GenBank ID and source organism are provided where applicable. Three artificial ligases are also provided. DLX differs from Hin DNA Ligase at 1 amino acid —designated as the underlined emboldened letter. DLXd differs from Hin DNA Ligase at 2 amino acids —designated as the underlined emboldened letters. DLXd2 is 22 amino acids shorter than Hin DNA Ligase and differs from Hin DNA Ligase at 2 amino acids, designated as the underlined emboldened letters.

[0016] **Figure 3:** Ligation of short oligonucleotides with various ligases. Ligation of short oligonucleotides with (A) CV ligase, (B) DLXd ligase and (C) MnM ligase. Forward ligation reactions were performed under the following conditions : 2.0 μM ligase, 2-5 μM short oligo, 2.0 nM primer/template (tethered to magnetic beads) and proceeded for 20 minutes at 15°C. The ligation efficiency was calculated as the as the

ratio of peak areas determined by CE where a FAM labeled primer was used. Efficiency = ligated/(ligated + unligated).

[0017] **Figure 4:** Ligation of short oligonucleotides with various ligases. Ligation of short oligonucleotides with (A) CV ligase, (B) DLXd ligase and (C) MnM ligase. Reverse ligation reactions were performed under the following conditions : 2.0 μM ligase, 2-5 μM short oligo, 2.0 nM primer/template (tethered to magnetic beads) and proceeded for 20 minutes at 15°C. The ligation efficiency was calculated as the as the ratio of peak areas determined by CE where a FAM labeled primer was used. Efficiency = ligated/(ligated + unligated).

[0018] **Figure 5:** Ligation of 2-mers. Ligation reaction in the forward direction was performed under the following conditions : 2.0 μM DLXd, 123 μM dinucleotide (5'-CG-3'), 2.0 nM primer/template (tethered to magnetic beads) and proceeded for 20 minutes at 15°C. The ligation efficiency was calculated as the as the ratio of peak areas determined by CE where a FAM labeled primer was used. Efficiency = ligated/(ligated + unligated).

Definitions

[0019] "Degenerate", with respect to a position in a polynucleotide that is one of a population of polynucleotides, means that the identity of the base of the nucleoside occupying that position varies among different members of the population. A population of polynucleotides in this context is optionally a mixture of polynucleotides within a single continuous phase (e.g., a fluid). The "position" can be designated by a numerical value assigned to one or more nucleotides in a polynucleotide, generally with respect to the 5' or 3' end. For example, the terminal nucleotide at the 3' end of an extension probe may be assigned position 1. Thus in a pool of extension probes of structure 3'-XXXNXXXX-5', the N is at position 4. A position is said to be k-fold degenerate if it can be occupied by nucleosides having any of k different identities. For example, a position that can be occupied by nucleosides comprising either of 4 different bases is 4-fold degenerate.

[0020] Along similar lines, it should be understood that a statement that a result has occurred (e.g., ligation, binding) is intended to indicate that the result has occurred at a significant or substantial level or an enhanced level compared to when it has not occurred. For example. Ligation is said to have not occurred if it is not significant, insubstantial or

greatly reduced (e.g., reduced by at least 80%, 90 %, 95% or 99% compared to when ligation does occur (e.g., under the conditions described in the last paragraph).

[0021] The terms "microparticle," "beads" "microbeads", etc., refer to particles (optionally but not necessarily spherical in shape) having a smallest cross-sectional length (e.g., diameter) of 50 microns or less, preferably 10 microns or less, 3 microns or less, approximately 1 micron or less, approximately 0.5 microns or less, e.g., approximately 0.1, 0.2, 0.3, or 0.4 microns, or smaller (e.g., under 1 nanometer, about 1-10 nanometer, about 10-100 nanometers, or about 100-500 nanometers). Microparticles (e.g., Dynabeads from from Dynal, Oslo, Norway) may be made of a variety of inorganic or organic materials including, but not limited to, glass (e.g., controlled pore glass), silica, zirconia, cross-linked polystyrene, polyacrylate, polymethymethacrylate, titanium dioxide, latex, polystyrene, etc. Magnetization can facilitate collection and concentration of the microparticle-attached reagents (e.g., polynucleotides or ligases) after amplification, and facilitates additional steps (e.g., washes, reagent removal, etc.). In certain embodiments of the invention a population of microparticles having different shapes sizes and/or colors can be used. The microparticles can optionally be encoded, e.g., with quantum dots such that each microparticle can be individually or uniquely identified.

[0022] The term "sequence" refers to sequence information about a polynucleotide or polypeptide or any portion of the polynucleotide or polypeptide that is two or more units (nucleotides or amino acids) long. The term can also be used as a reference to the polynucleotide or polypeptide molecule itself or a relevant portion thereof. Polynucleotide sequence information relates to the succession of nucleotide bases on the polynucleotide, and in a polypeptide relates to the succession of amino acid side chains in the polypeptide or portion thereof. For example, if the polynucleotide contains bases Adenine, Guanine, Cytosine, Thymine, or Uracil, the polynucleotide sequence can be represented by a corresponding succession of letters A, G, C, T, or U), e.g., a DNA or RNA molecule. Sequences shown herein are presented in a 5'-→3' orientation unless otherwise indicated.

[0023] "Perfectly matched duplex" in reference to probes and template polynucleotides means that one forms a double stranded structure with the other such that each nucleoside in the double stranded structure undergoes Watson-Crick basepairing with a nucleoside on the other. The term also comprehends the pairing of nucleoside analogs, such as deoxyinosine, nucleosides with 2-aminopurine bases, and the like, that

may be employed to reduce the degeneracy of the probes, whether or not such pairing involves formation of hydrogen bonds.

[0024] The term "polymorphism" is given its ordinary meaning in the art and refers to a difference in genome sequence among individuals of the same species. A "single nucleotide polymorphism" (SNP) refers to a polymorphism at a single position.

[0025] "Probes", "oligonucleotides" or "primers" are intended to be interchangeable terms herein, so that any one of these can be taken as a reference to another. These are polynucleotides not necessarily limited to any length. Where so wished, these can be less than 100 nucleotides long, sometimes less than 30 nucleotides long, e.g., less than 20 nucleotides, optionally less than 12 nucleotides, for example less than eight nucleotides in length. In some cases, these are 2, 3, 4, 5, 6, 7, 8, or more nucleotides in length. In some cases, these are 3 or 4 nucleotides in length.

[0026] A "polynucleotide," also called a "nucleic acid," is a linear polymer of two or more nucleotides joined by covalent internucleosidic linkages, or variant or functional fragment thereof. A sequence of letters, such as "ATGCCTG," is intended to represent a polynucleotide sequence in the 5'-→3' order from left to right unless otherwise specified. In naturally occuring examples of these, the internucleoside linkage is typically a phosphodiester bond. However, other examples optionally comprise other internucleoside linkages, such as phosphorothiolate linkages and may or may not comprise a phosphate group. In other cases, the polynucleotide can contain non-nucleotidic backbones, for example, polyamide (e.g., peptide nucleic acids (PNAs)) and polymorpholino and other synthetic sequence-specific nucleic acid polymers providing that the polymers contain nucleobases in a configuration which allows for base pairing and base stacking, such as is found in DNA and RNA.

[0027] As used herein, "polynucleotide," "oligonucleotide", "probe", "primer", "template", "nucleic acid" and the like can be taken to refer to a populations or pools of individual molecules that are substantially identical across their entire length or across a relevant portion of interest. For example, the term "template" can indicate a plurality of template molecules that are substantially identical, etc. In the case of polynucleotides that are degenerate at one or more positions, it will be appreciated that the degenerate polynucleotide comprises a plurality of polynucleotide molecules, which have sequences that are substantially identical only at the nondegenerate position(s) and differ in sequence at the degenerate positions. Thus, reference to "a" polynucleotide (e.g., "a" primer, probe, oligonucleotide, template, etc.) can be taken to mean a population of

polynucleotide molecules that are substantially identical over at least a portion of interest, such that the plural nature of the population need not be explicitly indicated, but can if so desired. These terms are also intended to provide adequate support for a claim that explicitly specifies a single polynucleotide molecule itself. It will be understood that members of a population need not be 100% identical, e.g., a certain number of "errors" may occur during the course of synthesis. Preferably at least 90%, at least 95%, at least 99%, or more of the members of a population are substantially identical. Preferably the percent identity of at least 95% or more preferably at least 99% of the members of the population to a reference nucleic acid molecule is at least 98%, 99%, 99.9% or greater. Percent identity may be computed by comparing two optimally aligned sequences, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions, and multiplying the result by 100 to yield the percentage of sequence identity. It will be appreciated that in certain instances a nucleic acid molecule such as a template, probe, primer, etc., may be a portion of a larger nucleic acid molecule that also contains a portion that does not serve a template, probe, or primer function. In that case individual members of a population need not be substantially identical with respect to that portion.

[0028] The nucleotides of a polynucleotide can have any combination of bases, including those mentioned herein, for example uracil, adenine, thymine, cytosine, guanine, inosine, xathanine hypoxathanine, isocytosine, isoguanine, etc. Optionally, the polynucleotide is a DNA having the nucleotide bases A, C, T and/or G. Optionally, the polynucleotide is an RNA having the nucleotide bases A, C, T and/or U.

[0029] Polynucleotides include double- and single-stranded DNA, as well as double- and single-stranded RNA, DNA:RNA hybrids, peptide-nucleic acids (PNAs) and hybrids between PNAs and DNA or RNA, and also include known types of modifications, for example, labels which are known in the art, methylation, "caps," substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.), with negatively charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), and with positively charged linkages (e.g., aminoalklyphosphoramidates, aminoalkylphosphotriesters), those containing pendant moieties, such as, for example, proteins (including nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen,

etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide or oligonucleotide. Polynucleotides can optionally be attached to one or more non-nucleotide moieties such as labels and other small molecules, large molecules such proteins, lipids, sugars, and solid or semi-solid supports, for example through either the 5' or 3' end. Labels include any moiety that is detectable using a detection method of choice, and thus renders the attached nucleotide or polynucleotide similarly detectable using a detection method of choice. Optionally, the label emits electromagnetic radiation that is optically detectable or visible. In some cases, the nucleotide or polynucleotide is not attached to a label, and the presence of the nucleotide or polynucleotide is directly detected, and/or the generation of byproducts of ligation such as PPi or NMN is detected. Optionally, the presence of the nucleotide, polynucleotide or byproduct is sensed by a chemical field-effect transistor, e.g., where the charge on the gate electrode is generated by a chemical process. Optionally, the chemical field-effect transistor is an ion-sensitive field-effect transistor.

[0030] Where two or more reagents are labeled, the labels are preferably distinguishable from each other with the detection method of choice. For example, the labels can be spectrally resolvable, i.e., distinguishable on the basis of their spectral characteristics, particularly fluorescence emission wavelength, under conditions of operation. In other instances, the label may comprise a signal-generating compound (SGC). A SGC is optionally a substance that it itself detectable in an assay of choice, or capable of reacting to form a chemical or physical entity (i.e., a reaction product) that is detectable in an assay of choice. Representative examples of reaction products include precipitates, fluorescent signals, compounds having a color, and the like. Representative SGC include e.g., bioluminescent compounds (e.g., luciferase), fluorophores (e.g., below), bioluminescent and chemiluminescent compounds, radioisotopes (e.g., ^{131}I, ^{125}I, ^{14}C, ^{3}H, ^{35}S, ^{32}P and the like), enzymes (e.g., below), binding proteins (e.g., biotin, avidin, streptavidin and the like), magnetic particles, chemically reactive compounds (e.g., colored stains), labeled oligonucleotides; molecular probes (e.g., CY3, Research Organics, Inc.), and the like. Representative fluorophores include fluorescein isothiocyanate, succinyl fluorescein, rhodamine B, lissamine, 9,10-diphenlyanthracene, perylene, rubrene, pyrene and fluorescent derivatives thereof such as isocyanate, isothiocyanate, acid chloride or sulfonyl chloride, umbelliferone, rare earth chelates of lanthanides such as Europium (Eu) and the like. Signal generating compounds also

include SGC whose products are detectable by fluorescent and chemiluminescent wavelengths, e.g., sequencing dyes, luciferase, fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series; compounds such as luminol, isoluminol, acridinium salts, and the like; bioluminescent compounds such as luciferin; fluorescent proteins (e.g., GFP or variants thereof); and the like. The subject SGC are optionally detectable using a visual or optical method; preferably, with a method amenable to automation such as a spectrophotometric method, a fluorescence method, a chemiluminescent method, an electrical nanometric method involving e.g., a change in conductance, impedance, resistance and the like and a magnetic field method. Some SGC's are optionally detectable with the naked eye or with a signal detection apparatus when at an appropriate concentration.

[0031] A "nucleotide" refers to a nucleotide, nucleosideor analog thereof. Optionally, the nucleotide is an N- or C-glycoside of a purine or pyrimidine base. (e.g., deoxyribonucleoside containing 2-deoxy-**D**-ribose or ribonucleoside containing **D**-ribose). Examples of other analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides.

[0032] Nucleotide bases or nucleobases usually have a substituted or unsubstituted parent aromatic ring or rings. In certain embodiments, the aromatic ring or rings contain at least one nitrogen atom. In certain embodiments, the nucleotide base is capable of forming Watson-Crick and/or Hoogsteen hydrogen bonds with an appropriately complementary nucleotide base. Exemplary nucleotide bases and analogs thereof include, but are not limited to, purines such as 2-aminopurine, 2,6-diaminopurine, adenine (A), ethenoadenine, N6-A2-isopentenyladenine (6iA), N6-A2-isopentenyl-2-methylthioadenine (2ms6iA), N6-methyladenine, guanine (G), isoguanine, N2-dimethylguanine (dmG), 7-methylguanine (7 mG), 2-thiopyrimidine, 6-thioguanine (6sG) hypoxanthine and 06-methylguanine; 7-deaza-purines such as 7-deazaadenine (7-deaza-A) and 7-deazaguanine (7-deaza-G); pyrimidines such as cytosine (C), 5-propynylcytosine, isocytosine, thymine (T), 4-thiothymine (4sT), 5,6-dihydrothymine, 04-methylthymine, uracil (U), 4-thiouracil (4sU) and 5,6-dihydrouracil (dihydrouracil; **D);** indoles such as nitroindole and 4-methylindole; pyrroles such as nitropyrrole; nebularine; base (Y); etc. In certain embodiments, nucleotide bases are universal nucleotide bases. Additional exemplary nucleotide bases can be found, e.g., in Fasman, 1989, Practical Handbook of Biochemistry and Molecular Biology, pp. 385-394, CRC

Press, Boca Raton, Fla., and the references cited therein. A nucleoside is usually a compound having a nucleotide base covalently linked to the C-1′ carbon of a pentose sugar. In certain embodiments, the linkage is via a heteroaromatic ring nitrogen. Typical pentose sugars include, but are not limited to, those pentoses in which one or more of the carbon atoms are each independently substituted with one or more of the same or different —R, —OR, —NRR or halogen groups, where each R is independently hydrogen, (C1-C6) alkyl or (C5-C14) aryl. The pentose sugar may be saturated or unsaturated. Exemplary pentose sugars and analogs thereof include, but are not limited to, ribose, 2'-deoxyribose, 2'-(Cl-C6)alkoxyribose, 2'-(C5-C14)aryloxyribose, 2',3'-dideoxyribose, 2',3'-didehydroribose, 2'-deoxy-3'-haloribose, 2'-deoxy-3'-fluororibose, 2'-deoxy-3'-chlororibose, 2'-deoxy-3'-aminoribose, 2'-deoxy-3'-(Cl-C6)alkylribose, 2'-deoxy -3'-(Cl-C6)alkoxyribose and 2'-deoxy-3'-(C5-C14)aryloxyribose. One or more of the pentose carbons of a nucleoside may be substituted with a phosphate ester, as disclosed in US Pat. No 7255994. In certain embodiments, the nucleosides are those in which the nucleotide base is a purine, a 7-deazapurine, a pyrimidine, a universal nucleotide base, a specific nucleotide base, or an analog thereof. Nucleotide analogs include derivatives in which the pentose sugar and/or the nucleotide base and/or one or more of the phosphate esters of a nucleoside may be replaced with its respective analog. Exemplary pentose sugar analogs and nucleotide base analog are described above. Exemplary phosphate ester analogs include, but are not limited to, alkylphosphonates, methylphosphonates, phosphoramidates, phosphotriesters, phosphorothioates, phosphorodithioates, phosphoroselenoates, phosphorodiselenoates, phosphoroanilothioates, phosphoroanilidates, phosphoroamidates, boronophosphates, etc., and may include associated counterions. Other nucleotide analogs are nucleotide analog monomers which can be polymerized into polynucleotide analogs in which the DNA/RNA phosphate ester and/or sugar phosphate ester backbone is replaced with a different type of linkage. Exemplary polynucleotide analogs include, but are not limited to, peptide nucleic acids, in which the sugar phosphate backbone of the polynucleotide is replaced by a peptide backbone.

[0033] The internucleoside linkages can be a phosphodiester linkage, although other linkages (e.g., scissile linkages which can be substantially cleaved under conditions in which phosphodiester linkages are not substantially cleaved) can be used. For example, a linkage that contains an AP endonuclease sensitive site, for example an abasic residue, a residue containing a damaged base that is a substrate for removal by a DNA glycosylase,

or another residue or linkage that is a substrate for cleavage by an AP endonuclease, or a disaccharide nucleoside.

[0034] The adjectival term "hybridized" optionally refers to two polynucleotides which are bonded to each other by two or more sequentially adjacent base pairings. The term "hybridization" refers to the process by which polynucleotides become hybridized to each other. Two single-stranded polynucleotides can be regarded as "complementary" if when hybridized together the longer polynucleotide forms a single-stranded overhang and the shorter polynucleotide can be efficiently ligated to a third adjacent polynucleotide that forms a perfectly-matched duplex with the single-stranded overhang. Where the single-stranded overhang is less than eight nucleotides, it can be arbitrarily lengthened to eight nucleotides by adding a random combination of nucleotides to the overhang.

[0035] Similarly, nucleotide residues can be regarded as complementary if when both are base-paired with each other within two hybridized polynucleotides, either nucleotide can be ligated in a template-driven ligation reaction when situated as the terminal nucleotide in its polynucleotide. Nucleotides that are efficiently incorporated by DNA polymerases opposite each other during DNA replication under physiological conditions are also considered complementary. In an embodiment, complementary nucleotides can form base pairs with each other, such as the A-T/U and G-C base pairs formed through specific Watson-Crick type hydrogen bonding between the nucleobases of nucleotides and/or polynucleotides positions antiparallel to each other. The complementarity of other artificial base pairs can be based on other types of hydrogen bonding and/or hydrophobicity of bases and/or shape complementarity between bases.

[0036] In appropriate instances, polynucleotides can be regarded as complementary when they can undergo cumulative base pairing at two or more individual corresponding positions in antiparallel orientation, as in a hybridized duplex. Optionally there can be "complete" or "total" complementarity between a first and second polynucleotide sequence where each nucleotide in the first polynucleotide sequence can undergo a stabilizing base pairing interaction with a nucleotide in the corresponding antiparallel position on the second polynucleotide. "Partial" complementarity describes polynucleotide sequences in which at least 20%, but less than 100%, of the residues of one polynucleotide are complementary to residues in the other polynucleotide. A "mismatch" is present at any position in which the two opposed nucleotides are not complementary. In some ligation assays, a polynucleotide can undergo substantial template-dependent ligation even when it has one or more mismatches to its hybridized

template. Optionally, the polynucleotide has no more than 4, 3, or 2 mismatches, e.g., 0 or 1 mismatch, with its template. In some assays, the polynucleotide will not undergo substantial template-dependent ligation unless it is at least 60% complementary, e.g., at least about 70%, 80%, 85%, 90%, 95%, 99% or 100% complementary to its template.

[0037] As used herein, a "biological sample" refers to a sample of tissue or fluid isolated from an individual, including but not limited to, for example, plasma, serum, spinal fluid, semen, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs, and also samples of in vitro cell culture constituents (including but not limited to conditioned medium resulting from the growth of cells in cell culture medium, putatively virally infected cells, recombinant cells, and cell components).

[0038] Sequence identity (also called homology) refers to similarity in sequence of two or more sequences (e.g., nucleotide or polypeptide sequences). In the context of two or more homologous sequences, the percent identity or homology of the sequences or subsequences thereof indicates the percentage of all monomeric units (e.g., nucleotides or amino acids) that are the same (i.e., about 70% identity, preferably 75%, 80%, 85%, 90%, 95% or 99% identity). The percent identity can be over a specified region, when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection. Sequences are said to be "substantially identical" when there is at least 90% identity at the amino acid level or at the nucleotide level. Preferably, the identity exists over a region that is at least about 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 50, or 100 residues in length, or across the entire length of at least one compared sequence. A preferred algorithm for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al, Nuc. Acids Res. 25:3389-3402 (1977). Other methods include the algorithms of Smith & Waterman, Adv. Appl. Math. 2:482 (1981), andNeedleman & Wunsch, J. Mol. Biol. 48:443 (1970), etc. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions.

[0039] In the claims, any active verb (or its gerund) is intended to indicate the corresponding actual or attempted action, even if no actual action occurs. For example, the verb "hybridize" and gerund form "hybridizing" and the like refer to actual

hybridization or to attempted hybridization by contacting nucleic acid sequences under conditions suitable for hybridization, even if no actual hybridization occurs. Similarly, "detecting" and "detection" when used in the claims refer to actual detection or to attempted detection, even if no target is actually detected.

[0040] "Nonspecific hybridization" is used to refer to any unintended or insignificant hybridization, for example hybridization to an unintended polynucleotide sequence other than the intended target polynucleotide sequence. The uninentended polynucleotide sequence can be on the same or different polynucleotide from the intended target. In some cases, the only intended hybridization can be from Watson-Crick base pairing between two polynucleotides. Other kinds of intended base pairings can include base pairing between corresponding analogs of such nucleotides or between iso-cytidine and iso-guanine. In some cases where hybridization is only intended between complementary bases, any bonding between non-complementary bases is considered to be non-specific hybridization.

[0041] In reference to ligation of two polynucleotides, the "proximal" terminus of either polynucleotide is the terminus that is intended to be ligated to the other polynucleotide. This is generally the terminus that is contacted by the active site of the ligase, or the terminus that is eventually ligated to the other polynucleotide, while the opposite terminus is the "distal" terminus. The terminal nucleotide residue at the proximal terminus can be termed the proximal nucleotide, and the proximal nucleotide position optionally designated as position 1, or -1 depending on which side of the ligation site we are referring to, the penultimate nucleotide position as position 2 or -2, etc. With reference to two adjacently-hybridized polynucleotides, the proximal terminus is generally the terminus of one polynucleotide that is closer to the other polynucleotide. In some non-limiting instances of template-dependent ligation, the proximal termini of both polynucleotides are hybridized adjacently to each other.

[0042] "Support", as used herein, refers to a structure or matrix on or in which ligation reagents, e.g., nucleic acid molecules, microparticles, and the like may be immobilized so that they are significantly or entirely prevented from diffusing freely or moving with respect to one another. The reagents can for example be placed in contact with the support, and optionally covalently or noncovalently attached or partially/completely embedded

[0043] A "universal base", as used herein, is a base that is complementary to more than one other base. Fully universal bases can pair with any of the bases typically found

in naturally occurring nucleic acids. The base need not be equally capable of pairing with each of the naturally occurring bases. Alternatively, the universal base may pair only or selectively with two or more bases but not all bases. Optionally the universal base pairs only or selectively with purines, or alternatively with pyrimidines. If so desired, two or more universal bases can be included at a particular position in a probe. A number of universal bases are known in the art including, but not limited to, inosine, hypoxanthine, 3-nitropyrrole, 4- nitroindole, 5-nitroindole, 4-nitrobenzimidazole, 5-nitroindazole, 8-aza-7-deazaadenine, 6H,8H-3,4-dihydropyrimido[4,5-c][1,2]oxazin-7-one, 2-amino-6-methoxyaminopurine, etc. Hypoxanthine is one preferred fully univeral base. Nucleosides comprising hypoxanthine include, but are not limited to, inosine, isoinosine, 2'-deoxy inosine, and 7-deaza-2'-deoxyinosine, 2-aza-2'deoxyinosine.

[0044] "Purified" generally refers to isolation of a substance (compound, polynucleotide, protein, polypeptide, polypeptide composition) such that the substance comprises a significant percent, such as a higher proportion than it is naturally found (e.g., greater than 2%, greater than 5%, greater than 10%, greater than 20%, greater than 50%, or more, sometimes more than 90%, 95% or 99%) of the sample in which it resides. In certain embodiments, a substantially purified component comprises at least 50%, 80%-85%, or 90-95% of the sample. Techniques for purifying polynucleotides and polypeptides of interest are well-known in the art and include, for example, ion-exchange chromatography, affinity chromatography and sedimentation according to density. "Isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original or naturally-occurring environment of the polynucleotide.

[0045] Exemplary ligases comprise a polypeptide. The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, or any variant or functional fragment thereof. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers.

[0046] The term "amino acid" includes naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar

to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, .gamma.-carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0047] Variants or derivatives of a given nucleotide sequence or polypeptide sequence are optionally conservatively modified variants. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences.

[0048] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. (see e.g., Creighton, Proteins (1984)).

Sequence identity (also called homology) refers to similarity in sequence of two or more sequences (e.g., nucleotide or polypeptide sequences). In the context of two or more homologous sequences, the percent identity or homology of the sequences or subsequences thereof indicates the percentage of all monomeric units (e.g., nucleotides or amino acids) that are the same (i.e., about 70% identity, preferably 75%, 80%, 85%, 90%, 95% or 99% identity). The percent identity can be over a specified region, when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual

inspection. Sequences are said to be "substantially identical" when there is at least 90% identity at the amino acid level or at the nucleotide level. This definition also refers to the complement of a test sequence. Preferably, the identity exists over a region that is at least about 25, 50, or 100 residues in length, or across the entire length of at least one compared sequence. A preferred algorithm for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al, Nuc. Acids Res. 25:3389-3402 (1977). Other methods include the algorithms of Smith & Waterman, Adv. Appl. Math. 2:482 (1981), and Needleman & Wunsch, J. Mol. Biol. 48:443 (1970), etc. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements specifically hybridize to each other under stringent conditions, such as those described herein. Nucleic acids that do not specifically hybridize to each other under stringent conditions are still substantially identical if the polypeptides which they encode are substantially identical.

[0049] Two polynucleotides selectively (or specifically) hybridize to each other if they bind significantly or detectably to each other under stringent hybridization conditions when present in a complex polynucleotide mixture such as total cellular or library DNA. For selective or specific hybridization, a positive signal is at least two times background, preferably 10 times background hybridization. Optionally, stringent conditions are selected to be about 5-10° C. lower than the thermal melting point for the specific sequence at a defined ionic strength pH. Stringent conditions are optionally in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30° C. for short probes (e.g., 10 to 50 nucleotides) and at least about 60° C. for long probes (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. Exemplary stringent hybridization conditions can be as following: 50% formamide, 5.times.SSC, and 1% SDS, incubating at 42° C , or, 5.times.SSC, 1% SDS, incubating at 65° C , with wash in 0.2.times.SSC, and 0.1% SDS at 65° C.

Detailed Description

[0050] Among other novel and surprising information presented herein, the novel and surprising enzymatic ligation of short polynucleotides is presented herein.

1) LIGATIONS

[0051] Ligation herein refers to the enzymatic formation of a covalent bond between the termini of two or more or polynucleotides strands. "Ligation" involves the formation of a covalent bond or linkage between the 5' and 3' termini of two or more nucleic acids, e.g. oligonucleotides and/or polynucleotides, optionally in a template-driven reaction. The nature of the bond or linkage may vary widely and the ligation is preferably achieved enzymatically. The nature of the bond or linkage can vary widely. Non-limiting exemplary ligations are carried out enzymatically to form a phosphodiester linkage between a 5' terminal nucleotide of a polynucleotide strand with a 3' terminal nucleotide of a polynucleotide.

[0052] The ligation can be one or more of the following types of ligation described herein. A first type of enzymatic ligation involves the formation of a covalent bond between a first terminus of a first polynucleotide strand and a second different terminus of a second polynucleotide strand. The first and second polynucleotide termini can be on different polynucleotide strands, or can both be on the same polynucleotide strand (resulting in circularization). Optionally, the first and second polynucleotide strands are not both hybridized to a third polynucleotide. Optionally, the termini of the first and second polynucleotide strand are joined irrespective of their sequences (e.g., blunt-end ligation, or non-homologous end joining). In another variation, two double-stranded polynucleotides with protruding single-stranded portions that are complementary to each other can be ligated (e.g., cohesive-end ligation). A third type of ligation (template-dependent ligation) is described further below.

[0053] In any one of the methods described herein, the polynucleotide strands can be in single-stranded format or are hybridized to complementary strands in double-stranded format. In blunt-end ligation, both polynucleotide strands to be ligated are hybridized to two different complementary strands such that no overhang exists.

[0054] Methods are provided to ligate two polynucleotides. An exemplary ligation method achieves ligation between a first terminus of a first polynucleotide sequence and a second terminus of a second polynucleotide sequence. For ease of reference, the first polynucleotide sequence is called the "initializing probe" or "primer," the second polynucleotide called the "extension probe" or "probe." A third polynucleotide sequence that is optionally present (e.g., in template-dependent ligation) is termed the template or target sequence. Any one or more of the primer (initializing probe), probe (extension

probe) and/or template sequences can be located on the same polynucleotide strand, or on different polynucleotide strands. In a one-strand system, the primer, probe and template are all on the same polynucleotide strand. In an example of a two-strand system, either the probe or primer (but not both) are on the same strand as the template (e.g., hybridization between the template sequence and the primer or probe sequences forms a stem-loop structure or hairpin). In another example of a two-strand system, the probe or primer are both on the same strand. In a three-strand system, the template, primer and probe are all on separate polynucleotide strands. Any ligation method described herein can be performed in a one-strand, two-strand or three-strand system.

[0055] Optionally, ligation converts a linear polynucleotide strand into a circular polynucleotide strand (e.g., in a one-stranded to two-stranded system). Optionally, ligation reduces the number of polynucleotide strands by one (e.g., in a two-stranded or three-stranded system).

[0056] Ligation optionally creates a bond between a terminal nucleotide of the probe with the terminal nucleotide of the primer. Optionally, the proximal terminus of the primer and/or probe is ligated. The terminal nucleotide of the primer can be the 5' terminal nucleotide and the terminal nucleotide of the extension probe can be the 3' terminal nucleotide. Alternatively, the terminal nucleotide of the primer can be the 3' terminal nucleotide and the terminal nucleotide of the extension probe can be the 5' terminal nucleotide. The 5' terminus of a polynucleotide for example has the fifth carbon in the sugar-ring of the deoxyribose or ribose at its terminus, optionally with a phosphate group attached to it, where the phosphate group is capable of forming a phosphodiester bond with a 3' terminal nucleotide. The 3' terminal nucleotide optionally has a 3'-hydroxyl group that is capable of forming a phosphodiester bond with a 5' terminal nucleotide. Ligation optionally results in the formation of a phophodiester bond.

[0057] Any of the polynucleotides no matter how designated (e.g., as "probes" or "primers" or "templates") can be of any sequence, any length, in any form and from any source. The polynucleotides can comprise a naturally-occurring sequence or be highly homologous to a naturally-occurring sequence, and/or derived from a naturally occurring sequence. The naturally occurring sequence can be any portion of a gene, a regulatory sequence, genomic DNA or fragment, cDNA, RNA including mRNA and rRNA, or others. The polynucleotides can optionally comprise any artificial sequence as well. The polynucleotide can be derived or obtained from a sample such as a diagnostic sample. The polynucleotide can be a secondary product of a reaction - for example a ligation

product from a ligation reaction or assay such as those described herein, an extended probe from a PCR reaction, or PCR amplification product, ("amplicon"), the product of an invasive cleavage reaction, etc. The polynucleotide can have a 5' phosphate, or can alternatively lack a 5' phosphate.

[0058] The ligation product of any one reaction can optionally be subjected to further ligation and/or non-ligation reactions in turn. For example, the ligation product can be used as the primer (initializing probe) or extension probe and/or template in a subsequent ligation. Also for example, it can be used as a template and/or primer for a polymerase extension reaction, such as in PCR. The probe, primer, template and/or ligation product optionally can be subjected to any one or more modifications before or after ligation. For example, the probe, primer, template and/or ligation product can be cleaved enzymatically or chemically (for example at scissile linkages), treated with exo- or endonucleases, kinases, phosphatases, etc. The ends of a double-stranded product can be blunt-ended or filled in, capped, or adenylated, etc.

[0059] Optionally, the probe is not more than 20 consecutive nucleotides long, for example not more than 15, 12, 10, 8, 7 consecutive nucleotides, preferably not more than 6, 5, 4 3, or 2 consecutive nucleotides. Optionally, the probe is at least 2, 3, 4, 5, 6 or 7 nucleotides long. In some instances the probe is from any of the specified minimum lengths (e.g., 2, 3, 4, 5, 6 or 7 nucleotides long) and is not more than 20, 15, 12, 10, 8, 7 nucleotides, preferably not more than 6, 5, 4 3, or 2 nucleotides. In some examples, the probe is a 2-mer, 3-mer, 4-mer, 5-mer, 6-mer, 7-mer, 8-mer, 9-mer, 10-mer, 11-mer, 12-mer, 13-mer, 14-mer, 15-mer or 20-mer, or any combination of such oligonucleotides.

[0060] Optionally, the primer is not more than 20 consecutive nucleotides long, for example not more than 15, 12, 10, 8, 7 consecutive nucleotides, preferably not more than 6, 5, 4, 3, or 2 consecutive nucleotides. In some examples, the primer is one or more 2-mer, 3-mer, 4-mer, 5-mer, 6-mer, 7-mer, 8-mer, 9-mer, 10-mer, 11-mer, 12-mer, 13-mer, 14-mer, 15-mer or 20-mer, or any combination of such oligonucleotides.

[0061] It should be understood that the probe or primer (or template, if present) can be "mixed" or "composite," i.e., comprising a mixture of one or more polynucleotides of different sequences.

[0062] Optionally, the ligation is performed using CV ligase in combination with one or more probes that is at least 3 nucleotides long and not more than 6 or 5 nucleotides long. Optionally, the one or more probes are at least 3 nucleotides long and not more than 4 nucleotides long. In other examples the one or more probes are at least 4

nucleotides long and not more than 5 nucleotides long. Alternatively all of the one or more probes probe can be 3-mers. Otherwise all of the one or more probes probe can be 4-mers.

[0063] When the ligation is performed using DLX, DLXd, DLXd2 ligase, then optionally ligation is performed with one or more probes that is at least 2 or 3 nucleotides long and not more than 6 or 5 nucleotides long. Optionally, the one or more probes are at least 3 nucleotides long and not more than 4 nucleotides long. In other examples the one or more probes are at least 4 nucleotides long and not more than 5 nucleotides long. Alternatively all of the one or more probes probe can be 3-mers. Otherwise all of the one or more probes probe can be 4-mers.

[0064] The ligation can be a template-dependent ligation. In template-dependent ligation, ligation between a primer sequence and a probe sequence occurs upon hybridization of at least a portion of either or both sequences to a template sequence. In some instances, both probes must hybridize to the template for significant ligation to occur. In a typical example, template-dependent ligation cannot take place unless both polynucleotides are hybridized to the template sequence. The portion of the primer or probe that is hybridized to the target sequence is generally at least two nucleotides long. The hybridized portion is optionally not more than 20 consecutive nucleotides long, for example not more than 15, 12, 10, 8, 7 consecutive nucleotides, preferably not more than 6, 5, 4, 3, or 2 consecutive nucleotides. The hybridized portion is optionally a terminal portion of the first or second polynucleotide (e.g., a portion that includes the 5' or 3' terminal nucleotide). For example, the hybridized portion can consist of the terminal 2, 3, 4, 5, 6, 7, 8, 10, 15 or 20 nucleotides of the 5' or 3' end.

[0065] Optionally, ligation occurs when no mismatch is present within one or more hybridized portions. In other cases, ligation occurs when one, two or three mismatches can be present within one or more hybridized portions. In some cases ligation does not occur when the terminal nucleotide and/or second-most terminal nucleotide and/or third-most terminal nucleotide is mismatched. As mentioned, the terminal nucleotides can be the 5'- or 3'- terminal nucleotides of the polynucleotide.

[0066] Optionally the template, if present, is not more than 11 nucleotides in length, for example not more 10, 9, 8, 7, 6, 5, or 4 nucleotides. Optionally the template is one or more N-mers, where N is 4, 5, 6, 7, 8, 9, 10 or 11.

[0067] Optionally, template-dependent ligation of a nucleic acid comprises: a) providing a first oligonucleotide having less than 6 nucleotides; b) providing a second

oligonucleotide; c) bringing the 3' termini of one of the first and second oligonucleotides into proximity with the 5' termini of the other oligonucleotide; and d) ligating the first and the second oligonucleotides. Optionally, the first oligonucleotide has a length of 5 nucleotides. Optionally, the first oligonucleotide has a length of 4 nucleotides. Optionally, the first oligonucleotide has a length of 3 nucleotides. Optionally, the ligation is performed using a small-footprint ligase (SFL). Optionally, the second oligonucleotide includes a sequence complementary to a portion of a template nucleic acid. Optionally, the second oligonucleotide is hybridized to the template nucleic acid at the region of complementarity. Optionally, the first oligonucleotide has a sequence complementary to the template nucleic acid. Optionally, the first oligonucleotide is hybridized to the template nucleic acid at the region of complementarity, and wherein a terminus of the first oligonucleotide is adjacent to a terminus of the second oligonucleotide.

[0068] In some variations, (e.g., "nick ligation" or "template-dependent" ligation), both primer and probe must hybridize adjacently to each other on the template for ligation to occur. Optionally, the probe and primer are adjacently hybridized and can be ligated only when a terminal nucleotide of the primer is hybridized to a first nucleotide of the template and a terminal nucleotide of the extension probe is hybridized to a second nucleotide of the template, where the first and second nucleotides on the template are not separated by an intervening nucleotide of the template. In other embodiments, intervening nucleotides may be present between the first and second nucleotides on the template (optionally a few nucleotides, e.g., not more than 1, 2, 3, 5, 10 or 15 nucleotides). In such embodiments, a "gap-filling" step can be performed to extend the 3' terminus of the probe or probe before it can be ligated to the 5' terminus of the other.

[0069] Optionally, at least one of the probe, the template (if the ligation is template-dependent) and/or the primer is immobilized while another of these three is labeled. For example in ligation sequencing the template and/or primer can be immobilized and the probe can be labeled.

[0070] A probe can for example be N nucleotide residues in length, where N is from 2 to 10, e.g., 2, 3, or 4. N can also be less than 6, for example if the proximal terminus of the probe is its 3' terminus.

[0071] Optionally, ligation is a "forward" ligation (i.e., ligation of the 3' terminus of the probe to the 5' terminus of the primer). Alternatively, "reverse" ligation can be achieved, where the 5' terminus of the probe is ligated to the 3' terminus of the primer.

[0072] A probe can also be of length N, and can comprise a proximal portion that is perfectly hybridized to the template and is L nucleotides long, where the probe's L+1th nucleotide is mismatched with the template. L can be, for example, from 2 to 8, and furthermore can be less than 6 if the proximal terminus of the probe is its 3' terminus. In other embodiments, L can be 2, 3, 4, 5, 6, 7 or 8.

[0073] The ligation can be repeated at least once, for any desired number of cycles. Optionally, any ligation product of a previous ligation reaction is used as the primer of a next ligation. Optionally, all ligations extend the ligation product in the same direction. For example, all ligation reactions can be forward ligations or all can be reverse ligations. In other embodiments, some ligations can be forward and some reverse. Optionally any unligated primer is rendered unligatable before initiating the next ligation. If so desired (e.g., in ligation sequencing), the method further comprises detecting whether the probe has ligated to the primer before repeating the next ligation reaction.

[0074] Where so desired, any ligation product of the previous ligation reaction can be used as the template of the next ligation reaction, e.g., in a ligase chain reaction.

[0075] Optionally, the 5' end of the probe less than 6 nucleotides long is ligated to the 3' end of the primer by a SFL such as CV ligase. For example the probe is 2, 3 or 4 nucleotides long. If so desired, the primer is also a short oligonucleotides. For example, the primer can be less than 6 nucleotides, e.g., 3 or 4 nucleotides long.

[0076] The ligation should produce a significant or detectable amount of ligation product. Optionally, the efficiency of ligation is at least 5%, sometimes at 10%, 20%, 30%, 50%, 60%, 70%, 75%, 80%, 85%, 90% or 95%. The efficiency of ligation (in percentage terms) can in some embodiment be regarded as the percent portion of ligation reagent that is ligated to form ligation product at the end of the ligation reaction. Efficiency is optionally determined after a ligation reaction has reach equilibrium such that increasing the ligation time will not result in a substantial increase of ligation product formed. Generally, a ligation reaction can be said to have reached equilibrium after 20 minutes. For example, a ligation reaction in which 90% of the primer or probe is ligated can be said to have proceeded at 90% efficiency. The ligation reagent used to measure ligation efficiency is optionally whichever reagent that is in lower concentration than the others. Optionally, the other reagents and conditions are non-limiting to the ligation efficiency (e.g., other reagents are present in excess or at a concentration that is at least equal to or higher than the limiting reagent).

[0077] In some embodiments, the SFL can ligate a short probe that is shorter than N nucleotides at least X% as efficiently as the SFL can ligate the corresponding N-mer. N is optionally 4, 5, 6, 7, 8, 10, 12, 15 or 20. In some embodiments N is 6 or 7. X is optionally at least 30%, 50%, 60%, 70%, 80% or 90%. In some embodiments of template-dependent ligation, the length of short probe is Y residues, and the Y proximal residues of the corresponding longer N-mer are identical to the probe, and the distal N-Y residues of the corresponding longer N-mer are perfectly complementary to the template. Y is for example 2, 3, 4, 5 or 6.

[0078] In some embodiments, the SFL can ligate a short probe that is shorter than N nucleotides when the short probe is conjugated to a dye approximately as efficiently as the SFL can ligate the unconjugated probe. N is optionally 4, 5, 6, 7, 8, 10, 12, 15 or 20. In some embodiments N is 6 or 7. In other embodiments, the SFL can ligate the short probe conjugated to a dye at least 30%, 50%, 60%, 70%, 80% or 90% as efficiently as the SFL can ligate the unconjugated probe. Exemplary dyes include Cy5.

[0079] It is understood that ligation efficiency (whether expressed in absolute or relative terms) may increase or decrease depending on the exact reaction conditions used. Optionally, the ligation efficiency is measured when the primer or probe is at a concentration of about 10^{-9} to 10^{-4} M, for example at about 10^{-8}, 10^{-7}, 10^{-6}, or 10^{-5} M. In certain applications, for example sequencing applications, a working concentration often used in the range of 10^{-8} to 10^{-5}, e.g., 10^{-7}or 10^{-6} M of probe. Where a mixture of probes are used, the probe concentration is the concentration of only those probes that are capable of being ligated in that particular ligation reaction (e.g., probe(s) complementary to the template). Thus other probes that are not capable of participating in the ligation reaction are optionally not considered when calculating the concentration of the probe of interest. Optionally, the concentration of probe is between 1 picomolar and 1 millimolar, for example about 0.01-100 μM, e.g., 1-10 μM, e.g., 1-5 μM. In the case of 2-mers, the concentration is optionally increased to 10-1000 μM, for example about 100 μM. Optionally, the concentration of ligase is between 1 picomolar and 1 millimolar, e.g., 1-2 micromolar.. Optionally, the ligation assay is performed at 15-35°C, for example 15 °C, 20 °C, 25 °C or 30 °C. Where two or more reagents are involved and the concentration of one particular reagent is specified, the other reagents are optionally in excess and/or not at a concentration that is limiting for the ligation.

[0080] Ligation can be performed under in vitro conditions that have been experimentally determined to be suitable or optimal for ligase activity. Preferably, the

reaction conditions of choice are (i) substantially similar to in vivo or physiological conditions in which a naturally-occurring form of the ligase being used is active, or (ii) have been experimentally determined to result in a ligation efficiency that is comparable to or better than the efficiency obtained using conditions of type (i). If exemplary in vitro ligation conditions are specified herein for a particular SFL, then substantially similar reaction conditions are generally appropriate for that particular ligase. In other embodiments, the conditions are such that the reference ligation assay produces significant or detectable ligation within 30 minutes, within 10 minutes, within 1 minute, or within ten seconds. Another non-limiting example of a significant or detectable efficiency of ligation generates in the range of 100 pM of ligation product, optionally about 1000 pM or 10,000 pM.

[0081] Optionally, relative efficiency can be expressed as relative percent efficiency, which can be calculated as A/B x 100, where A is the percent of test reagent (e.g., probe) ligated in a test assay and B is the percent of the reference reagent (e.g., reference probe) that is ligated in a reference assay. Where the relative efficiency of ligation is specified in comparative or relative terms by comparison to a reference ligation assay, it is implicit that all other reagents and conditions (e.g., temperature, concentration of all reagents, pH, concentration of requisite ions such as Mg++ and Mn++, concentration of requisite cofactors such as NAD and/or ATP, salts, buffers, molar concentrations of all reagents, including enzyme, template, probe, primer, oligonucleotides, etc) are otherwise kept identical. For example, a proviso that a SFL can ligate a short (e.g., less than 6 nucleotides) probe at least X% as efficiently as the SFL can ligate a corresponding octanucleotide, can be taken to mean that the two different ligation assays all reagents except for the probes (e.g., primer, template, enzymes and any other reagents) and all reaction conditions (e.g., temperature, reagent concentrations, concentrations of any other reagents, etc) are kept the same for practical purposes.

[0082] Optionally, the ligase has a better ligation efficiency than T4 DNA ligase, for example in any method described herein. In an embodiment, the ligation efficiency is higher than that of T4 DNA ligase for the same mix of probe(s), primer(s) and template(s), in any ligation method and chosen conditions, including any described herein. The ligation efficiency is for example at least 5% higher than T4 ligase, optionally at least 10%, 15% or 20% higher. The increase in efficiency should be statistically reliable and significant, e.g., with a confidence interval of at least 95%, 99%, 99.9%, 99.99%, or 99.999999%. In an example, the SFL shows higher efficiency than T4

DNA ligase when ligating a probe of 8 nucleotides or less to a primer in the forward or reverse direction. The ligase, template, probe, primer and/or ligation assay conditions are for example any described herein.

[0083] The ligase optionally has good ligation fidelity. The ligation fidelity can be assessed as the percentage of incorrect ligation events for a given combination of ligase, template, primer and probe. An incorrect ligation event is one in which the probe or the primer is not perfectly complementary to the template, or the ligation product is not perfectly complementary to the template. In an embodiment, the ligation fidelity is higher than that of T4 DNA ligase for the same mix of probe(s), primer(s) and template(s), in any ligation method and chosen conditions, including any described herein. The ligation fidelity is for example at least 5% higher than T4 ligase, optionally at least 10%, 15% or 20% higher. The increase in fidelity should be statistically reliable and significant, e.g., with a confidence interval of at least 95%, 99%, 99.9%, 99.99%, or 99.999999%. In an example, the SFL shows higher fidelity than T4 DNA ligase when ligating a probe of 8 nucleotides or less to a primer in the forward or reverse direction. The ligase, template, probe, primer and/or ligation assay conditions are for example any described herein.

2) SMALL FOOTPRINT LIGASES

[0084] Optionally, the enzymatic ligation of polynucleotides is achieved by a small footprint ligase (SFL). For example, any ligation method provided herein can use a ligase shown in Table 1A, IB or 1C. A SFL is a ligase that can ligate short polynucleotides. As used herein, the term "ligase" is intended to include any fragment or variant or derivative of that ligase. The fragment or variant or derivative optionally possesses one or more functional activities of a ligase. A SFL optionally comprises a polypeptide having any one or more of the following activities: (1) nucleophilic attack on ATP or NAD^+ resulting in release of PPi or NMN and formation of a covalent ligase-adenylate intermediate; (2) transferring the adenylate to the 5'-end of the 5'-phosphate-terminated DNA strand to form DNA-adenylate (e.g., the 5'-phosphate oxygen of the DNA strand attacks the phosphorus of ligase-adenylate); and (3) formation of a covalent bond joining the polynucleotide termini and liberation of AMP (e.g., by the attack by the 3'-OH on DNA-adenylate). Optionally, the SFL can mediate any one or more of the following bond transformations: from phosphoanhydride (ATP) to phosphoramidate (ligase-

adenylate); from phosphoramidate (ligase-adenylate) to phosphoanhydride (DNA-adenylate); or from phosphoanhydride (DNA-adenylate) to phosphodiester (sealed DNA). Thus, exemplary SFLs can comprise a polypeptide sequence that is homologous to or a variant of a known SFL sequence or any portion thereof. Exemplary SFLs optionally have amino acid sequence identity of at least 70%, optionally at least 85%, optionally at least 90, 95%, 97% or 99%, with a known ligase or known SFL.

[0085] Representative examples of SFLs include CV ligase, DLX, DLXd, DLXd2 and MnM ligase. A preferred SFL is Chlorella Virus ligase. Some exemplary ligases are identified and their GI or accession numbers are provided in Table 1A below:

Table 1A

PRK08224		
Organism	**Protein name**	**Accession**
B.Acidobacteria		
Candidatus Koribacter versatilis Ellin345Candidatus Koribacter (1 proteins)	ATP-Dependent DNA Ligase	YP_592504
Candidatus Solibacter usitatus Ellin6076Candidatus Solibacter (1 proteins)	ATP-Dependent DNA Ligase	YP_826317
CActinobacteria		
Acidothermus cellulolyticus llBAcidothermus (1 proteins)	ATP-Dependent DNA Ligase	YP_873134
Actinosynnema mirum DSM 43827Actinosynnema (1 proteins)	ATP-Dependent DNA Ligase	YP_003099374
Arthrobacter aurescens TClArthrobacter (3 proteins)	ATP-Dependent DNA Ligase	YP_949544
Arthrobacter chlorophenolicus A6Arthrobacter (3 proteins)	ATP-Dependent DNA Ligase	YP_002489901
Arthrobacter sp. FB24Arthrobacter (3 proteins)	ATP-Dependent DNA Ligase	YP_833558
Beutenbergia cavernae DSM 12333Beutenbergia (1 proteins)	ATP-Dependent DNA Ligase	YP_002880505
Catenulispora acidiphila DSM 44928Catenulispora (2 proteins)	ATP-Dependent DNA Ligase	YP_003116519

Catenulispora acidiphila DSM 44928Catenulispora (2 proteins)	ATP-Dependent DNA Ligase	YP_003 116565
Frankia alni ACN14aFrankia (2 proteins)	ATP-Dependent DNA Ligase	YP_712338
Frankia sp. EANlpecFrankia (2 proteins)	ATP-Dependent DNA Ligase	YP_00 150943 3
Kineococcus radiotolerans SRS30216Kineococcus (1 proteins)	ATP-Dependent DNA Ligase	YP_00 13 60406
Kytococcus sedentarius DSM 20547Kytococcus (1 proteins)	ATP-Dependent DNA Ligase	YP_003 149340
Mycobacterium abscessus ATCC 19977Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_001701033
Mycobacterium avium 1(MMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_879648
Mycobacterium avium subsp. paratuberculosis K-l (Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	NP_959275
Mycobacterium gilvum PYR-GCKMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_00 1132524
Mycobacterium gilvum PYR-GCKMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_00 1132543
Mycobacterium marinum MMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_001 853525
Mycobacterium smegmatis str. MC2 155Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_890520
Mycobacterium smegmatis str. MC2 155Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_890521
Mycobacterium sp. JLSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_001073538
Mycobacterium sp. JLSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_001073546
Mycobacterium sp. JLSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_001073574
Mycobacterium ulcerans Agy99Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_907815
Mycobacterium vanbaalenii PYR-	ATP-Dependent DNA	YP_956315

1Mycobacterium (26 proteins)	Ligase	
Mycobacterium vanbaalenii PYR-1Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_956321
Mycobacterium tuberculosis H37RaMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_001285120
Mycobacterium tuberculosis H37RvMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	NP_2 18248
Mycobacterium bovis AF2122/97Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	NP_857396
Mycobacterium bovis BCG str. Pasteur 1173P2Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_979871
Mycobacterium bovis BCG str. Tokyo 172Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_002646832
Mycobacterium tuberculosis CDC1551Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	NP_338389
Mycobacterium tuberculosis F1 1Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_00 1289690
Mycobacterium tuberculosis KZN 1435Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_003033779
Mycobacterium sp. KMSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_940984
Mycobacterium sp. MCSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_642076
Mycobacterium sp. KMSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_941006
Mycobacterium sp. MCSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_642099
Nakamurella multipartita DSM 44233Nakamurella (1 proteins)	ATP-Dependent DNA Ligase	YP_003200226
Nocardia farcinica IFM 10152Nocardia (1 proteins)	ATP-Dependent DNA Ligase	YP_1 18771
Nocardioides sp. JS614Nocardioides (1 proteins)	ATP-Dependent DNA Ligase	YP_922117
Rhodococcus erythropolis PR4Rhodococcus (3 proteins)	ATP-Dependent DNA Ligase	YP_002768423
Rhodococcus jostii RHA1 Rhodococcus (3	ATP-Dependent DNA	YP_705046

proteins)	Ligase	
Rhodococcus opacus B4Rhodococcus (3 proteins)	ATP-Dependent DNA Ligase	YP_002782360
Saccharopolyspora erythraea NRRL 2338Saccharopolyspora (1 proteins)	ATP-Dependent DNA Ligase	YP_001104098
Salinispora arenicola CNS-205 Salinispora (2 proteins)	ATP-Dependent DNA Ligase	YP_001536378
Salinispora tropica CNB-440Salinispora (2 proteins)	ATP-Dependent DNA Ligase	YP_001 158390
Streptomyces avermitilis MA-4680Streptomyces (3 proteins)	ATP-Dependent DNA Ligase	NP_822873
Streptomyces coelicolor A3(2)Streptomyces (3 proteins)	ATP-Dependent DNA Ligase	NP_630780
Streptomyces griseus subsp. griseus NBRC 13350Streptomyces (3 proteins)	ATP-Dependent DNA Ligase	YP_00 1822536
F.Chlamydiae/Verrucomicrobia		
Opitutus terrae PB90-lOpitutus (1 proteins)	ATP-Dependent DNA Ligase	YP_001821013
N.Alphaproteobacteria		
Bradyrhizobium japonicum USDA llOBradyrhizobium (3 proteins)	ATP-Dependent DNA Ligase	NP_771853
Bradyrhizobium sp. BTAilBradyrhizobium (3 proteins)	ATP-Dependent DNA Ligase	YP_00123 6299
Bradyrhizobium sp. ORS278Bradyrhizobium (3 proteins)	ATP-Dependent DNA Ligase	YP_00 1202307
Chelativorans sp. BNClChelativorans (1 proteins)	ATP-Dependent DNA Ligase	YP_675242
Mesorhizobium loti MAFF303099Mesorhizobium (2 proteins)	ATP-Dependent DNA Ligase	NP_108245
Mesorhizobium loti MAFF303099 (plasmid)Mesorhizobium (2 proteins)	ATP-Dependent DNA Ligase	NP_109531
Methylocella silvestris BL2Methylocella (1 proteins)	ATP-Dependent DNA Ligase	YP_002363964
Nitrobacter hamburgensis X14Nitrobacter (1	ATP-Dependent DNA	YP_579055

proteins)	Ligase	
Phenylobacterium zucineum HLKlPhenylobacterium (1 proteins)	ATP-Dependent DNA Ligase	YP_002131547
Rhizobium leguminosarum bv. trifolii WSM2304 (plasmid)Rhizobium (2 proteins)	ATP-Dependent DNA Ligase	YP_002279148
Rhizobium sp. NGR234 (plasmid)Rhizobium (2 proteins)	ATP-Dependent DNA Ligase	YP_002823307
	ATP-Dependent DNA Ligase	
Sinorhizobium medicae WSM419 (plasmid)Sinorhizobium (2 proteins)	ATP-Dependent DNA Ligase	YP_001312861
Sinorhizobium meliloti 1021 (plasmid)Sinorhizobium (2 proteins)	ATP-Dependent DNA Ligase	NP_436551
P.Deltaproteobacteria		
Anaeromyxobacter dehalogenans 2CP-1Anaeromyxobacter (5 proteins)	ATP-Dependent DNA Ligase	YP_002491286
Anaeromyxobacter dehalogenans 2CP-CAnaeromyxobacter (5 proteins)	ATP-Dependent DNA Ligase	YP_464028
Anaeromyxobacter sp. Fwl09-5Anaeromyxobacter (5 proteins)	ATP-Dependent DNA Ligase	YP_001378773
Anaeromyxobacter sp. Fwl09-5Anaeromyxobacter (5 proteins)	ATP-Dependent DNA Ligase	YP_001381200
Anaeromyxobacter sp. KAnaeromyxobacter (5 proteins)	ATP-Dependent DNA Ligase	YP_002 133229
PRK09125		
Organism	**Protein name**	**Accession**
O.Betaproteobacteria		
Acidovorax sp. JS42Acidovorax (1 proteins)	DNA ligase	YP_986978
Aromatoleum aromaticum EbNlAromatoleum (1 proteins)	DNA ligase	YP_161050
Azoarcus sp. BH72Azoarcus (1 proteins)	DNA ligase	YP_934633
Candidatus Accumulibacter phosphatis clade IIA str. UW-1 Candidatus Accumulibacter (1 proteins)	DNA ligase	YP_003 169249
Dechloromonas aromatica RCBDechloromonas (1 proteins)	DNA ligase	YP_2 84461

Diaphorobacter sp. TPSYDiaphorobacter (1 proteins)	DNA ligase	YP_002553689
Herminiimonas arsenicoxydansHerminiimonas (1 proteins)	DNA ligase	YP_00 1100009
Leptothrix cholodnii SP-6Leptothrix (1 proteins)	DNA ligase	YP_00 179 1742
Methylibium petroleiphilum PMlMethylibium (1 proteins)	DNA ligase	YP_001020556
Neisseria gonorrhoeae FA 1090Neisseria (7 proteins)	DNA ligase	YP_209054
Neisseria gonorrhoeae NCCPl 1945Neisseria (7 proteins)	DNA ligase	YP_002002827
Neisseria meningitidis 053442Neisseria (7 proteins)	DNA ligase	YP_001598310
Neisseria meningitidis FAM18Neisseria (7 proteins)	DNA ligase	YP_975951
Neisseria meningitidis MC58Neisseria (7 proteins)	DNA ligase	NP_275038
Neisseria meningitidis Z2491Neisseria (7 proteins)	DNA ligase	YP_002341892
Neisseria meningitidis alphal4Neisseria (7 proteins)	DNA ligase	YP_003082363
Polaromonas naphthalenivorans CJ2Polaromonas (2 proteins)	DNA ligase	YP_9 82249
Polaromonas sp. JS666Polaromonas (2 proteins)	DNA ligase	YP_549233
Rhodoferax ferrireducens T 118Rhodoferax (1 proteins)	DNA ligase	YP_522700
Thauera sp. MZlTThauera (1 proteins)	DNA ligase	YP_002353773
Thiobacillus denitrificans ATCC 25259Thiobacillus (1 proteins)	DNA ligase	YP_3 14570
Variovorax paradoxus SI lOVariovorax (1 proteins)	DNA ligase	YP_002944627
Verminephrobacter eiseniae EF01-2Verminephrobacter (1 proteins)	DNA ligase	YP_998235

P.Deltaproteobacteria		
Desulfobacterium autotrophicum HRM2Desulfobacterium (1 proteins)	LigA2	YP_002604477
Myxococcus xanthus DK 1622Myxococcus (1 proteins)	DNA ligase	YP_628883
Q.Epsilonproteobacteria		
Arcobacter butzleri RM4018Arcobacter (1 proteins)	ATP-dependent DNA ligase	YP_oo1489632
Campylobacter concisus 13826Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_001467307
Campylobacter curvus 525.92Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_001407695
Campylobacter fetus subsp. fetus 82-40Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_892536
Campylobacter hominis ATCC BAA-381Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_001406356
Campylobacter jejuni RM 122 1Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_17981 1
Campylobacter jejuni subsp. doylei 269.97Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_001398949
Campylobacter jejuni subsp. jejuni 81-176Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_001001312
Campylobacter jejuni subsp. jejuni 81116Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_00 1483 144
Campylobacter jejuni subsp. jejuni NCTC 11168Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_002345037
Campylobacter lari RM2100Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_002574655
Sulfurimonas denitrificans DSM 1251Sulfurimonas (1 proteins)	DNA ligase	YP_393098
R.Gammaproteobacteria		
Actinobacillus succinogenes 130ZActinobacillus (1 proteins)	ATP-dependent DNA ligase	YP_001344487
Aggregatibacter actinomycetemcomitans D11S-1Aggregatibacter (2 proteins)	ATP-dependent DNA ligase	YP_003256304
Aggregatibacter aphrophilus	ATP-dependent DNA ligase	YP_003007537

NJ8700Aggregatibacter (2 proteins)		
Alcanivorax borkumensis SK2Alcanivorax (1 proteins)	ATP-dependent DNA ligase	YP_694422
Aliivibrio salmonicida LFI1238Aliivibrio (3 proteins)	ATP-dependent DNA ligase	YP_002262821
Vibrio fischeri ESI 14Aliivibrio (3 proteins)	ATP-dependent DNA ligase	YP_204833
Vibrio fischeri MJ11Aliivibrio (3 proteins)	ATP-dependent DNA ligase	YP_002156265
Alteromonas macleodii 'Deep ecotype'Alteromonas (1 proteins)	ATP-dependent DNA ligase	YP_002127707
Mannheimia succiniciproducens MBEL55EBasfia (1 proteins)	ATP-dependent DNA ligase	YP_088131
Colwellia psychrerythraea 34HColwellia (1 proteins)	ATP-dependent DNA ligase	YP_271053
Haemophilus influenzae 86-028NPHaemophilus (3 proteins)	ATP-dependent DNA ligase	YP_248841
Haemophilus influenzae PittEEHaemophilus (3 proteins)	ATP-dependent DNA ligase	YP_001290961
Haemophilus influenzae PittGGHaemophilus (3 proteins)	ATP-dependent DNA ligase	YP_001293088
Haemophilus somnus 129PTHistophilus (2 proteins)	ATP-dependent DNA ligase	YP_719536
Haemophilus somnus 2336Histophilus (2 proteins)	ATP-dependent DNA ligase	YP_001783642
Idiomarina loihiensis L2TRIdiomarina (1 proteins)	ATP-dependent DNA ligase	YP_156435
Marinobacter aquaeolei VT8Marinobacter (1 proteins)	ATP-dependent DNA ligase	YP_960951
Marinomonas sp. MWYL1Marinomonas (1 proteins)	ATP-dependent DNA ligase	YP_001341226
Photobacterium profundum SS9Photobacterium (1 proteins)	ATP-dependent DNA ligase	YP_132765
Pseudoalteromonas atlantica T6cPseudoalteromonas (2 proteins)	ATP-dependent DNA ligase	YP_659659
Pseudoalteromonas haloplanktis TAC125Pseudoalteromonas (2 proteins)	ATP-dependent DNA ligase	YPJ40675

Psychromonas ingrahamii 37Psychromonas (1 proteins)	ATP-dependent DNA ligase	YP_942593
Shewanella amazonensis SB2B Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_927870
Shewanella baltica OS155Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_oo1050227
Shewanella baltica OS 185 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_00 13 66044
Shewanella baltica OS 195 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_001554317
Shewanella baltica OS223 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_002358357
Shewanella frigidimarina NCIMB 400Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_750174
Shewanella halifaxensis HAW-EB4Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_001673966
Shewanella loihica PV-4Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_00 10937 13
Shewanella oneidensis MR- 1Shewanella (18 proteins)	ATP-dependent DNA ligase	NP_7 17802
Shewanella pealeana ATCC 700345 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_00 1502366
Shewanella piezotolerans WP3 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_0023 12387
Shewanella sediminis HAW-EB3 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_00 1474374
Shewanella sp. ANA-3 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_870036
Shewanella sp. MR-4 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_734321
Shewanella sp. MR-7 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_738313
Shewanella woodyi ATCC 51908Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_00 1760369
Shewanella putrefaciens CN-32Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_00 1183272
Shewanella sp. W3- 18-1 Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_963655

Thiomicrospira crunogena XCL-2Thiomicrospira (1 proteins)	ATP-dependent DNA ligase	YP_391938
Vibrio cholerae MJ-1236Vibrio (9 proteins)	ATP-dependent DNA ligase	YP_002878565
Vibrio parahaemolyticus RIMD 22 1063 3Vibrio (9 proteins)	DNA ligase	NP_797856
Vibrio splendidus LGP32Vibrio (9 proteins)	DNA ligase	YP_002417130
Vibrio vulnificus CMCP6Vibrio (9 proteins)	DNA ligase	NP_761477
Vibrio vulnificus YJ016Vibrio (9 proteins)	DNA ligase	NP_934427
Vibrio cholerae M66-2Vibrio (9 proteins)	DNA ligase	YP_002810248
Vibrio cholerae 0 1 biovar El Tor str. N 16961 Vibrio (9 proteins)	DNA ligase	NP_231 182
Vibrio cholerae 0 395Vibrio (9 proteins)	DNA ligase	YP_oo 12 17094
Vibrio cholerae 0 395Vibrio (9 proteins)	DNA ligase	YP_0028 19900
PHA0454		
Organism	**Protein name**	**Accession**
b.Viruses		
Enterobacteria phage 13aT7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_002003941
Enterobacteria phage BA14T7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_002003458
Enterobacteria phage EcoDSlT7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_002003747
Enterobacteria phage KlFT7-like viruses (16 proteins)	ATP-dependent DNA ligase	YPJ38096
Enterobacteria phage T3T7-like viruses (16 proteins)	ATP-dependent DNA ligase	NP_523305
Enterobacteria phage T7T7-like viruses (16 proteins)	ATP-dependent DNA ligase	NP_041963
Klebsiella phage K1 1T7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_002003797
Kluyvera phage KvplT7-like viruses (16 proteins)	DNA ligase	YP_002308390
Morganella phage MmPlT7-like viruses (16	ATP-dependent DNA ligase	YP_002048633

proteins)		
Pseudomonas phage gh-lT7-like viruses (16 proteins)	ATP-dependent DNA ligase	NP_8 13751
Salmonella phage phiSG-JL2T7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_00 1949754
Vibriophage VP4T7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_249578
Yersinia pestis phage phiAl 122T7-like viruses (16 proteins)	ATP-dependent DNA ligase	NP_848267
Yersinia phage BerlinT7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_9 18989
Yersinia phage Yepe2T7-like viruses (16 proteins)	ATP-dependent DNA ligase	YP_002003318
Yersinia phage phiYe03-12T7-like viruses (16 proteins)	ATP-dependent DNA ligase	NP_052075
Enterobacteria phage LKAlphiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_00 1522868
Enterobacteria phage phiKMVphiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	NP_877456
Pseudomonas phage LKD16phiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_00 1522807
Pseudomonas phage LUZ19phiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_00 167 1961
Pseudomonas phage PT2phiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_002117800
Pseudomonas phage PT5phiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_002117741
Pseudomonas phage phikF77phiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_002727838
CLSZ2445448		
Organism	**Protein name**	**Accession**
a.Eukaryota		
Paramecium tetraurelia strain d4-2Paramecium (5 proteins)	DNA ligase	XP_00 1347270
Paramecium tetraurelia strain d4-2Paramecium (5 proteins)	hypothetical protein	XP_00 1422985

Paramecium tetraurelia strain d4-2Paramecium (5 proteins)	hypothetical protein	XP_00 143 1968
Paramecium tetraurelia strain d4-2Paramecium (5 proteins)	hypothetical protein	XP_001435874
Paramecium tetraurelia strain d4-2Paramecium (5 proteins)	hypothetical protein	XP_00 1460273
Tetrahymena thermophilaTetrahymena (1 proteins)	ATP dependent DNA ligase	XP_00101 1861
CLSP2344013		
Organism	**Protein name**	**Accession**
b.Viruses		
Enterobacteria phage Felix Olunclassified Myoviridae (4 proteins)	Putative DNA ligase	NP_944942
Enterobacteria phage WV8unclassified Myoviridae (4 proteins)	hypothetical protein	YP_002922879
Erwinia phage phiEa2 l-4unclassified Myoviridae (4 proteins)	putative DNA ligase	YP_002456101
Escherichia phage rv5unclassified Myoviridae (4 proteins)	ATP-dependent DNA ligase	YP_002003586
PRK07636		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Bacillus clausii KSM-K16Bacillus	ATP-dependent DNA ligase	YP_1 76304
Bacillus subtilis subsp. subtilis str. 168Bacillus	ATP-dependent DNA ligase	NP_3 89932
Bacillus licheniformis ATCC 14580Bacillus	ATP-dependent DNA ligase	YP_078721
Bacillus licheniformis ATCC 14580Bacillus	ATP-dependent DNA ligase	YP_091 132
Geobacillus sp. Y412MC10Geobacillus	ATP dependent DNA ligase	YP_003240778
Paenibacillus sp. JDR-2Paenibacillus	ATP dependent DNA ligase	YP_003009892
CLSK2551528		
Organism	**Protein name**	**Accession**
J.Firmicutes		

Geobacillus sp. Y412MC10Geobacillus (1 proteins)	ATP dependent DNA ligase	YP_003245332
Paenibacillus sp. JDR-2Paenibacillus (1 proteins)	ATP dependent DNA ligase	YP_003013681
CLSK2532515		
Organism	**Protein name**	**Accession**
B.Acidobacteria		
Candidatus Solibacter usitatus Ellin6076Candidatus Solibacter (1 proteins)	ATP dependent DNA ligase	YP_829024
E.Bacteroides/Chlorobi		
Flavobacteriaceae bacterium 3519-10unclassified Flavobacteriaceae (1 proteins)	ATP-dependent DNA ligase	YP_003095681
CLSK2470953		
Organism	**Protein name**	**Accession**
CActinobacteria		
Arthrobacter chlorophenolicus A6 (plasmid)Arthrobacter (2 proteins)	ATP dependent DNA ligase	YP_002478051
Arthrobacter chlorophenolicus A6 (plasmid)Arthrobacter (2 proteins)	ATP dependent DNA ligase	YP_002478427
Nocardioides sp. JS614Nocardioides (1 proteins)	ATP dependent DNA ligase	YP_923463
CLSK2469924		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Alicyclobacillus acidocaldarius subsp. acidocaldarius DSM 446Alicyclobacillus (1 proteins)	ATP dependent DNA ligase	YP_003185050
Brevibacillus brevis NBRC 100599Brevibacillus (1 proteins)	putative ATP-dependent DNA ligase	YP_002773127
CLSK2340991		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Phenylobacterium zucineum HLK1 (plasmid)Phenylobacterium (2 proteins)	ATP dependent DNA ligase	YP_002128561
Phenylobacterium zucineum HLK1	ATP-dependent DNA ligase	YP_002128631

(plasmid)Phenylobacterium (2 proteins)		
CLSK2333706		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Candidatus Desulforudis audaxviator MP104CCandidatus Desulforudis (1 proteins)	ATP dependent DNA ligase	YP_001716762
Natranaerobius thermophilus JW/NM-WN-LFNatranaerobius (1 proteins)	ATP dependent DNA ligase	YP_001916325
CLSK2303611		
Organism	**Protein name**	**Accession**
CActinobacteria		
Streptomyces coelicolor A3(2)Streptomyces (2 proteins)	ATP-dependent DNA ligase	NP_631399
Streptomyces griseus subsp. griseus NBRC 13350Streptomyces (2 proteins)	putative ATP-dependent DNA ligase	YP_00 182 8202
CLSK962101		
Organism	**Protein name**	**Accession**
CActinobacteria		
Nocardioides sp. JS614Nocardioides (1 proteins)	ATP dependent DNA ligase	YP_922436
Salinispora arenicola CNS-205Salinispora (2 proteins)	DNA polymerase LigD ligase region	YP_001539124
Salinispora tropica CNB-440Salinispora (2 proteins)	ATP dependent DNA ligase	YP_001160776
CLSK915249		
Organism	**Protein name**	**Accession**
CActinobacteria See CLSK2303611 above		
Streptomyces avermitilis MA-4680 (plasmid)Streptomyces (2 proteins)	putative ATP-dependint DNA ligase	NP_828839
Streptomyces sp. HK1 (plasmid)Streptomyces (2 proteins)	putative ATP-dependent DNA ligase	YP_001661618
CLSK899085		
Organism	**Protein name**	**Accession**
O.Betaproteobacteria		

Burkholderia cenocepacia HI2424 (plasmid)Burkholderia (3 proteins)	ATP dependent DNA ligase	YP_840498
Burkholderia cenocepacia J23 15 (plasmid)Burkholderia (3 proteins)	putative ligase	YP_002235530
Burkholderia multivorans ATCC 17616 (plasmid)Burkholderia (3 proteins)	DNA polymerase LigD ligase subunit	YP_001573706
R.Gammaproteobacteria		
Pseudomonas putida (plasmid)Pseudomonas (1 proteins)	putative ligase	NP_542805
CLSK862724		
Organism	**Protein name**	**Accession**
A.Archaea		
Archaeoglobus fulgidus DSM 4304Archaeoglobus (1 proteins)	DNA ligase, putative	NP_070553
J.Firmicutes		
Desulfotomaculum reducens MI-1Desulfotomaculum (1 proteins)	ATP dependent DNA ligase	YP_001 113345
Moorella thermoacetica ATCC 39073Moorella (1 proteins)	ATP dependent DNA ligase, central	YP_430340
Pelotomaculum thermopropionicum SIPelotomaculum (1 proteins)	ATP-dependent DNA ligase	YP_0012 11793
Thermoanaerobacter pseudethanolicus ATCC 33223Thermoanaerobacter (2 proteins)	ATP dependent DNA ligase	YP_00 1664477
Thermoanaerobacter sp. X514Thermoanaerobacter (2 proteins)	ATP dependent DNA ligase	YP_00 16625 89
CLSK820690		
Organism	**Protein name**	**Accession**
A.Archaea		
uncultured methanogenic archaeon RC-Ienvironmental samples (1 proteins)	ATP-dependent DNA ligase	YP_686457
CActinobacteria		
Mycobacterium avium 104Mycobacterium (2 proteins)	DNA polymerase LigD ligase subunit	YP_882332
Mycobacterium avium subsp. paratuberculosis	hypothetical protein	NP_960263

K-l (Mycobacterium (2 proteins)		
Saccharopolyspora erythraea NRRL 2338Saccharopolyspora (1 proteins)	DNA ligase, ATP-dependent	YP_001 107793
N.Alphaproteobacteria		
Bradyrhizobium japonicum USDA 1lOBradyrhizobium (2 proteins)	DNA ligase	NP_774671
Bradyrhizobium sp. BTAilBradyrhizobium (2 proteins)	putative ATP-dependent DNA ligase	YP_001243518
CLSK808255		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Sinorhizobium medicae WSM419Sinorhizobium (2 proteins)	DNA polymerase LigD ligase region	YP_001326990
Sinorhizobium meliloti 1021 (plasmid)Sinorhizobium (2 proteins)	putative ATP-dependent DNA ligase protein	NP_437750
CLSK806855		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Agrobacterium tumefaciens str. C58 (plasmid)Agrobacterium (3 proteins)	ATP-dependent DNA ligase	NPJ95985
Agrobacterium tumefaciens str. C58 (plasmid)Agrobacterium (3 proteins)	ATP-dependent DNA ligase	NPJ96032
Agrobacterium tumefaciens str. C58 (plasmid)Agrobacterium (3 proteins)	ATP-dependent DNA ligase	NP_396609
Rhizobium etli CFN 42 (plasmid)Rhizobium (10 proteins)	putative DNA ligase (ATP) protein	YP_472413
Rhizobium etli CIAT 652Rhizobium (10 proteins)	probable ATP-dependent DNA ligase protein	YP_00 19773 17
Rhizobium etli CIAT 652 (plasmid)Rhizobium (10 proteins)	putative ATP-dependent DNA ligase protein	YP_001985803
Rhizobium leguminosarum bv. trifolii WSM1325 (plasmid)Rhizobium (10 proteins)	DNA polymerase LigD, ligase domain protein	YP_002973496
Rhizobium leguminosarum bv. trifolii WSM1325 (plasmid)Rhizobium (10 proteins)	DNA polymerase LigD, ligase domain protein	YP_002984974

Rhizobium leguminosarum bv. trifolii WSM1325 (plasmid)Rhizobium (10 proteins)	DNA polymerase LigD, ligase domain protein	YP_002984992
Rhizobium leguminosarum bv. trifolii WSM2304Rhizobium (10 proteins)	DNA polymerase LigD, ligase domain protein	YP_002281897
Rhizobium leguminosarum bv. trifolii WSM2304 (plasmid)Rhizobium (10 proteins)	DNA polymerase LigD, ligase domain protein	YP_002278005
Rhizobium leguminosarum bv. viciae 384 1 (plasmid)Rhizobium (10 proteins)	putative DNA ligase	YP_764723
Rhizobium leguminosarum bv. viciae 3841 (plasmid)Rhizobium (10 proteins)	putative DNA ligase	YP_771 149
Sinorhizobium meliloti (plasmid)Sinorhizobium (2 proteins)	putative ATP-dependent DNA ligase	YP_00 1965531
Sinorhizobium meliloti 1021 (plasmid)Sinorhizobium (2 proteins)	ATP-dependent DNA ligase	NP_435470
CLSK762775		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Rhodococcus jostii RHA1 (plasmid)Rhodococcus (2 proteins)	ATP-dependent DNA ligase	YP_708952
Rhodococcus opacus B4 (plasmid)Rhodococcus (2 proteins)	putative ATP-dependent DNA ligase	YP_002776886
CLSK761995		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Nitrobacter hamburgensis X14Nitrobacter (1 proteins)	ATP dependent DNA ligase	YP_579015
Rhodopseudomonas palustris BisB5Rhodopseudomonas (2 proteins)	ATP dependent DNA ligase	YP_569297
Rhodopseudomonas palustris TIE-1Rhodopseudomonas (2 proteins)	DNA polymerase LigD, ligase domain protein	YP_00 199 1309
CLSK523944		
Organism	**Protein name**	**Accession**
R.Gammaproteobacteria		
Pseudomonas fluorescens (plasmid)Pseudomonas (3 proteins)	putative ATP-dependent DNA ligase	YP_002887417
Pseudomonas putida (plasmid)Pseudomonas (3 proteins)	putative ligase fragment	NP_863069

Pseudomonas sp. ND6 (plasmid)Pseudomonas (3 proteins)	ATP-dependent DNA ligase	NP_943185
CLSK390680		
Organism	**Protein name**	**Accession**
R.Gammaproteobacteria		
Mesorhizobium loti MAFF303099Mesorhizobium (3 proteins)	ATP-dependent DNA ligase	NP_108227
Mesorhizobium loti MAFF303099Mesorhizobium (3 proteins)	hypothetical protein	NPJ08282
Mesorhizobium loti MAFF303099 (plasmid)Mesorhizobium (3 proteins)	DNA ligase-like protein	NP_109396

A subset of ligases of interest is in Table IB below.

Table IB

PRK08224		
B.Acidobacteria		
Bacteria; Fibrobacteres/Acidobacteria group; Acidobacteria; unclassifed Acidobacteria; Candidatus Koribacter; Candidatus Koribacter versatiiis		
Candidatus Solibacter usitatus Ellin6076Candidatus Solibacter (1 proteins)	ATP-Dependent DNA Ligase	YP_826317
CActinobacteria		
Bacteria; Actinobacteria; Actinobacteria (class); Actinobacteridae; Actinomycetales; Corynebacterineae; Mycobacteriaceae; Mycobacterium; Mycobacterium marinum		
Mycobacterium gilvum PYR-GCKMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_00 1132524
Mycobacterium vanbaalenii PYR-1 Mycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_956315
Mycobacterium sp. MCSMycobacterium (26 proteins)	ATP-Dependent DNA Ligase	YP_642076
F.Chlamydiae/Verrucomicrobia		
Bacteria; Chlamydiae/Verrucomicrobia group; Verrucomicrobia; Opitutae; Opitutales; Opitutaceae; Opitutus; Opitutus terrae		

Opitutus terrae PB90-lOpitutus (1 proteins)	ATP-Dependent DNA Ligase	YP_001821013
PRK09125		
Organism	**Protein name**	**Accession**
O.Betaproteobacteria		
Neisseria meningitidis Z2491Neisseria (7 proteins)	DNA ligase	YP_002341892
Thiobacillus denitrificans ATCC 25259Thiobacillus (1 proteins)	DNA ligase	YP_314570
Variovorax paradoxus S110Variovorax (1 proteins)	DNA ligase	YP_002944627
Verminephrobacter eiseniae EF01-2Verminephrobacter (1 proteins)	DNA ligase	YP_998235
	-	-
P.Deltaproteobacteria		
Desulfobacterium autotrophicum HRM2Desulfobacterium (1 proteins)	LigA2	YP_002604477
Myxococcus xanthus DK 1622Myxococcus (1 proteins)	DNA ligase	YP_628883
	-	-
Q.Epsilonproteobacteria		
Campylobacter jejuni subsp. jejuni NCTC 11168Campylobacter (10 proteins)	ATP-dependent DNA ligase	YP_002345037
Sulfurimonas denitrificans DSM 1251Sulfurimonas (1 proteins)	DNA ligase	YP_393098
	-	-
R.Gammaproteobacteria		
Aggregatibacter aphrophilus NJ8700Aggregatibacter (2 proteins)	ATP-dependent DNA ligase	YP_003007537
Haemophilus influenzae PittEEHaemophilus (3 proteins)	ATP-dependent DNA ligase	YP_001290961
Shewanella baltica OS195Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_001554317
Shewanella loihica PV-4Shewanella (18 proteins)	ATP-dependent DNA ligase	YP_001093713
Vibrio cholerae M66-2Vibrio (9 proteins)	DNA ligase	YP_0028 10248
	-	-
PHA0454		
Organism	**Protein name**	**Accession**
b.Viruses		
Viruses; dsDNA viruses, no RNA stage; Caudovirales; Podoviridae; Autographivirinae; phiKMV-iike viruses		
Pseudomonas phage LKD 16phiKMV-like viruses (7 proteins)	ATP-dependent DNA ligase	YP_001522807
CLSZ2445448		

Organism	Protein name	Accession
a.Eukaryota		
Eukaryota; Alveolata; Ciliophora; Intramacronucleata; Oligohymenophorea; Peniculida; Parameciidae; Paramecium; Paramecium tetraurelia		
Paramecium tetraurelia strain d4-2Paramecium (5 proteins)	DNA ligase	XP_00 1347270
PRK07636		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Bacteria; Firmicutes; Bacilli; Bacillales; Bacillaceae; Bacillus; Bacillus clausii		
Bacillus subtilis subsp. subtilis str. 168Bacillus	ATP-dependent DNA ligase	NP_389932
Bacteria; Firmicutes; Bacilli; Bacillales; Bacillaceae; Geobacillus		
Geobacillus sp. Y412MC10Geobacillus	ATP dependent DNA ligase	YP_003240778
CLSK2551528		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Bacteria; Firmicutes; Bacilli; Bacillales; Bacillaceae; Geobacillus		
Geobacillus sp. Y412MC10Geobacillus (1 proteins)	ATP dependent DNA ligase	YP_003245332
	-	-
CLSK2470953		
Organism	**Protein name**	**Accession**
CActinobacteria		
Bacteria; Actinobacteria; Actinobacteria (class); Actinobacteridae; Actinomycetales; Micrococcineae; Micrococcaceae; Arthrobacter; Arthrobacter chlorophenolicus		
Arthrobacter chlorophenolicus A6 (plasmid)Arthrobacter (2 proteins)	ATP dependent DNA ligase	YP_002478427
CLSK2469924		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Bacteria; Firmicutes; Bacilli; Bacillales; Alicyclobacillaceae; Alicyclobacillus; Alicyclobacillus acidocaldarius; Alicyclobacillus acidocaldarius subsp. acidocaldarius		
Alicyclobacillus acidocaldarius subsp. acidocaldarius DSM 446Alicyclobacillus	ATP dependent DNA ligase	YP_003 185050
CLSK2340991		

Organism	Protein name	Accession
N.Alphaproteobacteria		
Bacteria; Proteobacteria; Alphaproteobacteria; Caulobacterales; Caulobacteraceae; Phenylobacterium; Phenylobacterium zucineum		
Phenylobacterium zucineum HLK1 (plasmid)Phenylobacterium (2 proteins)	ATP-dependent DNA ligase	YP_002128631
	-	-
CLSK2333706		
Organism	**Protein name**	**Accession**
J.Firmicutes		
Bacteria; Firmicutes; Clostridia; Clostridiales; Peptococcaceae; Candidatus Desulforudis; Candidatus Desulforudis audaxviator		
Candidatus Desulforudis audaxviator MP104CCandidatus Desulforudis (1 proteins)	ATP dependent DNA ligase	YP_001716762
	-	-
CLSK962101		
Organism	**Protein name**	**Accession**
CActinobacteria		
Bacteria; Actinobacteria; Actinobacteria (class); Actinobacteridae; Actinomycetales; Micromonosporineae; Micromonosporaceae; Salinispora; Salinispora arenicola	-	-
Salinispora arenicola CNS-205 Salinispora (2 proteins)	DNA polymerase LigD ligase region	YP_001539124
Salinispora tropica CNB-440Salinispora (2 proteins)	ATP dependent DNA ligase	YP_001160776
	-	-
CLSK915249		
Organism	**Protein name**	**Accession**
CActinobacteria See CLSK2303611 above		
Bacteria; Actinobacteria; Actinobacteria (class); Actinobacteridae; Actinomycetales; Streptomycineae; Streptomycetaceae; Streptomyces; Streptomyces coelicolor		
Streptomyces avermitilis MA-4680 (plasmid)Streptomyces (2 proteins)	putative ATP-dependint DNA ligase	NP_828839
Streptomyces sp. HK1 (plasmid)Streptomyces (2 proteins)	putative ATP-dependent DNA ligase	YP_001661618
CLSK862724		
Organism	**Protein name**	**Accession**
A.Archaea		
Archaea; Euryarchaeota; Archaeoglobi; Archaeoglobales; Archaeoglobaceae; Archaeoglobus; Archaeoglobus fulgidus		

Archaeoglobus fulgidus DSM 4304Archaeoglobus (1 proteins)	DNA ligase, putative	NP_070553
J.Firmicutes		
Pelotomaculum thermopropionicum SIPelotomaculum (1 proteins)	ATP-dependent DNA ligase	YP_0012 11793
Thermoanaerobacter pseudethanolicus ATCC 33223Thermoanaerobacter (2 proteins)	ATP dependent DNA ligase	YP_00 1664477
CLSK820690		
Organism	**Protein name**	**Accession**
A.Archaea		
Archaea; Euryarchaeota; environmental samples		
uncultured methanogenic archaeon RC-Ienvironmental samples (1 proteins)	ATP-dependent DNA ligase	YP_686457
N.Alphaproteobacteria		
Bacteria; Proteobacteria; Alphaproteobacteria; Rhizobiales; Bradyrhizobiaceae; Bradyrhizobium; Bradyrhizobium japonicum		
Bradyrhizobium japonicum USDA 1lOBradyrhizobium (2 proteins)	DNA ligase	NP_774671
Bradyrhizobium sp. BTAil Bradyrhizobium (2 proteins)	putative ATP-dependent DNA ligase	YP_001243518
CLSK808255		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Bacteria; Proteobacteria; Alphaproteobacteria; Rhizobiales; Rhizobiaceae; Sinorhizobium/Ensifer group; Sinorhizobium; Sinorhizobium medicae		
Sinorhizobium medicae WSM419Sinorhizobium (2 proteins)	DNA polymerase LigD ligase region	YP_00 13 26990
Sinorhizobium meliloti 1021 (plasmid)Sinorhizobium (2 proteins)	putative ATP-dependent DNA ligase protein	NP_437750
CLSK806855		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Bacteria; Proteobacteria; Alphaproteobacteria; Rhizobiales; Rhizobiaceae; Rhizobium/Agrobacterium group; Agrobacterium; Agrobacterium tumefaciens		
Agrobacterium tumefaciens str. C58 (plasmid)Agrobacterium (3 proteins)	ATP-dependent DNA ligase	NP_396032
Rhizobium leguminosarum bv. trifolii WSM1325	DNA polymerase	YP_002973496

(plasmid)Rhizobium (10 proteins)	LigD, ligase domain protein	
Rhizobium leguminosarum bv. trifolii WSM2304 (plasmid)Rhizobium (10 proteins)	DNA polymerase LigD, ligase domain protein	YP_002278005
CLSK390680		
Organism	**Protein name**	**Accession**
N.Alphaproteobacteria		
Bacteria; Proteobacteria; Alphaproteobacteria; Rhizobiales; Phyllobacteriaceae; Mesorhizobium; Mesorhizobium loti		
Mesorhizobium loti MAFF303099Mesorhizobium (3 proteins)	hypothetical protein	NP_108282

Some exemplary ligases are identified and their GI or accession numbers are provided in Table 1C below:

TABLE 1C

CV DNA Ligase, GenBank ID AAC96909. 1, from Paramecium bursaria Chlorella virus 1: MAITKPLLAATLENIEDVQFPCLATPKIDGIRSVKQTQMLSRTFKPIRNSVMNRLL TELLPEGSDGEISIEGATFQDTTSAVMTGHKMYNAKFSYYWFDYVTDDPLKKYI DRVEDMKNYITVHPHILEHAQVKIIPLIPVEINNITELLQYERDVLSKGFEGVMIRK PDGKYKFGRSTLKEGILLKMKQFKDAEATIISMTALFKNTNTKTKDNFGYSKRST HKSGKVEEDVMGSIEVDYDGWFSIGTGFDADQRRDFWQNKESYIGKMVKFKY FEMGSKDCPRFPVFIGIRHEEDR
MnM DNA Ligase, GenBank ID YP_333052.1, from Burkholderia pseudomallei 1710b (equivalent sequence to ABA50091) MSGVPYGFKPNLAATLTKPELIKFPVWASPKIDGIRCVFFGGVAYSRSLKPIPNPV VQEFAKAYANLLEGLDGELTVGSPTDANCMQNSMAVMSKAAAPDFTFHVFDW FHPAQAHIEFWQRSDVVEDRIVQFYDRYPEVDIRAAPQVLCTSLAHLDTNEARW LADGYEGMMIRDHCGRYKFGRSTEREGGLVKVKRFTDAEAIVIGFEEEMHNANE AKRDATGRTERSTSKAGLHGKGTLGALWKNERGIVFNIGTGFTAAQRADYWA NHPSLFGKMVKFKHFDHGTVDAPRHPVFIGFRHPEDM
Hin DNA Ligase, GenBank ID P44121, from Haemophilus influenza MKFYRTLLLFFASSFAFANSDLMLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQ LLTRQGQRLSPPAYFIKDFPPFAIDGELFSERNHFEEISTITKSFKGDGWEKLKLYV FDVPDAEGNLFERLAKLKAHLLEHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGE

GWVRNPNAPYERKRSSQILKLKTARGEECTVIAHHKGKGQFENVMGALTCKN HRGEFKIGSGFNLNERENPPPIGSVITYKYRGITNSGKPRFATYWREKK
DLX DNA Ligase, artificial ligase derived from Hin DNA ligase from Haemophilus influenza: MKFYRTLLLFFASSFAFANSDLMLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQ LLTRQGQRLSPPAYFIKDFPPFAIDGELFSERNHFEEISSITKSFKGDGWEKLKLYV FDVPDAEGNLFERLAKLKAHLLEHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGE GWVRNPNAPYERKRSSQILKLKTARGEECTVIAHHKGKGQFENVMGALTCKNH RGEFKIGSGFNLNERENPPPIGSVITYKYRGITNSGKPRFATYWREKK
DLXd DNA Ligase, artificial ligase derived from Hin D ligase from Haemophilus influenza: MKFYRTLLLFFASSFAFANSDLMLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQ LLTRQGQRLSPPAYFIKDFPPFAIDGELFSERNHFEEISSITKSFKGDGWEKLKLYV FDVPDAEGNLFERLAKLKAHLLEHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGE GWVRNPNAPYERKRSSQILKLKTARDEECTVIAHHKGKGQFENVMGALTCKNH RGEFKIGSGFNLNERENPPPIGSVITYKYRGITNSGKPRFATYWREKK
DLXd2 DNA Ligase (Gammaproteobacteria, Haemophilus influenza) (modified) MLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQLLTRQGQRLSPPAYFIKDFPPFA IDGELFSERNHFEEISSITKSFKGDGWEKLKLYVFDVPDAEGNLFERLAKLKAHLL EHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGEGVVVRNPNAPYERKRSSQILKL KTARDEECTVIAHHKGKGQFENVMGALTCKNHRGEFKIGSGFNLNERENPPPIGS VITYKYRGITNSGKPRFATYWREKK

[0086] The SFL is in one aspect an enzyme that can mediate the formation of a covalent bond between two polynucleotide termini, e.g., a 3'-OH terminus and a 5'-P04 terminus are joined together to form a phosphodiester bond. In some instances, DNA ligation entails any one or more of three sequential nucleotidyl transfer steps, discussed below. All three chemical steps depend on a divalent cation cofactor. In one aspect, the SFL is an ATP-dependent ligase or a NAD^+-dependent ligase.

[0087] Optionally, the SFL is Chlorella virus DNA ligase (ChVLig). Ho, et al, J Virol, 71(3): 1931-19374 (1997) or functional fragment or variant thereof. For example the SFL can comprise any one or more domains characteristic of a ligase, e.g., an N-terminal nucleotidyltransferase (NTase) domain and/or a C-terminal OB domain. The OB domain optionally comprises a five-stranded antiparallel beta-barrel plus an alpha-helix. Within the NTase domain is an adenylate-binding pocket composed of the six peptide motifs that define the covalent NTase enzyme family of polynucleotide ligases. Optionally, the NTase domain can comprise any one or more of the ligase amino acid

motifs I, la, III, Ilia, IV, V, and VI preferably all six motifs. Motif I (e.g., KxDGxR or a "KXDG" motif) optionally contains a lysine. Exemplary sequences for each motif in CV ligase are ATPKIDGIR (motif I), SRT (motif la), EGSDGEIS (motif III), YWFDY (motif Ilia), EGVMIR (motif IV), LLKMK (motif V). Motif 1 preferably contains a lysine residue. Other examples of motif I include CELKLDGLA, VEHKVDGLS, CEPKLDGLA, CELKLDGVA, AEIKYDGVR, CEYKYDGQR, VDYKYDGER, FEIKYDGAR, FEGKWDGYR, AREKIHGTN, ACEKVHGTN, ILTKEDGSL, and VEEKVDGYN. Examples of motif 1a include TRG, SRT, SRR, SRN, SRS, KRT, KRS, SKG and TRG. Examples of motif III include LEVRGEVF, VEVRGECY, LEVRGEVY, LEARGEAF, FMLDGELM, EGSDGEIS, FILDTEAV, FIIEGEIV, AIVEGELV, VVLDGEAV, YQVFGEFA, LVLNGELF, FTANFEFV and LILVGEMA. Examples of motif Ilia include FCYGV, FLYTV, TFYAL, ICHGL, NAYGI, FVYGL, KLYAI, YWFDY, YAFDI, FLFDL, NLFDV, WAFDL, YVFDI, FAFDI, ILLNA, AND FLFDV. Examples of motif IV include DGVVIK, DGIVIK, DGVVVK, DGTVLK, EGLIVK, EGVMIR, EGLMVK, EGVMVK, EGLMAK, EGVIAK, EGYVLK, EGVVIR, EGYVAV, and EGIIMK. Examples of motif V include AVAFK, AIAYK, ALAYK, AIAYK,WWKMK, LLKMK, WLKLK, WIKLK, WLKIK, WVKDK, AIKCK, IIKLR, HFKIK and IVKYV. The SFL optionally comprises all six motifs. Optionally all six motifs are found together in a naturally-occurring ligase, such as a SFL identified herein. Optionally, the SFL is not an RNA-capping enzyme.

[0088] The ligase optionally comprises any functional portion of a SFL. The ligase can be homologous to a SFL or any functional portion thereof, for example more than 75%, 85%, 90%, 95% or 99% homologous at the amino acid level.

[0089] Optionally, any of the ligation methods described herein is performed by an SFL that is not CV ligase or a functional fragment or derivative thereof. Optionally, the SFL is not T4 DNA ligase or functional fragment or variant thereof. Optionally, the SFL is less than 70%, 80% or 90% identical to T4 DNA ligase. In some examples, the SFL is not a ligase that was known by effective filing date of this application to efficiently ligate oligonucleotides shorter than 6 nucleotides in length. In some examples, the SFL is not a ligase that was known by January 11, 201 1, to efficiently ligate oligonucleotides shorter than 6 nucleotides in length.

[0090] In a typical assay, a probe that is 2, 3, 4, 5 or 6 nucleotides in length is ligated in template-dependent manner to a primer using an SFL. Optionally, the 3' end of the probe is ligated to the 5' end of the primer, or vice versa. Optionally, the SFL is CV

ligase. The efficiency of ligation is for example more than 5%, 10%, 20%, 30%, or 50%. In other instances a probe that is 6, 7, 8, 9, 10, 11 or 12 nucleotides in length is ligated in template-dependent manner to a primer using an SFL. Optionally, the 5' end of the probe is ligated to the 3' end of the primer, or vice versa. Optionally, the SFL is CV ligase. The efficiency of ligation is for example more than 80%, 90% or 95%.

[0091] In any ligation described herein, ligation product is optionally detected. Ligation can be detected by any known method or method described herein. For example the primer and/or template can be immobilized on a support and the probe labeled. The label on the ligated immobilized probe can be detected after non-ligated probe has been washed away. In other embodiments any one or more of the probe, primer or template is labeled. Any one or more of these reagents can optionally be immobilized.

[0092] In any ligation herein, the ligation can be repeated for a desired number of cycles, for example any reagent that has been subjected to a first ligation cycle is used as a reagent in a next ligation cycle. For example the primer, probe or template of a first ligation cycle can be used as primer, probe or template in a next ligation cycle. In some embodiments (e.g., ligation sequencing) the primer of a first cycle is used as primer in the next cycle. In other instances, the primer of a first cycle can be used a probe or template in the next, the probe of a first cycle can be used as primer or template, or the template of a fist cycle can be used as primer or probe the next.

[0093] The next cycle can be designed such that both ligated and unligated reagent of a first cycle can act as reagent in the next cycle. For example, the ligated and unligated primer of a first ligation cycle can be used as primer in the next cycle. Alternatively, the next cycle can be designed such that only a ligation product of the first cycle can act as a ligation reagent in the next cycle, and reagents that remain unligated in the first cycle will not act as reagents in the next cycle. In some examples, the unligated reagents of the previous cycle are "capped" or otherwise rendered unligatable before the next cycle of ligation is executed.

[0094] Any one or more ligases and/or ligation methods encompassed by the invention can optionally be used in one or more ligation assay formats, and/or are performed in the context of one or more specific ligation applications. Non-limiting examples of assay formats include: oligonucleotide ligation assay (OLA), a ligase chain reaction (LCR), a ligase detection reaction (LDR) and combination assays such as the OLA coupled with the polymerase chain reaction (PCR), e.g., OLA-PCR and PCR-OLA, the Combined Chain Reaction (CCR; a combination of PCR and LCR) and PCR-LDR

(see, e.g., Landegren et al, Science 241:1077-80, 1988; Barany, Proc. Natl. Acad. Sci. 88:189-93, 1991; Grossman etal, Nucl. Acids Res. 22(21):4527-34, 1994; Bi and Stambrook, Nucl. Acids Res. 25(14):2949-51, 1997; Zirvi et al, Nucl. Acids Res., 27(24):e40, 1999; U.S. Pat. No. 4,988,617; and PCT Publication Nos. WO 97/31256 and WO 01/92579. Non-limiting examples of specific applications include: amplification of template, detection and/or quantification of the presence of a particular nucleic acid, e.g., in a diagnostic sample, ligation sequencing, single nucleotide polymorphism (SNP) analysis, SNP genotyping, mutation detection, identification of single copy genes, detecting microsatellite repeat sequences, and DNA adduct mapping, among other things. See also Whitely et al, U.S. Pat. No. 4,883,750; Letsinger et al, U.S. Pat. No. 5,476,930; Fung et al, U.S. Pat. No. 5,593,826; Kool, U.S. Pat. No. 5,426,180; Landegren et al, U.S. Pat. No. 5,871,921; Xu and Kool, Nucleic Acids Research, 27: 875-881 (1999); Higgins et al, Methods in Enzymology, 68: 50-71 (1979); Engler et al, The Enzymes, 15-3-29 (1982); and Namsaraev, U.S. patent publication 2004/01 10213.

[0095] In an embodiment, the method of ligation comprises or consists of a proximity ligation assay (PLA). PLAs typically involve at least three steps. The first step is typically the binding of first and second probes (e.g., antibody probes) to a ligand (e.g., a protein of interest) such that the probes are in close proximity to another. Each of the probes typically contain an oligonucleotide. The oligonucleotides are brought into proximity to one another with the binding of the probes and, in the second step, are then ligated to one another (e.g., the ligation event). The ligated oligonucleotides may then be amplified and detected to determine the presence of the ligand with a sample (e.g., a biological sample).

[0096] An exemplary PLA assay comprises the steps of determining the presence or absence of a target protein in a sample, comprising (a) contacting the target protein with at least a first and second binding agent, each binding agent having binding specificity for the protein and being adjoined to at least one polynucleotide, (b) ligating the oligonucleotides on the first and second binding agent to one another using a ligase to produce a target nucleic acid and amplifying the target nucleic acid; (c) detecting whether amplified target nucleic acid is present or not, and (d) concluding that the target protein is present in the sample if a significant amount of amplified target nucleic acid is detected, and/or concluding that the target protein is absent from the sample if a significant amount of amplified target nucleic acid is not detected. Optionally, step (d) alternatively or additionally comprises measuring or otherwise assessing the amount of

amplified target nucleic acid, and taking the amount of amplified nucleic acid as an indicator of the amount of target protein present in the sample.

[0097] In any methods described herein, polynucleotide ligation probes can be used for detection of a target nucleic acid. The ligation probe is optionally capable of binding to a target nucleic acid of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation. As used herein, a probe may include natural (i.e., A, G, C, or T) or modified bases (7-deazaguanosine, inosine, etc.). In addition, the bases in a probe may be joined by a linkage other than a phosphodiester bond, so long as it does not interfere with hybridization. Thus, for example, probes may be peptide nucleic acids in which the constituent bases are joined by peptide bonds rather than phosphodiester linkages. It will be understood by one of skill in the art that probes may bind target sequences lacking complete complementarity with the probe sequence depending upon the stringency of the hybridization conditions. The probes are preferably directly labeled as with isotopes, chromophores, lumiphores, chromogens, or indirectly labeled such as with biotin to which a streptavidin complex may later bind. By assaying for the presence or absence of the probe, one can detect the presence or absence of the select sequence or subsequence.

[0098] The oligonucleotide ligation assay (OLA) is a convenient, highly-stringent method that permits distinction among known DNA sequence variants (Landegren, 1988). Multiplex analysis of highly polymorphic loci is useful for identification of individuals, e.g., for paternity testing and in forensic science, organ transplant donor-receiver matching, genetic disease diagnosis, prognosis, and pre-natal counseling, and other genetic-based testing which depend on the discrimination of single-base differences at a multiplicity of loci (Delahunty, 1996). For example, different assays where two PNA-DNA chimeras, a wild-type (WT) sequence chimera and a mutant sequence chimera, bear different fluorescent dyes. Only when the mutant sequence is present in the target sample, will the mutant sequence chimera ligate to the adjacently annealed second probe (oligo) if the mutant base pair is at the ligation site.

a) Sequence determination

[0099] In some embodiments, successive cycles of ligation can be performed, where the ligation product of a previous cycle is used as primer, probe and/or template in a succeeding cycle.

[00100] An exemplary use of such repetitive ligation is ligation sequencing. A template to be sequenced optionally contains a primer-binding region and polynucleotide region of unknown sequence. A primer with a ligatable terminus (e.g., a free 3' OH group or 5' phosphate group) is annealed to the primer binding region. An extension probe is hybridized to the template adjacently to the primer. The proximal nucleotide of the probe forms a complementary base pair with unknown nucleotide in the template. The extension probe is then ligated to the primer, optionally with an SFL, resulting in an extended duplex. Following ligation, the label attached to extension probe is optionally detected. The process is repeated for a desired number of cycles, using the ligation product of one cycle as the primer of the next cycle. Optionally, the extension probe has a non-ligatable distal terminus, and is then cleaved to provide a ligatable extended duplex.

[00101] In one example, the 3' terminus of the primer is ligated to the 5' terminus of the extension probe. The optional step of cleavage can be done for example at a phosphorothiolate linkage using $AgNO_3$ or another salt that provides Ag^+ ions, leaving a phosphate group at the 3' end of the extended duplex. Phosphatase treatment is used to generate an extendable probe terminus on the extended duplex.

[00102] In one-base encoding, the label corresponds to the identity of nucleotide X. Thus nucleotide Y is identified as the nucleotide complementary to nucleotide X. In other encodings, the label does not have a one-to-one correspondence with the identity of any particular nucleotide in the template.

[00103] Also provided are probe families for use in various ligation methods herein, e.g., sequencing. The probe families are optionally characterized in that each probe family comprises a plurality of labeled oligonucleotide probes of different sequence and, at each position in the sequence, a probe family comprises at least 2 probes having different bases at that position. Probes in each probe family comprise the same label. Preferably the probes comprise a scissile internucleoside linkage. The scissile linkage can be located anywhere in the probe. Preferably the probes have a moiety that is not extendable by ligase at one terminus. Preferably the probes are labeled at a position between the scissile linkage and the moiety that is not extendable by ligase, such that cleavage of the scissile linkage following ligation of a probe to an extendable probe

terminus results in an unlabeled portion that is ligated to the extendable probe terminus and a labeled portion that is no longer attached to the unlabeled portion.

[00104] In multiple-base encodings, the probes in each probe family preferably comprise at least j nucleosides **X**, wherein j is at least 2, and wherein each **X** is at least 2-fold degenerate among the probes in the probe family. Probes in each probe family further comprise at least k nucleosides N, wherein k is at least 2, and wherein N represents any nucleoside. In general, j + k is equal to or less than 100, typically less than or equal to 30. Nucleosides **X** can be located anywhere in the probe. Nucleosides **X** need not be located at contiguous positions. Similarly nucleosides N need not be located at contiguous positions. In other words, nucleosides **X** and N can be interspersed. Nevertheless, nucleosides **X** can be considered to have a 5'->3' sequence, with the understanding that the nucleosides need not be contiguous. For example, nucleosides **X** in a probe of structure $\mathbf{X_A}$**NXGNNXCN** would be considered to have the sequence AGC. Similarly, nucleosides N can be considered to have a sequence.

[00105] Nucleosides **X** can be identical or different but are not independently selected, i.e., the identity of each **X** is constrained by the identity of one or more other nucleosides **X** in the probe. Thus in general only certain combinations of nucleosides **X** are present in any particular probe and within the probes in any particular probe family. In other words, in each probe, the sequences of nucleosides **X** can only represent a subset of all possible sequences of length j. Thus the identity of one or more nucleotides in **X** limits the possible identities for one or more of the other nucleosides.

[00106] Nucleosides N are preferably independently selected and can be A, G, C, or T (or, optionally, a degeneracy-reducing nucleoside). Preferably the sequence of nucleosides N represents all possible sequences of length k, except that one or more N may be a degeneracy-reducing nucleoside. The probes thus contain two portions, of which the portion consisting of nucleosides N is referred to as the unconstrained portion and the portion consisting of nucleosides **X** is referred to as the constrained portion. As described above, the portions need not be contiguous nucleosides. Probes that contain a constrained portion and an unconstrained portion are referred to herein as partially constrained probes. Preferably one or more nucleosides in the constrained portion is at the proximal end of the probes, i.e., at the end that contains the nucleoside that will be ligated to the extendable probe terminus, which can be either the 5' or 3' end of the oligonucleotide probe in different embodiments of the invention.

[00107] Since the constrained portion of any oligonucleotide probe can only have certain sequences, knowing the identity of one or more of the nucleosides in the constrained portion of a probe, either by itself, or optionally in combination with the identity of the label on the probe, provides information about one or more of the other nucleotides in the constrained portion. The information may or may not be sufficient to precisely identify one or more of the other nucleosides, but it will be sufficient to eliminate one or more possible nucleotide combinations and/or permutations in the constrained portion. Optionally, the information is not sufficient to eliminate any possible identity of any one individual nucleotide in the constrained portion. In certain preferred embodiments, knowing the identity of one nucleoside in the constrained portion of a probe is sufficient to precisely identify each of the other nucleosides in the constrained portion, i.e., to determine the identity and order of the nucleosides that comprise the constrained portion.

[00108] As in the one-base-encoding sequencing methods described above, the most proximal nucleoside in an extension probe that is complementary to the template is ligated to an extendable terminus of an initializing oligonucleotide (in the first cycle of extension, ligation, and detection) and to an extendable terminus of an extended oligonucleotide probe in subsequent cycles of extension, ligation, and detection. Detection of the associated label determines the name of the probe family to which the newly ligated probe belongs. Since each position in the constrained portion of the probe is at least 2-fold degenerate, the name of the probe family does not in itself identify any nucleotide in the constrained portion. However, since the sequence of the constrained portion is one of a subset of all possible sequences of length j, identifying the probe family does eliminate certain possibilities for the sequence of the constrained portion. The constrained portion of the probe constitutes its sequence determining portion. Therefore, eliminating one or more possibilities for the identity of one or more nucleosides in the constrained portion of the probe by identifying the probe family to which it belongs eliminates one or more possibilities for the identity of a nucleotide in the template to which the extension probe hybridizes. In preferred embodiments of the invention the partially constrained probes comprise a scissile linkage between any two nucleosides.

[00109] In certain embodiments the partially constrained probes have the general structure $(X)_j(N)_k$, in which X represents a nucleoside, $(X)_j$ is at least 2-fold degenerate at each position such that X can be any of at least 2 nucleosides having different base-

pairing specificities, N represents any nucleoside, j is at least 2, k is between 1 and 100, and at least one N or X other than the X at the probe terminus comprises a detectable moiety. Preferably $(N)_k$ is independently 4-fold degenerate at each position so that, in each probe, $(N)_k$ represents all possible sequences of length k, except that one or more positions in $(N)_k$ may be occupied by a degeneracy-reducing nucleotide. Nucleosides in $(X)_j$ can be identical or different but are not independently selected. In other words, in each probe, $(X)_j$ can only represent a subset of all possible sequences of length j. Thus the identity of one or more nucleotides in $(X)_j$ limits the possible identities for one or more of the other nucleosides. The probes thus contain two portions, of which $(N)_k$ is the unconstrained portion and $(X)_j$ is the constrained portion.

[00110] In certain preferred embodiments of the invention the partially constrained probes have the structure 5'-(X)j(N)kNB*-3' or 3'-(X)j(N)kNB*-5', wherein N represents any nucleoside, NB represents a moiety that is not extendable by ligase, * represents a detectable moiety, $(X)_j$ is a constrained portion of the probe that is at least 2-fold degenerate at each position, nucleosides in $(X)_j$ can be identical or different but are not independently selected, at least one internucleoside linkage is a scissile linkage, j is at least 2, and k is between 1 and 100, with the proviso that a detectable moiety may be present on any nucleoside N or X other than the X at the probe terminus instead of, or in addition to, NB. The scissile linkage can be between two nucleosides in $(X)_j$, between the most distal nucleotide in $(X)_j$ and the most proximal nucleoside in $(N)_k$, between nucleosides within (N)k, or between the terminal nucleoside in (N)k and NB. Preferably the scissile linkage is a phosphorothiolate linkage.

[00111] A plurality of probe families is referred to as a "collection" of probe families. Probes in each probe family in a collection of probe families are labeled with a label that is distinguishable from labels used to label other probe families in the collection. Each probe family preferably has its own defined set of sequences, which optionally do not overlap with any other probe family. Preferably the combination of sets of defined sequences for probe families in a collection of probe families includes all possible sequences of the length of the sequence-determining portion. Preferably a collection of probe families comprises or consists of 4 distinguishably labeled probe families.

[00112] Preferably the sequence-determining portions of the probes in each probe family are the same length, and preferably the sequence-determining portions of probe families in a collection of probe families are of the same length. Preferably the

sequencing-determining portion is a constrained portion that is at least 2 nucleosides in length.

[00113] In some instances, a series of ligation cycles starting from a particular primer allows partial determination of a sequence, i.e., the identification of individual nucleotides spaced apart from one another in a template. Optionally, in order to gather more complete information, a plurality of reactions is performed in which each reaction utilizes a different initializing oligonucleotide i. The initializing oligonucleotides i bind to different portions of the binding region. Preferably the initializing oligonucleotides bind at positions such the extendable termini of the different initializing oligonucleotides are offset by 1 or more nucleotides from each other when hybridized to the template. For example, as shown in Fig. 3, sequencing reactions 1...N are performed. Initializing oligonucleotides ii. .. i_n have the same length and bind such that their terminal nucleotides hybridize to successive adjacent positions in the template. Extension probes ei...e_n thus bind at successive adjacent regions of the template and are ligated to the extendable termini of the initializing oligonucleotides. Terminal nucleotide of probe e_n ligated to i_n is complementary to nucleotide of polynucleotide region, i.e., the first unknown polynucleotide in the template. In the second cycle of extension, ligation, and detection, terminal nucleotide of probe e_{i2} is complementary to nucleotide of polynucleotide region, i.e., the second nucleotide of unknown sequence. Likewise, terminal nucleotides of extension probes ligated to duplexes initialized with initializing oligonucleotides i_{12}, i_{13}, i_4, and so on, will be complementary to the third, fourth, and fifth nucleotides of unknown sequence. It will be appreciated that the initializing oligonucleotides may bind to regions progressively further away from the polynucleotide region rather than progressively closer to it.

[00114] The spacer function of the non-terminal nucleotides of the extension probes allows the acquisition of sequence information at positions in the template that are considerably removed from the position at which the initializing oligonucleotide binds without requiring a correspondingly large number of cycles to be performed on any given template.

a. *Capping*

[00115] In any one or more repetitive ligation methods herein, it is possible that fewer than all probes with extendable termini participate in a successful ligation reaction in each cycle of extension, ligation, and cleavage. It will be appreciated that if such probes participated in succeeding cycles, the accuracy of each nucleotide identification step

could progressively decline. In certain embodiments of the invention a capping step is included to prevent those extendable termini that do not undergo ligation from participating in future cycles. When sequencing in the 5'->3' direction using extension probes containing a 3'-0-P-S-5' phosphorothiolate linkage, capping may be performed by extending the unligated extendable termini with a DNA polymerase and a non-extendable moiety, e.g., a chain-terminating nucleotide such as a dideoxynucleotide or a nucleotide with a blocking moiety attached, e.g., following the ligation or detection step. When sequencing in the 3'->5' direction using extension probes containing a 3'-S-P-0-5' phosphorothiolate linkage, capping may be performed, e.g., by treating the template with a phosphatase, e.g., following ligation or detection. Other capping methods may also be used.

[00116] It is contemplated that any ligation assay or method herein can be highly multiplexed such that a large number of assays (e.g., greater than 1,000) can be performed in parallel, e.g., simultaneously.

[00117] Any multiplexed ligation assay can optionally be conducted on solid substrates where one or more ligation reagents (e.g., the ligase, template, probe and/or primer) can be immobilized on a solid support or surface. Optionally, the primers, probe and/or template can be attached to different portions of a solid substrate in the form of an array. Optionally, the template, primer or probe can be covalently attached to the solid substrate.

[00118] Optionally, one or more ligation reagents are labeled (e.g., template, probe and/or primer) so that ligation products may be discriminated from each other. Alternatively, ligation products can be distinguished based on: (i) size using electrophoresis or chromatography and/or (ii) detectable labels (Grossman, 1994). For example, multiplexed ligation assays can be conducted on a single sample in a single vessel.

[00119] Any of reagents herein (e.g., primer, probe and/or template) can be optionally immobilized on a solid phase. The solid phase optionally comprises a surface to which one or more reactants may be attached electrostatically, hydrophobically, or covalently. Representative solid phases include e.g.: nylon 6; nylon 66; polystyrene; latex beads; magnetic beads; glass beads; polyethylene; polypropylene; polybutylene; butadiene-styrene copolymers; silastic rubber; polyesters; polyamides; cellulose and derivatives; acrylates; methacrylates; polyvinyl; vinyl chloride; polyvinyl chloride; polyvinyl fluoride; copolymers of polystyrene; silica gel; silica wafers glass; agarose; dextrans; liposomes; insoluble protein metals; and, nitrocellulose. Representative solid phases can be formed

into appropriate articles such as beads (e.g., microparticles), tubes, strips, disks, filter papers, plates and the like.

[00120] In an embodiment, any one of the following can be attached to a solid support (e.g., a bead): the SFL, one or more polynucleotide reagents (e.g., an initializing probe, an extension probe, a target DNA or template, a 3' terminal or 5' terminal polynucleotide).

[00121] If so desired, one or more labels can be coupled to any reagent of interest, e.g., the SFL or an antibody that binds specifically to the SFL, one or more polynucleotides (e.g., the template, the 5'-terminal polynucleotide, the 3'-terminal polynucleotide, the template, the initializing probe, the extension probe, etc.

Compositions

[00122] Also provided is a polypeptide comprising or consisting essentially of the amino acid sequence of an SFL provided herein, generally provided as GenBank Accession Nos. in the Tables, or a fragment or variant thereof. The fragment or variant thereof preferably can ligate short oligonucleotides at an efficiency comparable to its parent enzyme. Optionally, the variants or fragments of the SFLs are at least 70%, 80, 90%, 95%, 99% identical to the parent SFL. In an example, the SFL is a ligase derived from Hin DNA ligase (e.g., DLX, DLXd or DLXd2) or any fragment or variant thereof that still retains one or more mutant residues shown in Figure 2, and/or has one or more C-terminal amino acids deleted, e.g., 22 C-terminal amino acids deleted. For example, the mutant Hin DNA ligase is at least 70% identical to Hin D ligase sequence provided in Figure 2 or in GenBank Accession No. P44121, which ligase comprises an amino acid mutation at position 193 of the Hin D ligase sequence provided in Figure 2 or in GenBank Accession No. P44121. Optionally the amino acid mutation consists of changing the glycine at position 193 to aspartic acid or glutamic acid.

[00123] Also provided is a nucleic acid encoding the novel SFLs or fragments or variants described herein. Also provided are genes of the novel SFL which comprise sequences that direct expression of the SFL. Also provided are nucleic acid vectors comprising a nucleic acid encoding the novel SFL and a host cell comprising such a vector. Also provided is an antibody that can bind specifically to the novel SFL but not to its naturally-occurring parent.

[00124] Optionally, the novel SFL or nucleic acid or vector or host cell or antibody is purified, isolated or recombinant.

[00125] Also provided is a method of making any one or more ligases described herein comprising: expressing the SFL in a host cell, e.g., by culturing said host cells under conditions such that the ligase is expressed; and optionally recovering or purifiying said ligase.

Kits

[00126] Also provided are kits comprising components for performing ligation reactions according to the disclosure. Kits can contain an SFL or functional variant or fragment thereof. Kits can alternatively or additionally include one or more oligonucleotide probes less than 12 nucleotides in length, (e.g., less than 8, 7, 6, 5, 4, 3 or 2 nucleotides in length), and/or primer oligonucleotides. In some embodiments, a kit can include CV ligase and one or more oligonucleotides probes less than 6 nucleotides in length. One or more probes for example comprises a 5'-phosphate and/or a label. The label is optionally attached to the 5' terminus, or alternatively to the 3' terminus. Optionally, one or more probes are cleavable.

[00127] The kits optionally provide one or more primers, probes and/or templates described herein. The primers and/or probes can have any one or more features or characteristics described herein. For example the probes can comprise a scissile (e.g., phosphorothiolate) linkage. The kits may contain a cleavage reagent suitable for cleaving phosphororothiolate linkages, e.g., AgN03 and appropriate buffers in which to perform the cleavage. The probes can comprise a trigger residue such as a nucleoside containing a damaged base or an abasic residue. The kits may contain a cleavage reagent suitable for cleaving a linkage between a nucleoside and an adjacent abasic residue and/or a reagent suitable for removing a damaged base from a polynucleotide, e.g., a DNA glycosylase. Certain kits contain oligonucleotide probes that comprise a disaccharide nucleotide and contain periodate as a cleavage reagent. In certain embodiments the kits contain a collection of distinguishably labeled oligonucleotide probe families or collections described herein. Optionally the kit does not comprise a polymerase. Optionally the kit does not comprise an enzyme other than a ligase, phosphatase or kinase. Optionally the kit does not comprise an enzyme other than a SFL that has one or more activities mentioned herein. The kits may include ligation reagents (e.g., ligase, buffers, etc.) and

instructions for practicing the particular embodiment of the invention. Appropriate buffers for the other enzymes that may be used, e.g., phosphatase, polymerases, may be included. In some cases, these buffers may be identical. Kits may also include a support, e.g. magnetic beads, which are either pre-attached to primers, primers or templates or are derivatised to be capable of attaching to such molecules. The beads may be functionalized with a primer for performing PCR amplification. Other optional components include washing solutions; vectors for inserting templates for PCR amplification; PCR reagents such as amplification primers, thermostable polymerase, nucleotides; reagents for preparing an emulsion; reagents for preparing a gel, etc. Kits can also comprise a plurality of distinguishably labeled probes, which can be labeled such that the identity of the label provides information about the sequence of the probe. Kits can also comprise other or additional compositions or reagents for use in ligation sequencing determination protocol. Optionally, the identity of the label provides the exact identity of a nucleotide occupying one degenerate position in the probe. For example, the identity of the label optionally eliminates one or more combinations or permutations of nucleotides at two or more degenerate positions. The probes are for example degenerate at two or more constrained positions, where the identity of a nucleotide at one constrained position eliminates at least one possible identity of a nucleotide at another constrained position. Optionally, knowing the identity of a constrained residue in that probe further eliminates at least one possible identity for another constrained residue in the probe.

[00128] Unless otherwise apparent from the context, any feature can be claimed in combination with any other, or be claimed as not present in combination with another feature. A feature can be for example any variation, step, feature, property, composition, method, step, degree, level, component, material, substance, element, mode, variable, aspect, measure, amount or embodiment.

[00129] Many features described herein are intended to be optional. If any feature is not explicitly indicated as being necessary, it is to be regarded as optional. Non-limiting examples of language indicating that a feature is optional include terms such as "variation," "where," "while," "when," "optionally," "include," "preferred," "especial," "recommended," "advisable," "particular," "should," "alternative," "typical," "representative," "various," "such as," "the like," "can," "may," "example," "embodiment," or " in an aspect" or "if or any combination and/or variation of such terms.

[00130] Any indication that a feature is optional is intended to provide adequate support for claims that include closed or exclusive or negative language (e.g., under 35 U.S.C. 112 or Art. 83 and 84 of EPC). Exclusive language specifically excludes the particular recited feature from including any additional subject matter. For example, if it is indicated that A can be drug X, such language is intended to provide support for a claim that explicitly specifies that A consists of X alone, or that A does not include any other drugs besides X. "Negative" language explicitly excludes the optional feature itself from the scope of the claims. For example, if it is indicated that element A can be X, such language is intended to provide support for a claim that explicitly specifies that A is not X.

[00131] Non-limiting examples exclusive or negative terms include "only," "solely," "consisting of," "consisting essentially of," "alone," "without", "in the absence of (e.g., other items of the same type, structure and/or function)" "excluding," "not", "doesn't", "cannot," or any combination and/or variation of such language.

[00132] Similarly, referents such as "a," "an," "said," or "the," are intended to support explicitly single or plural referents where so desired. Non-limiting examples of plural referents include "at least one," "one or more," "more than one," "two or more," "a multiplicity," "a plurality," "any combination of," "any permutation of," "any one or more of," etc.

[00133] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. Genbank records referenced by Genbank ID or accession number, particularly any polypeptide sequence, polynucleotide sequences or annotation thereof, are incorporated by reference herein. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

[00134] The following examples are provided for illustrative purposes and are not intended to limit the invention.

EXAMPLES

Example 1

[00135] This example describes ligation of short probes.

[00136] The oligonucleotide reagents were as follows. The short oligos in forward ligation (i.e., ligation of the 3' terminus of the probe to the 5' terminus of the primer) were: 8mer : 5'-CTCATTCG-3'; 6mer : 5'-TCATTCG-3' 5mer : 5'-ATTCG-3'; 4mer : 5'-TTCG-3'; 3mer : 5'-TCG-3'. Short oligos used for reverse ligation (i.e., ligation of the 5' terminus of the probe to the 3' terminus of the primer) were the same as forward ligation oligos except they have a 5' phosphate. All oligonucleotides were obtained from Integrated DNA Technologies. The forward primer was: P04-5'-CTGCTGTACCGTACATCCGC-3 '-6FAM. The reverse primer was: 5'-FAM-CTGCCCCGGGTTCCTCATTCTCT-3 '

[00137] Ligase Substrate Preparation: MyOne magnetic beads labeled with carboxylic acid, were obtained from Invitrogen. 5' amino labeled, 4 1-base oligonucleotide (CCA CTA CGC CTC CGC TTT CCT CTC TAT GGG CAG TCG GTG AT) was coupled to MyOne beads using standard amine coupling chemistry as taught in Nakajima et al, Bioconjugate Chem. 1995, 6(1), 123-130 (Figure 1b). PCR was used to extend this oligonucleotide using (CTG CCC CGG GTT CCT CAT TCT CTA TTC GCT GCT GTA CCG TAC ATC CGC CTT GGC CGT ACA GCA GAT CAC CGA CTG CCC ATA GAG AGG). The following 105 base ligation substrate was now tethered to MyOne beads (CCA CTA CGC CTC CGC TTT CCT CTC TAT GGG CAG TCG GTG ATC TGC TGT ACG GCC AAG GCG GAT GTA CGG TAC AGC AGC GAA TAG AGA ATG AGG AAC CCG GGG CAG, Figure 1a). The amount of 105-base oligo tethered to the bead was measured by hybridization of a fluorescently labeled "primer" oligo, with 3' fluorescein label (6FAM) for detection by capillary electrophoresis. The amount of fluorescence denatured from the template was compared to a standard curve.

[00138] Ligation reactions were performed in buffer containing 50 mM Tris-HCl, 10 mM MgCL2, 1 mM ATP, 1 mM DTT and 5% w/v PEG 8000 at pH 7.5 (ligase buffer). Primer oligonucleotide was annealed to template in ligase buffer by heating to 85 °C for 10 minutes followed by slow cooling to room temperature. In the case of forward ligation, the primer was 5' phosphorylated and a 3' 6FAM labeled. In the case of reverse ligation, the primer was 5' 6FAM labeled. Ligation reactions were performed in a 96 well plate

using 2 nM template/primer, 2.0 μM ligase, 2-5 μM short oligonucleotide in a total volume of 50 μL. The ligation reactions proceeded for 20 minutes at 15 °C. The reactions were stopped using 1% v/v SDS followed by magnetic separation of the templated beads from the solution. Beads were washed three times in 100 μL of 1% SDS prior to washing with 100 uL of 100% formamide. 5 μL of the supernatant containing denatured, FAM labeled primer and ligation product were then analyzed by capillary electrophoresis. The ligation efficiency was calculated as the ratio of peak areas determined by CE, where FAM labeled, unligated and ligated primer were separated, i.e., Efficiency = ligated /(ligated + unligated).

[00139] Shown in Figures 3-5 are a series of ligations of probes of different lengths with a variety of SFLs. In each panel, the ligation reaction is plotted as a function of the probe length. These data clearly demonstrate that small footprint ligases can ligate probe substrates as short as two nucleotides. By utilizing SFLs, the size of a sequencing probe set (e.g., for ligation sequencing in SOLiD™) can be reduced from the current set of 1024 8-mers to as few as 16 (in the case of di-mers), 64 (in the case of trimers), or 256 in the case of tetramers.

[00140] In another experiment, the ligation efficiency of SF Ligase was compared using the same experimental system as above to T4 DNA ligase, using 8-mer ligation sequencing probes that were conjugated or not conjugated to dyes. SFL the highest overall ligation efficiency for both the dark (chase) probe and the labeled sequencing probe. This is true at the 200 nM concentration of probe, which is currently used in SOLiD. Specifically, a mixture of 1024 probes is used in SOLiD, where each individual probe of the 1024 probes is present at a final working concentration of 200 nM. The other concentrations were 2000 nM of enzyme and 1 nM bead template, where ligation was performed at 15°C for 30 minutes. Results are shown in Table 2.

Table 2

Maximum ligation efficiency of 8mer probes by various ligase enzymes

Ligase	Dark	Cy 5
SFL	0.91 ± 0.01	0.82 ± 0.01
T4	0.67 ± 0.02	0.62 ± 0.02

Example 2

[00141] The fidelity of a small-footprint ligase (CV ligase) was determined to be surprisingly better than T4 DNA ligase in DNA sequencing by ligation on the SOLiD sequencing system. A 35-nucleotide DNA template was covalently attached to beads, such each magnetic bead had about 100,000 covalently bound DNA molecules on average. Approximately 40 million beads were subjected to a ligation sequencing reaction at 20 °C. The sequencing reaction ligated 8-mer oligonucleotide "probes" labeled with fluorescent dye onto a primer, and a total of seven consecutive ligation or probing events were performed on each template molecule. The approximate number of ligation events were therefore 100,000 (i.e., number of template molecules per bead) x 40,000,000 (i.e., number of beads) x 7 (number of ligation events per template) = 2.8 x 10^{13}.

[00142] Results are given in Table 3 below. 0MM= Percentage of all ligation products (which are the result of seven consecutive ligation events) with no mismatches; 3MM = Percentage of all ligation products (which are the result of seven consecutive ligation events) with less than 3 mismatches.

Table 3

Ligase	0MM	3MM
T4	20%	57%
SF	27%	65%

The sequencing by ligation data demonstrates that 20% of the time the ligation product was perfectly complementary to the template and formed by seven consecutive ligation events that were all correct. An estimate of the ligation fidelity (expressed as the percentage probability that a ligation event is correct, or "p") can be calculated from the equation: 0MM rate = $(p/100)^n$ where p is the percentage ligation fidelity and n is the number of ligation events per final ligation product (here, seven). Thus for T4 DNA ligase, the ligation fidelity is 79.5% and for SFL the ligation fidelity is 83%.

We claim:

1. A method of ligation comprising enzymatically ligating an oligonucleotide ("probe") and a polynucleotide ("primer"), wherein: the probe is N nucleotide residues in length, where N is from 2 to 7.

2. The method of claim 1, comprising enzymatically ligating an oligonucleotide ("probe") and a polynucleotide ("primer"), wherein: the probe is N nucleotide residues in length, where N is 2 or 3.

3. The method of claim 1, comprising enzymatically ligating a polynucleotide ("primer") to an oligonucleotide ("probe"), wherein (i) the probe is 4 or 5 nucleotide residues in length, and (ii) the ligase is not Paramecium Bursaria Chlorella Virus ligase (CV ligase) or a derivative thereof, or the 3' end of the probe is ligated to the 5' end of the primer, and (iii) more than 30% of the probe or primer is ligated.

4. The method of claim 1, comprising enzymatically ligating a polynucleotide ("primer") to an oligonucleotide ("probe"), wherein (i) the probe is 6 or 7 nucleotide residues in length, and (ii) the ligase is not CV ligase or a derivative thereof, and (iii) more than 50% of the probe or primer is ligated.

5. The method of any one of the preceding claims, wherein ligation is performed by a ligase listed in Table 1A, IB or 1C.

6. The method of any one of the preceding claims, wherein the probe and the primer are not hybridized to the same polynucleotide ("template") if they are different polynucleotides,

7. The method of claim 5, wherein the probe and primer are single-stranded.

8. The method of claim 7, wherein the ligation is performed prior to amplification in a proximity ligation assay.

9. The method of any one of claims 1-4, comprising ligating a proximal terminus of the probe to a proximal terminus of the primer, wherein the probe and the primer are both hybridized to a polynucleotide ("template") such that their proximal termini are adjacently hybridized to each other.

10. A method of claim 1, wherein:

a) the probe and the primer are both hybridized to a polynucleotide ("template") such that their proximal termini are adjacently hybridized to each other, where the proximal terminus of the probe is ligated to the adjacently-hybridized proximal terminus of the primer;

b) the probe is N nucleotide residues in length, where N is 2 or 3.

11. A method of template-dependent ligation comprising enzymatically ligating an oligonucleotide ("probe") and a polynucleotide ("primer"), wherein:

a) the probe and primer are both hybridized to the template such that their proximal termini are adjacent to each other;

b) the probe is of length N, and comprises a proximal portion, wherein the proximal portionis (i) perfectly hybridized to the template and is (ii) L nucleotides long, where the probe's L+lth nucleotide is mismatched with the template; and

c) L is from 2 to 8, and furthermore is less than 6 if the proximal terminus of the probe is its 3' terminus.

12. The method of any one of the preceding claims, wherein ligation is achieved with a small footprint ligase ("SFL") at substantial efficiency, and optionally

(a) at least 10% of the probe or primer is ligated, or

(b) the SFL ligates the proximal termini of the primer and the probe at least 50% as efficiently as the SFL can ligate the proximal termini of the primer and a corresponding octanucleotide whose N proximal residues are identical to the probe, and whose distal 12-N residues are perfectly complementary to the template.

13. The method of any one of the preceding claims, wherein the SFL is CV ligase, or alternatively the SFL is not CV ligase or a derivative thereof.

14. The method of any one of the preceding claims, wherein the primer is not more than 6 nucleotides in length, for example not more 5, 4, 3 or 2 nucleotides.

15. The method of any one of the preceding claims, wherein the template, if present, is not more than 11 nucleotides in length, for example not more 10, 9, 8, 7, 6, 5, 4, 3 or 2 nucleotides.

16. The method of any one of the preceding claims, wherein the proximal terminus of the probe is its 3' terminus and the proximal terminus of the primer is its 5' terminus.

17. The method of any one of claims 1 to 14, wherein the proximal terminus of the probe is its 5' terminus and the proximal terminus of the primer is its 3' terminus.

18. The method of claim 16 or 17, wherein N is 4.

19. The method of claim 16 or 17, wherein N is 3.

20. The method of claim 16 or 17, wherein N is 2.

21. The method of any one of the preceding claims, wherein the probe is labeled.

22. The method of any one of the preceding claims, wherein the primer or template is labeled.

23. The method of any one of the preceding claims, wherein at least two of the probe, primer and template are labeled.The method of any one of the preceding claims, wherein at least one of the probe, the template and/or the primer is immobilized.

24. The method of any one of the preceding claims, wherein the ligation is repeated at least once.

25. The method of claim 22, wherein any ligation product of a previous ligation reaction is used as the primer of a next ligation, where optionally any unligated primer is rendered unligatable before initiating the next ligation.

26. The method of claim 22, further comprising detecting whether the probe has ligated to the primer before repeating the ligation.

27. The method of claim 24, wherein the method provides information about the template sequence.

28. The method of claim 24, wherein ligation is performed in the presence of multiple probes that are at least partially complementary to the same target region on the template adjacent to the proximal terminus of the primer.

29. The method of claim 26, wherein at least two of the multiple probes are labeled distinguishably from each other.

30. The method of claim 27, wherein identifying the label on a ligated probe provides information about the template sequence.

31. The method of claim 22, wherein any ligation product of the previous ligation reaction is used as the template of the next ligation reaction.

32. The method of claim 24, wherein the method comprises a ligase chain reaction.

33. The method of any one of claims 1-16 and 18-32, comprising enzymatically ligating the 5' end of the probe and the 3' end of the primer with CV ligase, wherein N is less than 6.

34. The method of claim 33, wherein N is 2, 3 or 4.

35. A method of template-dependent ligation of an oligonucleotide ("probe") with a polynucleotide ("primer"), where the length of the probe is less than 8 nucleotides.

36. The method of claim 35, wherein the primer is also less than 8 nucleotides, for example not more 6, 5, 4, 3 or 2 nucleotides.

37. The method of claim 35 or 36, wherein the primer is 4 nucleotides long.

38. The method of claim 35 or 36, wherein the primer is 3 nucleotides long.

39. The method of any one of claims 35 to 38, wherein the SFL is CV ligase.

40. A kit comprising a small footprint ligase ("SFL") and an oligonucleotide probe less than N nucleotides in length, where N is from 2 to 7.

41. The kit of claim 40, wherein the SFL is not CV ligase or a derivative thereof and N is less than 6.

42. The kit of any one of claims 40-41, wherein the probe comprises a 5'-phosphate.

43. The kit of any one of claims 40-42, wherein the probe comprises a label.

44. The kit of claim 43, wherein the label is attached to the 5' terminus.

45. The kit of claim 43, wherein the label is attached to the 3' terminus.

46. The kit of any one of claims 40-45, wherein the probe is cleavable.

47. The kit of any one of claims 40-46, wherein the kit comprises a plurality of distinguishably labeled probes.

48. The kit of claim 47, wherein the probes in said plurality are degenerate at one or more nucleotide positions.

49. The kit of claim 48, wherein the probes are labeled such that the identity of the label provides information about a nucleotide occupying a degenerate position in the probe.

50. The kit of claim 49, wherein the identity of the label provides the exact identity of a nucleotide occupying one degenerate position in the probe.

51. The kit of claim 48, wherein the identity of the label eliminates one or more combinations or permutations of nucleotides at two or more degenerate positions.

52. The kit of any one of claims 47 to 51, wherein the probes are degenerate at two or more constrained positions, where the identity of a nucleotide at one constrained position eliminates at least one possible identity of a nucleotide at another constrained position.

53. The kit of claim 52, wherein knowing the identity of a constrained residue in that probe further eliminates at least one possible identity for another constrained residue in the probe.

54. A mutant Hin (Haemophilus Influenzae) DNA ligase comprising a sequence of DLX, DLXd or DLXd2 shown in Table 1C.

55. A mutant Hin DNA ligase consisting essentially of a sequence of DLX, DLXd or DLXd2 shown in Table 1C.

56. A mutant Hin DNA ligase that has at least 70% identity to Hin D ligase sequence provided in Table 1C or in GenBank Accession No. P44121, which ligase comprises an amino acid mutation at position 193 of Hin D ligase sequence provided in Table 1C or in

GenBank Accession No. P44121, optionally wherein said amino acid mutation consists of changing the glycine at position 193 to aspartic acid or glutamic acid.

57. The ligase of claim 56, wherein the ligase has at least 80% identity to Hin **D** ligase.

58. The ligase of claim 56, wherein the ligase is at least 90% identical to Hin **D** ligase.

59. The ligase of claim 56, wherein the ligase is at least 95% identical to Hin **D** ligase.

60. The ligase of claim 56, wherein the ligase is at least 99% identical to Hin **D** ligase.

61. The ligase of any one of claims 54-60, wherein the ligase is isolated, purified or recombinant.

62. A nucleic acid molecule encoding the ligase of any one of claims 54-61.

63. The nucleic acid of claim 62, wherein the nucleic acid is isolated, purified or recombinant.

64. A vector comprising the nucleic acid molecule of claim 62.

65. The vector of claim 64, wherein the vector is isolated, purified or recombinant.

66. A host cell comprising the vector of claim 64.

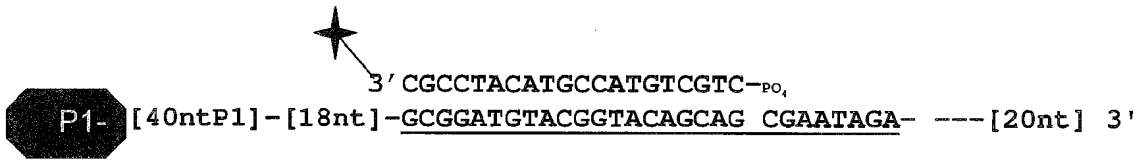
67. The host cell of claim 66, wherein the host cell is isolated, purified or recombinant.

68. A method of making a ligase comprising:

a. culturing the isolated recombinant host cell of claim 66 or 67 under conditions such that the ligase is expressed; and
b. recovering said ligase.

FIGURE 1

(A)


3′CGCCTACATGCCATGTCGTC–PO4
P1-
[40ntP1]-[18nt]-GCGGATGTACGGTACAGCAG CGAATAGA- ---[20nt] 3'

(B)

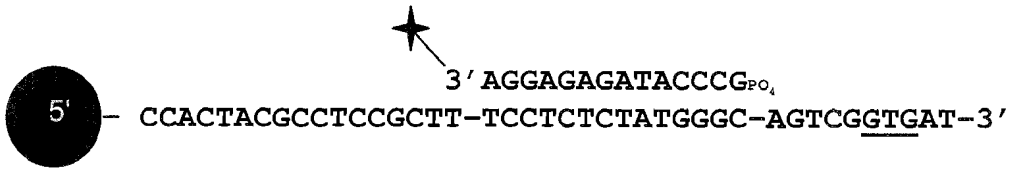

3′AGGAGAGATACCCGPO4
5'
– CCACTACGCCTCCGCTT-TCCTCTCTATGGGC-AGTCGGTGAT-3′

FIGURE 2

CV DNA Ligase, GenBank ID AAC96909.1, from Paramecium bursaria Chlorella virus 1:

MAITKPLLAATLENIEDVQFPCLATPKIDGIRSVKQTQMLSRTFKPIRNSVMNRLLTELL
PEGSDGEISIEGATFQDTTSAVMTGHKMYNAKFSYYWFDYVTDDPLKKYIDRVEDMK
NYITVHPHILEHAQVKIIPLIPVEINNITELLQYERDVLSKGFEGVMIRKPDGKYKFGRST
LKEGILLKMKQFKDAEATIISMTALFKNTNTKTKDNFGYSKRSTHKSGKVEEDVMGSIE
VDYDGVVFSIGTGFDADQRRDFWQNKESYIGKMVKFKYFEMGSKDCPRFPVFIGIRHE
EDR

MnM DNA Ligase, GenBank ID YP_333052.1, from Burkholderia pseudomallei 1710b (equivalent sequence to ABA50091)

MSGVPYGFKPNLAATLTKPELIKFPVWASPKIDGIRCVFFGGVAYSRSLKPIPNPVVQEF
AKAYANLLEGLDGELTVGSPTDANCMQNSMAVMSKAAAPDFTFHVFDWFHPAQAHI
EFWQRSDVVEDRIVQFYDRYPEVDIRAAPQVLCTSLAHLDTNEARWLADGYEGMMIR
DHCGRYKFGRSTEREGGLVKVKRFTDAEAIVIGFEEEMHNANEAKRDATGRTERSTSK
AGLHGKGTLGALVVKNERGIVFNIGTGFTAAQRADYWANHPSLFGKMVKFKHFDHGT
VDAPRHPVFIGFRHPEDM

Hin DNA Ligase, GenBank ID P44121, from Haemophilus influenza

MKFYRTLLLFFASSFAFANSDLMLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQLLTR
QGQRLSPPAYFIKDFPPFAIDGELFSERNHFEEIS**T**ITKSFKGDGWEKLKLYVFDVPDAE
GNLFERLAKLKAHLLEHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGEGVVVRNPNAP
YERKRSSQILKLKTAR**G**EECTVIAHHKGKGQFENVMGALTCKNHRGEFKIGSGFNLNE
RENPPPIGSVITYKYRGITNSGKPRFATYWREKK

DLX DNA Ligase, artificial ligase derived from Hin DNA ligase from Haemophilus influenza:

MKFYRTLLLFFASSFAFANSDLMLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQLLTR
QGQRLSPPAYFIKDFPPFAIDGELFSERNHFEEIS**S**ITKSFKGDGWEKLKLYVFDVPDAEG
NLFERLAKLKAHLLEHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGEGVVVRNPNAPY
ERKRSSQILKLKTARGEECTVIAHHKGKGQFENVMGALTCKNHRGEFKIGSGFNLNER
ENPPPIGSVITYKYRGITNSGKPRFATYWREKK

DLXd DNA Ligase, artificial ligase derived from Hin D ligase from Haemophilus influenza:

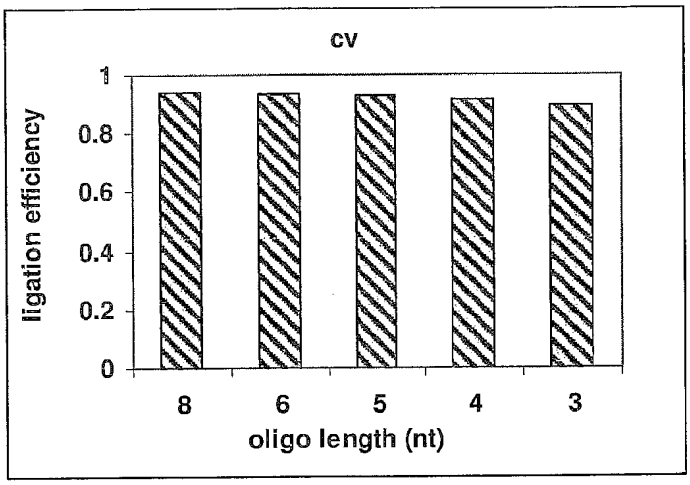
MKFYRTLLLFFASSFAFANSDLMLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQLLTR
QGQRLSPPAYFIKDFPPFAIDGELFSERNHFEEIS**S**ITKSFKGDGWEKLKLYVFDVPDAEG
NLFERLAKLKAHLLEHPTTYIEIIEQIPVKDKTHLYQFLAQVENLQGEGVVVRNPNAPY
ERKRSSQILKLKTAR**D**EECTVIAHHKGKGQFENVMGALTCKNHRGEFKIGSGFNLNER
ENPPPIGSVITYKYRGITNSGKPRFATYWREKK

DLXd2 DNA Ligase (Gammaproteobacteria, Haemophilus influenza) (modified)

MLLHTYNNQPIEGWVMSEKLDGVRGYWNGKQLLTRQGQRLSPPAYFIKDFPPFAIDGE
LFSERNHFEEIS**S**ITKSFKGDGWEKLKLYVFDVPDAEGNLFERLAKLKAHLLEHPTTYIE
IIEQIPVKDKTHLYQFLAQVENLQGEGVVVRNPNAPYERKRSSQILKLKTAR**D**EECTVIA
HHKGKGQFENVMGALTCKNHRGEFKIGSGFNLNERENPPPIGSVITYKYRGITNSGKPR
FATYWREKK

FIGURE 3

(A)


cv
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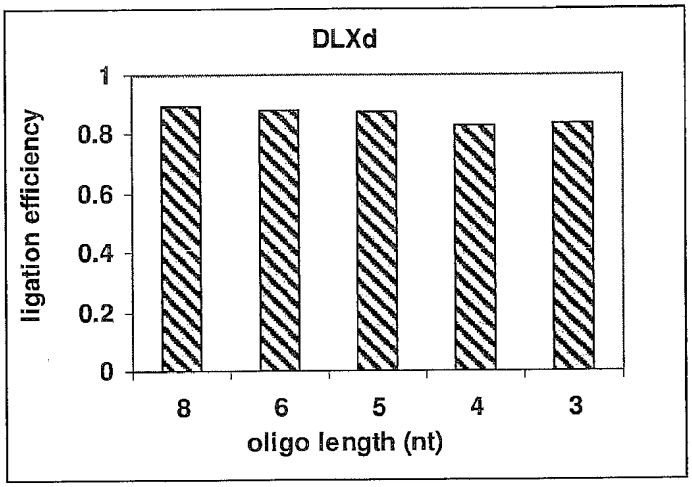
0.6
0.4
0.2
0
8
6
5
4
3
oligo length (nt)

(B)


DLXd
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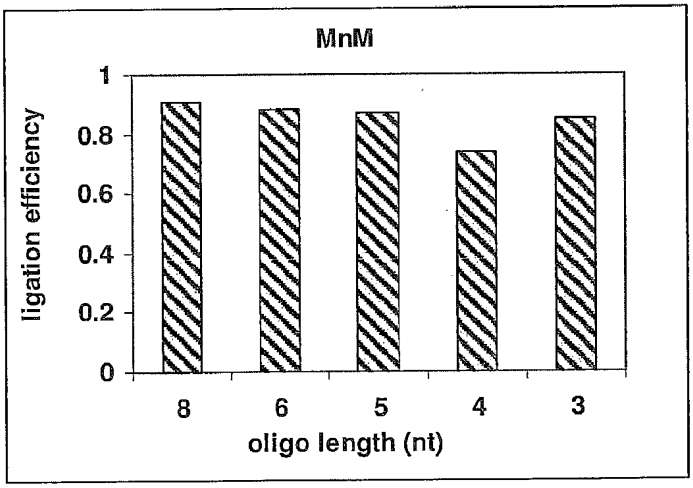
0.2
0
8
6
5
4
3
oligo length (nt)

(C)


MnM
ligation efficiency
1
0.8
0.6
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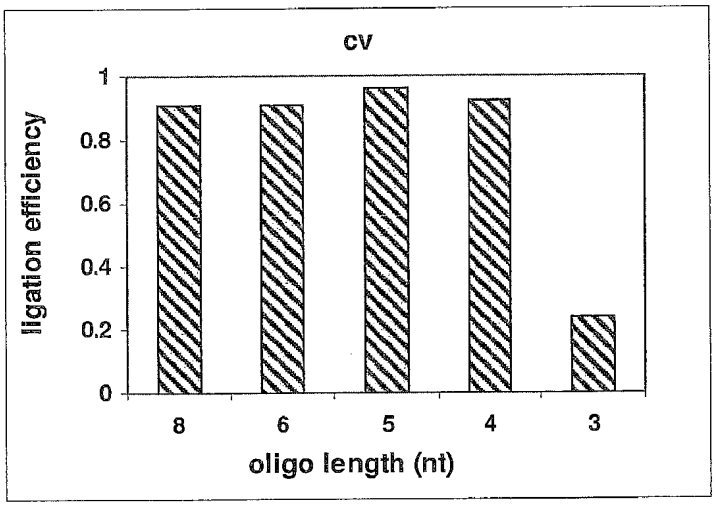
0.2
0
8
6
5
4
3
oligo length (nt)

FIGURE 4

(A)


cv
ligation efficiency
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0.6
0.4
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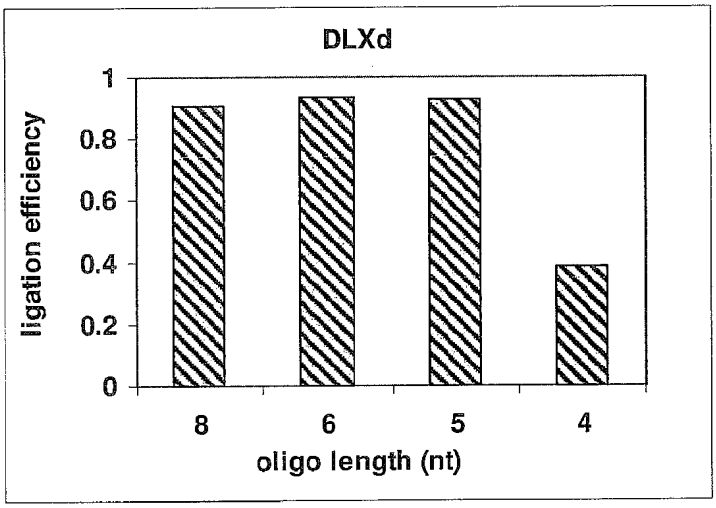
0
8
6
5
4
3
oligo length (nt)

(B)


DLXd
ligation efficiency
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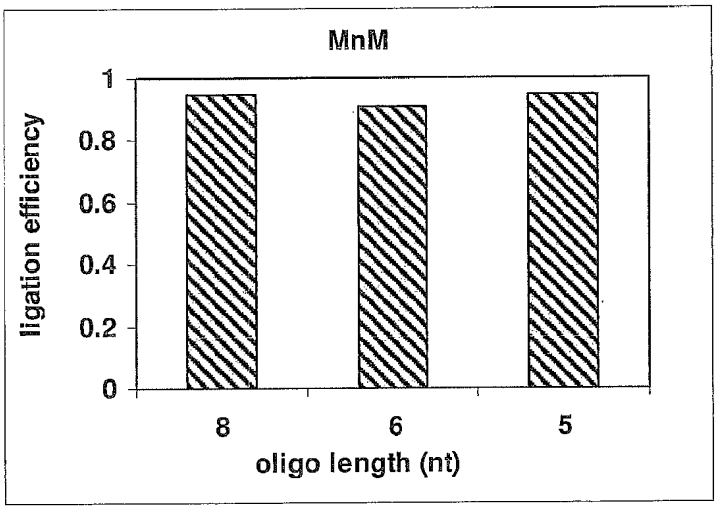
0.8
0.6
0.4
0.2
0
8
6
5
4
oligo length (nt)

(C)


MnM
ligation efficiency
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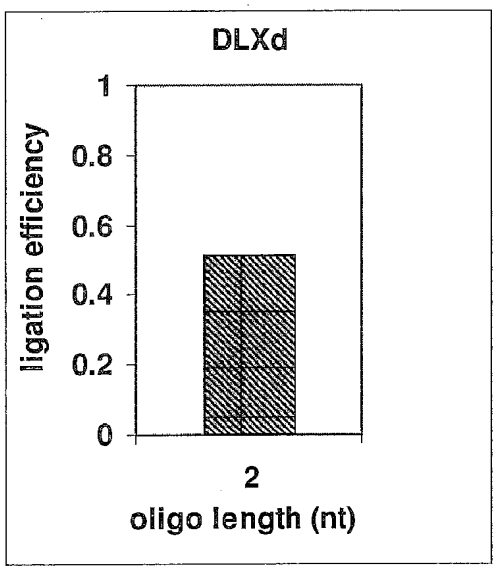
0.8
0.6
0.4
0.2
0
8
6
5
oligo length (nt)

FIGURE 5



PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

	1	CROWLEY, E. et al. "Liquid biopsy: monitoring cancer-genetics in the blood" Nat Rev Clin Oncology (2013) 8:472-478
	2	Extended European search report and opinion dated 12/07/2020 for EP Application No. 20183626.9.
	3	GREAVES, L.C. et al. "Quantification of mitochondrial DNA mutation load" Aging Cell (2009) 8(5): 566–572
	4	Guardant Health, Inc. Response to Notice of Opposition in EP3378952 filed March 29, 2021.
	5	Guardant Health, Inc. v. FMI Defendant's Answer and Counter Claims, filed January 14, 2021 (C.A. No. 20-1580 (LPS))
	6	Guardant Health, Inc. v. FMI Defendant's Answering Brief in Opposition to Plaintiff Guardant Health, Inc's Motion for Preliminary Injunction, filed March 5, 2021 (C.A. No. 20-1580 (LPS))
	7	Office action dated 06/23/2021 for US Application No. 16/913,965.
	8	Opposition to EP3524694, dated April 15, 2021 by Foundation Medicine, Inc.
	9	Opposition to EP3524694, filed April 16, 2021 by Maiwald International

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	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2021-07-09
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	AmirAli TALASAZ et al.	Confirmation No.:	3448
Application No.	16/672,267	Examiner:	Kenneth HORLICK
Filed:	January 7, 2020	Group Art Unit:	1637
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Customer No.	115823

NOTICE OF CONCURRENT PROCEEDINGS

Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 CFR 1.56, MPEP 2001.06(c) and other duties of disclosure, Applicant hereby notifies the Office of pleadings by defendant Foundation Medicine, Inc. ("FMI") in the ongoing litigation proceeding *Guardant Health, Inc. v. Foundation Medicine, Inc.* Civil Action No. 1:20-CV-01580-LPS, alleging inequitable conduct for improper inventorship against Applicant. The proceeding was filed in the United States District Court for the District of Delaware. The patents at issue in the litigation are US 10,501,810; US 10,704,085; US 10,704,086; US 10,793,916; US 10,801,063; US 9,840,743; and US 9,834,822.

Publicly available copies of documents describing the abovementioned pleadings by FMI are submitted herewith. If at any point the Examiner would like to be provided with copies of any additional contents of any related proceeding, Applicant will readily provide such copies upon request subject to relevant protective orders.

If any additional fee is due or to credit any overpayment, please charge any fees incorrected in connection with this submission or credit any overpayment to Deposit Account 60-2231 (GH0004US-CON3).

Respectfully submitted,

Date: July 9, 2021

By: /Timothy A. Hott/

Timothy A. Hott
Reg. No. 67,740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	AmirAli TALASAZ et al.	Confirmation No.:	3448
Application No.	16/672,267	Examiner:	Kenneth HORLICK
Filed:	January 7, 2020	Group Art Unit:	1637
Title:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Customer No.	115823

NOTICE OF CONCURRENT PROCEEDINGS

Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 CFR 1.56, MPEP 2001.06(c) and other duties of disclosure, Applicant hereby notifies the Office of pleadings by defendant Foundation Medicine, Inc. ("FMI") in the ongoing litigation proceeding *Guardant Health, Inc. v. Foundation Medicine, Inc.* Civil Action No. 1:20-CV-01580-LPS, alleging, among other contentions, grounds for invalidity of US 10,501,810; US 10,704,085; US 10,704,086; US 10,793,916; US 10,801,063; US 9,840,743; and US 9,834,822. The proceeding was filed in the United States District Court for the District of Delaware.

Copies of documents describing the abovementioned pleadings by FMI are submitted herewith. If at any point the Examiner would like to be provided with copies of any additional contents of any related proceeding, Applicant will readily provide such copies upon request subject to relevant protective orders.

If any additional fee is due or to credit any overpayment, please charge any fees incorrected in connection with this submission or credit any overpayment to Deposit Account 60-2231 (GH0004US-CON3).

Respectfully submitted,

Date: July 9, 2021

By: /Timothy A. Hott/

Timothy A. Hott
Reg. No. 67,740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

U.S. District Court
District of Delaware (Wilmington)
CIVIL DOCKET FOR CASE #: 1:20-cv-01580-LPS

Guardant Health, Inc. v. Foundation Medicine, Inc.
Assigned to: Judge Leonard P. Stark
Related Case: 1:17-cv-01616-LPS-CJB
Cause: 35:271 Patent Infringement

Date Filed: 11/23/2020
Jury Demand: Plaintiff
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

Plaintiff

Guardant Health, Inc.

represented by **Brian E. Farnan**
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V.

Defendant

Foundation Medicine, Inc.

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Counter Claimant

Foundation Medicine, Inc.

represented by **Karen Jacobs**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Jeremy A. Tigan
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

Guardant Health, Inc.

represented by **Brian E. Farnan**
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LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Derek C. Walter
(See above for address)
ATTORNEY TO BE NOTICED

Edward R. Reines
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Garland T. Stephens
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Justin L. Constant
(See above for address)
ATTORNEY TO BE NOTICED

Michael J. Farnan
(See above for address)
ATTORNEY TO BE NOTICED

Date Filed	#	Docket Text
11/23/2020	1	COMPLAINT filed with Jury Demand against Foundation Medicine, Inc. - Magistrate Consent Notice to Pltf. (Filing fee $400, receipt number ADEDC-3350084.) - filed by Guardant Health, Inc. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12, # 13 Exhibit 13, # 14 Exhibit 14, # 15 Exhibit 15, # 16 Exhibit 16, # 17 Exhibit 17, # 18 Exhibit 18, # 19 Exhibit 19, # 20 Exhibit 20, # 21 Exhibit 21, # 22 Exhibit 22, # 23 Exhibit 23, # 24 Civil Cover Sheet)(kmd) (Entered: 11/24/2020)
11/23/2020	2	Notice, Consent and Referral forms re: U.S. Magistrate Judge jurisdiction. (kmd) (Entered: 11/24/2020)
11/23/2020	3	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 10,501,810 B2; US 10,704,085 B2; US 10,704,086 B2; US 10,793,916 B2; US 10,801,063 B2; US 9,840,743 B2; US 9,834,822 B2. (kmd) (Entered: 11/24/2020)
11/23/2020	4	Summonses Issued (please complete the top portion of the form and print out for use/service). (kmd) (Entered: 11/24/2020)
11/25/2020		Case Assigned to Judge Leonard P. Stark. Please include the initials of the Judge (LPS) after the case number on all documents filed. (rjb) (Entered: 11/25/2020)
11/25/2020	5	SUMMONS Returned Executed by Guardant Health, Inc.. Foundation Medicine, Inc. served on 11/24/2020, answer due 12/15/2020. (Farnan, Michael) (Entered: 11/25/2020)
12/08/2020	6	MOTION for Pro Hac Vice Appearance of Attorney Edward R. Reines, Derek C. Walter, Garland T. Stephens, and Justin L. Constant - filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 12/08/2020)
12/10/2020	7	MOTION for Preliminary Injunction - filed by Guardant Health, Inc.. (Attachments: # 1 Text of Proposed Order, # 2 Rule 7.1.1 Certification, # 3 Certificate of Service)(Farnan, Brian) (Entered: 12/10/2020)
12/10/2020	8	[SEALED] OPENING BRIEF in Support re 7 MOTION for Preliminary Injunction filed by Guardant Health, Inc..Answering Brief/Response due date per Local Rules is 12/24/2020. (Farnan, Brian) (Entered: 12/10/2020)
12/10/2020		SO ORDERED, re 6 MOTION for Pro Hac Vice Appearance of Attorney Edward R. Reines, Derek C. Walter, Garland T. Stephens, and Justin L. Constant filed by Guardant Health, Inc. Signed by Judge Leonard P. Stark on 12/10/20. (ntl) (Entered: 12/10/2020)
12/10/2020	9	DECLARATION re 8 Opening Brief in Support *of Garland Stephens* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10)(Farnan, Brian) (Entered: 12/10/2020)
12/10/2020	10	[SEALED] DECLARATION re 8 Opening Brief in Support *of Gregory Cooper* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12, # 13 Exhibit 13, # 14 Exhibit 14, # 15 Exhibit 15, # 16 Exhibit 16, # 17 Exhibit 17, # 18 Exhibit 18, # 19 Exhibit 19, # 20 Exhibit 20, # 21 Exhibit 21, # 22 Exhibit 22, # 23 Exhibit 23)(Farnan, Brian) (Entered: 12/10/2020)
12/10/2020	11	DECLARATION re 8 Opening Brief in Support *of Daniel Simon* by Guardant Health, Inc.. (Farnan, Brian) (Entered: 12/10/2020)
12/11/2020	12	Joint STIPULATION TO EXTEND TIME to ANSWER complaint to January 14, 2021 - filed by Foundation Medicine, Inc.. (Jacobs, Karen) (Entered: 12/11/2020)
12/14/2020		SO ORDERED, re 12 Joint STIPULATION TO EXTEND TIME to ANSWER complaint to January 14, 2021 filed by Foundation Medicine, Inc. Signed by Judge Leonard P. Stark on 12/14/20. (ntl) (Entered: 12/14/2020)
12/15/2020		Pro Hac Vice Attorney Edward R. Reines,Derek C. Walter,Justin L. Constant for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (mal) (Entered: 12/15/2020)
12/16/2020		Pro Hac Vice Attorney Garland T. Stephens for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (mal) (Entered: 12/16/2020)
12/18/2020	13	REDACTED VERSION of 8 Opening Brief in Support by Guardant Health, Inc.. (Farnan, Michael) (Entered: 12/18/2020)
12/18/2020	14	REDACTED VERSION of 10 Declaration,, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-23)(Farnan, Michael) (Main Document 14 replaced on 12/21/2020) (ntl). (Entered: 12/18/2020)
12/21/2020		CORRECTING ENTRY: Corrected main document added to D.I. 14 per request of counsel. (ntl) (Entered: 12/21/2020)
12/23/2020	15	NOTICE OF SERVICE of Guardant Health, Inc.'s First Set of Requests for Production of Documents and Things to FMI (Nos. 1-10) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 12/23/2020)
12/23/2020	16	NOTICE OF SERVICE of Foundation Medicine, Inc.'s First Set of Requests for Production of Documents and Things to Guardant Health, Inc. filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 12/23/2020)
12/23/2020	17	MOTION for Pro Hac Vice Appearance of Attorney Eric J. Marandett, G. Mark Edgarton, Sophie F. Wang and Diane C. Seol - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 12/23/2020)
12/23/2020		SO ORDERED, re 17 MOTION for Pro Hac Vice Appearance of Attorney Eric J. Marandett, G. Mark Edgarton, Sophie F. Wang and Diane C. Seol filed by Foundation Medicine, Inc. Signed by Judge Leonard P. Stark on 12/23/20. (ntl) (Entered: 12/23/2020)
12/23/2020	18	STIPULATION and [Proposed] Order Regarding Preliminary Injunction Discovery and Briefing re 7 MOTION for Preliminary Injunction by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 12/23/2020)
01/04/2021	19	SO ORDERED, re 18 STIPULATION and [Proposed] Order Regarding Preliminary Injunction Discovery and Briefing -- A Motion Hearing (remote) is set for 5/14/2021 at 9:00 AM. Signed by Judge Leonard P. Stark on 1/4/21. (ntl) (Entered: 01/04/2021)
01/06/2021	20	NOTICE OF SERVICE of Plaintiff's Response to Foundation Medicine, Inc.'s First Set of Requests for Production of Documents and Things filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/06/2021)
01/06/2021	21	NOTICE OF SERVICE of Defendant Foundation Medicine, Inc.'s Responses and Objections to Plaintiff Guardant Health, Inc.'s First Set of Requests for Production of Documents and Things (Nos. 1-10) filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/06/2021)
01/14/2021	22	ANSWER to 1 Complaint,, with Jury Demand , COUNTERCLAIM against Guardant Health, Inc. by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1-37)(Tigan, Jeremy) (Entered: 01/14/2021)
01/25/2021	23	NOTICE OF SERVICE of (1) Deposition Notice of Gregory Cooper and (2) Deposition Notice of Daniel Simon filed by Foundation Medicine, Inc..(Simonetti, Sarah) (Entered: 01/25/2021)
02/04/2021	24	ANSWER to 22 Answer to Complaint, Counterclaim by Guardant Health, Inc..(Farnan, Michael) (Entered: 02/04/2021)
02/23/2021	25	PROPOSED ORDER Stipulated Protective Order by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/23/2021)
02/26/2021		SO ORDERED, re 25 Stipulated Protective Order filed by Foundation Medicine, Inc. Signed by Judge Leonard P. Stark on 2/25/21. (ntl) (Entered: 02/26/2021)
02/26/2021	26	[SEALED] ANSWERING BRIEF in Opposition re 7 MOTION for Preliminary Injunction filed by Foundation Medicine, Inc..Reply Brief due date per Local Rules is 3/5/2021. (Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	27	[SEALED] APPENDIX re 26 Answering Brief in Opposition -- *Volume 1 of 4 (Exhibits 1-50)* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1-16, # 2 Exhibit 17-32, # 3 Exhibit 33-42, # 4 Exhibit 43-50)(Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	28	[SEALED] APPENDIX re 26 Answering Brief in Opposition -- *Volume 2 of 4 (Exhibits 51-90)* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 51-58, # 2 Exhibit 59-75, # 3 Exhibit 76-90)(Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	29	[SEALED] APPENDIX re 26 Answering Brief in Opposition -- *Volume 3 of 4 (Exhibits 91-124)* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 91-100, # 2 Exhibit 101-112, # 3 Exhibit 113-124) (Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	30	[SEALED] APPENDIX re 26 Answering Brief in Opposition -- *Volume 4 of 4 (Exhibits 125-147)* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 125-139, # 2 Exhibit 140-147)(Tigan, Jeremy) (Attachment 1 replaced on 3/4/2021) (ntl). (Entered: 02/26/2021)
02/26/2021	31	[SEALED] DECLARATION re 26 Answering Brief in Opposition -- *Declaration of Stacey Gabriel, Ph.D.* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	32	[SEALED] DECLARATION re 26 Answering Brief in Opposition -- *Declaration of Gary Benson, Ph.D.* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	33	[SEALED] DECLARATION re 26 Answering Brief in Opposition -- *Declaration of Elizabeth Mansfield, Ph.D.* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/26/2021)

02/26/2021	34	DECLARATION re 26 Answering Brief in Opposition -- *Declaration of Ameet Malik* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/26/2021)
02/26/2021	35	DECLARATION re 26 Answering Brief in Opposition -- *Declaration of Neil D. Shore, M.D., F.A.C.S., C.P.I.* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Main Document 35 replaced on 3/10/2021) (ntl). (Entered: 02/26/2021)
02/26/2021	36	DECLARATION re 26 Answering Brief in Opposition -- *Declaration of Martin Dietrich, M.D., Ph.D.* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/26/2021)
03/04/2021		CORRECTING ENTRY: Corrected Attachment 1 added to D.I. 30 per request of counsel. (ntl) (Entered: 03/04/2021)
03/05/2021	37	STIPULATION TO EXTEND TIME for Plaintiff to file a Reply in Support of its Motion for Preliminary Injunction to 3/29/2021 - filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 03/05/2021)
03/05/2021	38	REDACTED VERSION of 26 Answering Brief in Opposition by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	39	REDACTED VERSION of 27 Appendix by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1-16, # 2 Exhibit 17-32, # 3 Exhibit 33-42, # 4 Exhibit 43-50)(Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	40	REDACTED VERSION of 28 Appendix by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 51-58, # 2 Exhibit 59-75, # 3 Exhibit 76-90)(Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	41	REDACTED VERSION of 29 Appendix by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 91-124)(Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	42	REDACTED VERSION of 30 Appendix, by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 125-147)(Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	43	REDACTED VERSION of 31 Declaration by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	44	REDACTED VERSION of 32 Declaration by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 03/05/2021)
03/05/2021	45	REDACTED VERSION of 33 Declaration by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 03/05/2021)
03/09/2021		SO ORDERED, re 37 STIPULATION TO EXTEND TIME for Plaintiff to file a Reply in Support of its Motion for Preliminary Injunction to 3/29/2021 filed by Guardant Health, Inc. Signed by Judge Leonard P. Stark on 3/9/21. (ntl) (Entered: 03/09/2021)
03/10/2021		CORRECTING ENTRY: Corrected document added to D.I. 35 per request of counsel. (ntl) (Entered: 03/10/2021)
03/29/2021	46	[SEALED] REPLY BRIEF re 2 MOTION for Preliminary Injunction filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 03/29/2021)
03/29/2021	47	[SEALED] DECLARATION re 46 Reply Brief *of Justin Odegaard* by Guardant Health, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J, # 11 Exhibit K, # 12 Exhibit L)(Farnan, Brian) (Entered: 03/29/2021)
03/29/2021	48	[SEALED] DECLARATION re 46 Reply Brief *of Justin Constant* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8)(Farnan, Brian) (Entered: 03/29/2021)
03/29/2021	49	[SEALED] DECLARATION re 46 Reply Brief *of Gregory Cooper, Ph.D.* by Guardant Health, Inc.. (Farnan, Brian) (Entered: 03/29/2021)
04/15/2021	50	STIPULATION and [Proposed] Order *Regarding Surreply Brief in Opposition to Guardant's Motion for Preliminary Injunction* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 04/15/2021)
04/16/2021		CORRECTING ENTRY: Letter filed 4/15/2021 at D.I. 51 removed at request of filer. (dlb) (Entered: 04/16/2021)
04/16/2021	51	[SEALED] MOTION for Leave to File *Amended Answer and Counterclaims* - filed by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Tigan, Jeremy) (Entered: 04/16/2021)
04/16/2021	52	[SEALED] Letter to The Honorable Leonard P. Stark from Jeremy A. Tigan regarding Motion for Leave to File Amended Answer and Counterclaims - re 51 MOTION for Leave to File *Amended Answer and Counterclaims*. (Attachments: # 1 Exhibit 1)(Tigan, Jeremy) (Entered: 04/16/2021)
04/20/2021		SO ORDERED, re 50 STIPULATION and [Proposed] Order Regarding Surreply Brief in Opposition to Guardant's Motion for Preliminary Injunction filed by Foundation Medicine, Inc. Signed by Judge Leonard P. Stark on 4/20/21. (ntl) (Entered: 04/20/2021)
04/20/2021	53	Letter to The Honorable Leonard P. Stark from Jeremy A. Tigan regarding Request for Teleconference - re 19 SO ORDERED, Set Hearings. (Tigan, Jeremy) (Entered: 04/20/2021)
04/21/2021	54	REDACTED VERSION of 46 Reply Brief by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/21/2021)
04/21/2021	55	REDACTED VERSION of 47 Declaration, *of Justin Odegaard* by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-L)(Farnan, Brian) (Entered: 04/21/2021)
04/21/2021	56	REDACTED VERSION of 48 Declaration, *of Justin Constant* by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-8)(Farnan, Brian) (Entered: 04/21/2021)
04/21/2021	57	REDACTED VERSION of 49 Declaration *of Gregory Cooper, Ph.D.* by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/21/2021)
04/21/2021	58	STIPULATION TO EXTEND TIME for Plaintiff to respond to Foundation Medicine, Inc.'s Motions for Leave to File Amended Answer and Counterclaims to 5/7/2021 - filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/21/2021)
04/22/2021	59	MOTION for Pro Hac Vice Appearance of Attorney Matthew Wolf - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 04/22/2021)
04/22/2021	60	ORAL ORDER: Having reviewed FMI's recent letter, IT IS HEREBY ORDERED that: (1) the parties shall submit a joint status report (not to exceed four pages in total), on April 26, setting out their position(s) for how the forthcoming remote hearing should proceed and any disputes relating to it; and (2) the Court will discuss such issues with the parties by teleconference on April 27 at 4:45 p.m. The parties and any interested members of the public can access the teleconference by dialing 877-336-1829 and using the access code 1408971. ORDERED by Judge Leonard P. Stark on 4/22/21. (ntl) (Entered: 04/22/2021)
04/22/2021	61	ORAL ORDER: IT IS HEREBY ORDERED that this case is referred to Magistrate Judge Christopher J. Burke, pursuant to 28 U.S.C. § 636(b), to hear and resolve all discovery disputes and all issues regarding scheduling. ORDERED by Judge Leonard P. Stark on 4/22/21. (ntl) (Entered: 04/22/2021)
04/23/2021		SO ORDERED, re 59 MOTION for Pro Hac Vice Appearance of Attorney Matthew Wolf filed by Foundation Medicine, Inc. Signed by Judge Leonard P. Stark on 4/23/21. (ntl) (Entered: 04/23/2021)
04/23/2021		SO ORDERED, re (58 in 1:20-cv-01580-LPS, 533 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME for Plaintiff to respond to Foundation Medicine, Inc.'s Motions for Leave to File Amended Answer and Counterclaims to 5/7/2021 filed by Guardant Health, Inc. Signed by Judge Leonard P. Stark on 4/22/21. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS (ntl) (Entered: 04/23/2021)
04/26/2021	62	Joint Letter to The Honorable Leonard P. Stark from Jeremy A. Tigan regarding D.I. 53 - re 53 Letter. (Tigan, Jeremy) (Entered: 04/26/2021)
04/27/2021	63	ORAL ORDER: Having reviewed the joint status report filed in C.A. No. 20-1580 (D.I. 62), and recognizing that the parties are also litigating C.A. No. 17-1616 and address matters relating to that action in the status report, IT IS HEREBY ORDERED that: (1) the May 13 spoliation evidentiary hearing in 17-1616 and May 14 preliminary injunction hearing in 20-1580 will be held in-person in Delaware, as jointly requested by the parties; (2) the Court would prefer to hear from the forensic experts by live testimony rather than relying solely on expert reports and deposition testimony; (3) each side will be allocated up to 3.5 hours for its presentation at the spoliation hearing, to be used however it wishes; (4) any witness who will testify at the hearing will be sequestered during opening statements; (5) Guardant will be permitted to examine Dr. Eltoukhy first, on direct examination, before FMI will be permitted to call him as an adverse witnesses - this order of presentation will be more helpful to the Court than the alternative presented by FMI, even recognizing that FMI is the moving party and bears the burden of proof; and (6) each side will be allocated up to 3 hours for its presentation at the preliminary injunction hearing and, as requested jointly by the parties, the Court will hear from the parties on an issue-by-issue basis (similar to at a claim construction hearing). IT IS FURTHER ORDERED that the teleconference scheduled for later today is CANCELLED. ORDERED by Judge Leonard P. Stark on 4/27/21. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS (ntl) Modified on 4/27/2021 (ntl). (Entered: 04/27/2021)
04/27/2021	64	ORAL ORDER: Pursuant to 28 U.S.C. § 636, IT IS HEREBY ORDERED that the following motion is referred to Magistrate Judge Christopher J. Burke: Motion for Leave to Amend Answer and Counterclaims (D.I. 51). ORDERED by Judge Leonard P. Stark on 4/27/21. (ntl) (Entered: 04/27/2021)
05/04/2021	65	MOTION for Pro Hac Vice Appearance of Attorney David I. Gindler - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 05/04/2021)
05/04/2021		SO ORDERED, re (65 in 1:20-cv-01580-LPS, 539 in 1:17-cv-01616-LPS-CJB) MOTION for Pro Hac Vice Appearance of Attorney David I. Gindler filed by Guardant Health, Inc. Signed by Judge Leonard P. Stark on 5/4/21. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS (ntl) (Entered: 05/04/2021)
05/04/2021	66	[SEALED] SUR-REPLY BRIEF re 2 MOTION for Preliminary Injunction filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 05/04/2021)
05/04/2021	67	[SEALED] APPENDIX re 66 Sur-Reply Brief -- *Volume 5 of 5 (Exhibits 148-152)* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibits 148-152)(Tigan, Jeremy) (Entered: 05/04/2021)
05/05/2021	68	REDACTED VERSION of 51 MOTION for Leave to File *Amended Answer and Counterclaims* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Tigan, Jeremy) (Entered: 05/05/2021)
05/05/2021	69	REDACTED VERSION of 52 Letter, by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1)(Tigan, Jeremy) (Entered: 05/05/2021)
05/05/2021	70	MOTION for Pro Hac Vice Appearance of Attorney Y. John Lu - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 05/05/2021)
05/06/2021		Pro Hac Vice Attorney David I. Gindler for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. Associated Cases: 1:20-cv-01580-LPS, 1:17-cv-01616-LPS-CJB.(kmd) (Entered: 05/06/2021)
05/06/2021		SO ORDERED, re 70 MOTION for Pro Hac Vice Appearance of Attorney Y. John Lu filed by Guardant Health, Inc. Signed by Judge Leonard P. Stark on 5/6/21. (ntl) (Entered: 05/06/2021)
05/07/2021	71	STIPULATION TO EXTEND TIME to EXTEND the deadlines for: (i) Plaintiff to respond to Foundation Medicine, Inc.'s Motions for Leave to File Amended Answer and Counterclaims and (ii) for Defendant to submit its Reply Briefs to (i) 5/17/2021and (ii) 5/27/2021 - filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 05/07/2021)
05/07/2021		SO ORDERED D.I. (71 in 1:20-cv-01580-LPS, 547 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME to EXTEND the deadlines for: (i) Plaintiff to respond to Foundation Medicine, Inc.'s Motions for Leave to File Amended Answer and Counterclaims and (ii) for Defendant to submit its Reply Briefs. Ordered by Judge Christopher J. Burke on 5/7/2021. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS(dlb) (Entered: 05/07/2021)
05/13/2021	72	ORAL ORDER: As discussed in Court today, IT IS HEREBY ORDERED that, pursuant to the parties' agreement, the following motions are WITHDRAWN and, accordingly, DENIED AS MOOT: Motion

		for Leave to File Amended Answer and Counterclaim (C.A. No. 20-1580 D.I. 51); Motion for Preliminary Injunction (C.A. No. 20-1580 D.I. 7); Motion for Sanctions (C.A. No. 17-1616 D.I. 467); Motion for Leave to File Amended Answer and Counterclaim (C.A. No. 17-1616 D.I. 529); and Motion to Strike (C.A. No. 17-1616 D.I. 549). IT IS FURTHER ORDERED that the parties shall submit a joint status report no later than May 28, if these cases have not been dismissed prior to that date. ORDERED by Judge Leonard P. Stark on 5/13/21. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS (ntl) (Entered: 05/13/2021)
05/13/2021		Minute Entry for proceedings held before Judge Leonard P. Stark - Hearing held on 5/13/2021. (Court Reporter B. Gaffigan.) Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS (ntl) (Entered: 05/13/2021)
05/24/2021	73	REDACTED VERSION of 66 Sur-Reply Brief by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 05/24/2021)
05/24/2021	74	REDACTED VERSION of 67 Appendix by Foundation Medicine, Inc.. (Attachments: # 1 Exhibits 148-152)(Tigan, Jeremy) (Entered: 05/24/2021)
05/28/2021	75	Joint STATUS REPORT by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 05/28/2021)
06/01/2021	76	Official Transcript of In-Court Hearing held on May 13, 2021 before Chief Judge Leonard P. Stark. Court Reporter Brian Gaffigan, email: gaffigan@verizon.net. Transcript may be viewed at the court public terminal or ordered/purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 6/22/2021. Redacted Transcript Deadline set for 7/2/2021. Release of Transcript Restriction set for 8/30/2021. (bpg) (Entered: 06/01/2021)
06/04/2021	77	ORAL ORDER: IT IS HEREBY ORDERED that a joint status report is due by June 18, 2021. ORDERED by Judge Leonard P. Stark on 6/4/21. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:20-cv-01580-LPS (ntl) (Entered: 06/04/2021)

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**1740**

Electronic Acknowledgement Receipt

EFS ID:	43211650
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	09-JUL-2021
Filing Date:	07-JAN-2020
Time Stamp:	15:03:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1740
RAM confirmation Number	E202179F04183007
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00731

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2021-07-09_GH0004US-CON3_OA3response.pdf	184296 ca899a13be9caea984ba6ad69d66b1b23fffc0b9	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	9	12
Applicant summary of interview with examiner	8	8
Claims	2	7
Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:

Information:

2	Letter specifying the conditions for filing under 37CFR1.97	2021-07-09_GH0004US-CON3_IDSTrans.pdf	143410 5c09979a54d525334833ad1dbd4dc28c4e25225f	no	4

Warnings:

Information:

3	Foreign Reference	WO_2012099832_A2.pdf	778659 b9088f1857dec7716802c1dbcf40e94e748526b2	no	79

Warnings:

Information:

4	Non Patent Literature	CROWLEY_NatRevClinOnc_2013_.pdf	1757154 42868307073f46f9d793304cc3ddd579b4db866e	no	13

Warnings:

Information:

5	Non Patent Literature	GREAVES_AgingCell_2009_566-572.pdf	196552 3b3a6326bd5821b8fc5bff9c6c95d920a5a749f5	no	7
Warnings:					
Information:					
6	Other Reference-Patent/App/Search documents	EP3378952_OppReply_2021-03-29.pdf	4241224 9c731daf95dc7abe71f59c79b834b16a1fc87f7e	no	76
Warnings:					
Information:					
7	Other Reference-Patent/App/Search documents	GH_FMI_Answer_2021-01-14.pdf	573488 7cb732f4a73f1f189aaed42c6943e347d019cb9a	no	73
Warnings:					
Information:					
8	Other Reference-Patent/App/Search documents	GH_FMI_AnsweringBrief_2021-03-05.pdf	426622 d36d25a8cbfe2bd799459e8018072192d8fb91f0	no	33
Warnings:					
Information:					
9	Other Reference-Patent/App/Search documents	OA_16913965_2021-06-23.pdf	640388 0983561611cc2a1beca353634f940e43ebdaa4c6	no	16
Warnings:					
Information:					
10	Other Reference-Patent/App/Search documents	EP3524694_FMI_Opposition_2021-04-15.pdf	4373772 06558436cf43ce1fca84bafb102e934d5fd5ca2e	no	58
Warnings:					
Information:					
11	Other Reference-Patent/App/Search documents	EP3524694_Maiwald_Opposition_2021-04-15.pdf	1915381 e0a000a029e7e6d6a8bc82fecb97bda581d40622	no	38
Warnings:					
Information:					

12	Information Disclosure Statement (IDS) Form (SB08)	2021-07-09_GH0004US-CON3_SB08.pdf	1053973 2bab73a8f8bcf5cd8a5d63aa1d7b81966574f21c	no	5
Warnings:					
Information:					
13	Other Reference-Patent/App/Search documents	EESR_20183626_9_2020-12-07.pdf	1408104 7beb1b91e3e4f7c5af44f73745cb67b76a952c62	no	12
Warnings:					
Information:					
14	Notice of concurrent proceedings / decisions	2021-07-09_GH0004US-CON3_NtcConcurrentProceedings_1580_IC.pdf	97752 4dd91ee1a7f176118e3fff1b7dde3ad0a058b97e	no	2
Warnings:					
Information:					
15	Notice of concurrent proceedings / decisions	2021-07-09_GH0004US-CON3_NtcConcurrentProceedings_1580_IV.pdf	421239 a01b6a513602a3c645209aadacc11c25a60bf2c5	no	6
Warnings:					
Information:					
16	Fee Worksheet (SB06)	fee-info.pdf	32410 60cefc9247407a00b1978873468061a1ed9b913d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	18244424		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Claims 61-90 were pending prior to entry of the above-referenced claim amendments. Claims 64, 74, 76-77, and 87-89 are amended herein. No new matter is being introduced by any of these claim amendments. Accordingly, upon entry of the above-referenced claim amendments, claims 61-90 will be pending.

Nonstatutory Double Patenting

Claims 61-90 stand provisionally rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 1-30 of copending U.S. Application No. 16/945,124. Without conceding to the merits of the rejection and solely to advance prosecution of this application, Applicant hereby submits a terminal disclaimer over the aforementioned pending application. Accordingly, it is respectfully requested that this rejection be withdrawn.

35 U.S.C. §102

Claims 61-62, 67, 69, 71-72, 74-75, 78-79, 81, 84, and 86-88 stand rejected under 35 U.S.C. § 102(a)(2) as being anticipated by Salk et al. (US 10,752,951, hereinafter referred to as "Salk").

1. *Salk's priority documents do not support "cfDNA" as recited in claims 61 and 78.*

Salk is a divisional application (U.S. Application No. 16/514,931) filed on July 17, 2019, claiming priority to USSN 16/120,091 (the '091 application). The '091 application claims priority to USSN 15/660,785 (the '758 application). The '785 application claims priority to USSN 14/386,800 (the '800 application), which is a U.S. national stage application of International Application No. PCT/US2013/032665, filed Mar. 15, 2013 claiming priority to U.S. Provisional Patent Application No. 61/613,413, filed Mar. 20, 2012; U.S. Provisional Patent Application No. 61/625,623, filed Apr. 17, 2012; and U.S. Provisional Patent Application No. 61/625,319, filed Apr. 17, 2012.

In articulating its rejection, the Office refers to certain claims of Salk ("It is readily apparent that the noted instant claims are substantially identical to claims 1-28 of Salk et al.

Thus, the claimed methods cannot be distinguished from the patented methods of Salk et al.," Office Action, p. 4). To the extent that the Salk claims are referenced with respect to the instant claims, Applicant submits that Salk does not disclose in its priority documents "cfDNA," or "circulating DNA" amongst other elements of Salk's claims. Accordingly, Applicant submits that Salk is not prior art under §102 (*See* MPEP 2136.06 "For prior art purposes, a U.S. patent or patent application publication that claims the benefit of an earlier filing date under 35 U.S.C. 120 of a prior nonprovisional application (i.e., a continuation, divisional, or continuation-in-part application) would be accorded the earlier filing date as its prior art date under pre-AIA 35 U.S.C. 102(e), **provided the earlier-filed application properly supports the subject matter relied upon in any rejection in compliance with 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph**" (emphasis added); MPEP 211 "The disclosure of a continuation application must be the same as the disclosure of the prior-filed application; i.e., the continuation must not include anything which would constitute new matter if inserted in the original application.")

Indeed, the Patent Trial and Appeal Board ("Board") in its Final Written Decision ("Decision") dated August 18, 2020 in IPR2019-000652 stated, "**Schmitt does not expressly teach that the target polynucleotide is cfDNA . . ."** (Decision, page 31, lines 6-7). To be clear, the Schmitt patent referenced in the Decision was US 9,752,188, which issued from the '800 application. As discussed above, Salk claims priority to the '800 application. Therefore, the priority documents of Salk do not support the disclosure of "cfDNA" as recited by the pending claims.

Moreover, the genus of circulating nucleic acids does not anticipate the species of cfDNA or circulating DNA.

2. *Salk does not disclose "non-uniquely tagging" as recited in claim 78.*

Applicant respectfully submits that at least claim 78 is novel over Salk because Salk does not disclose a tagging method for cfDNA molecules, much less "non-uniquely tagging a plurality of the double-stranded cfDNA molecules of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce non-uniquely tagged parent

polynucleotides, **wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the double-stranded cfDNA molecules that map to the mappable base position**" (emphasis added), as recited in claim 78.

In addition, Applicant respectfully submits that claim 66 recites similar subject matter to that recited in claim 78 and claim 66 was found to be free of the art by the Office (Office Action, p. 5).

For the reasons provided above, Applicant respectfully requests that the §102 rejection of independent claims 61 and 78 be withdrawn.

Claims 62, 67, 69, 71-72, 74-75, 79, 81, 84, and 86-88 depend from an include all elements of claims 61 and 71 and recite additional elements of particular advantage and utility. Salk does not meet all the elements of claims 61 and 78, much less the unique combination of claims 62, 67, 69, 71-72, 74-75, 79, 81, 84, and 86-88. Accordingly, Applicant respectfully requests that the §102 rejection of claims 62, 67, 69, 71-72, 74-75, 79, 81, 84, and 86-88 also be withdrawn.

35 U.S.C. §103

Claims 63-65, 68, 70, 73, 76-77, 80, 82-83, 85, and 89-90 stand rejected under 35 U.S.C. §103 as being unpatentable over Salk.

Applicant submits that claims 61 and 78 are not obvious over Salk because Salk does not teach, suggest, or disclose all elements of claims 61 and 78 (as stated above). Claims 63-65, 68, 70, 73, 76-77, 80, 82-83, 85, and 89-90 depend from and include all elements of claims 61 and 78 and recite additional elements of particular advantage and utility. Withdrawal of the rejection is respectfully requested.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or canceled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this Application are in condition for allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: July 9, 2021

By: /Timothy A. Hott/
Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

SUMMARY OF THE INTERVIEW

Applicant is appreciative of Examiner Horlick for extending the courtesy of a telephonic interview to Applicant's representative, Timothy Hott, on July 8, 2021. The interview involved a discussion regarding the disclosure and priority of the claims of the cited prior art (Salk et al., U.S. Patent No. 10,752,951).

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. – 60. (Cancelled).

61. (Previously presented): A method, comprising:

(a) providing a population of cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) tagging a plurality of the cfDNA molecules of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein duplex tags from the set of duplex tags are attached at both ends of a molecule of the plurality of the cfDNA molecules;

(c) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and

(e) reducing or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes to generate a plurality of consensus sequences representative of original cfDNA molecules from among the tagged parent polynucleotides, wherein the plurality of consensus sequences is generated from (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides, and (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides.

62. (Previously Presented): The method of claim 61, wherein the population of cfDNA molecules is obtained or derived from a sample from a subject having cancer.

63. (Previously Presented): The method of claim 61, wherein the plurality of cfDNA molecules comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules.

64. (Currently Amended): The method of claim 61, wherein the tagging comprises ligating the duplex tags ~~are ligated~~ to the plurality of the cfDNA molecules using more than a 10X excess of duplex tags as compared to the population of cfDNA molecules.

65. (Previously Presented): The method of claim 64, wherein at least 20% of the cfDNA molecules of the population are tagged with the duplex tags.

66. (Previously Presented): The method of claim 61, wherein the tagging comprises non-uniquely tagging the plurality of the cfDNA molecules with the set of duplex tags comprising molecular barcodes from the set of molecular barcodes, wherein the cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the cfDNA molecules that map to the mappable base position.

67. (Previously Presented): The method of claim 61, wherein the molecular barcodes of the set of molecular barcodes have pre-determined sequences.

68. (Previously Presented): The method of claim 61, wherein the molecular barcodes of the set of molecular barcodes have between 5 and 10,000 different molecular barcode sequences and have a length of between 5 and 20 base pairs.

69. (Previously Presented): The method of claim 61, further comprising enriching a plurality of the amplified progeny polynucleotides for target regions of interest prior to the sequencing to produce enriched progeny polynucleotides.

70. (Previously Presented): The method of claim 69, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1,

BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

71. (Previously Presented): The method of claim 69, further comprising amplifying a plurality of the enriched progeny polynucleotides prior to the sequencing.

72. (Previously Presented): The method of claim 61, wherein the duplex tags of the set of duplex tags are part of sequencing adapters.

73. (Previously Presented): The method of claim 72, wherein the sequencing adapters are Y-shaped adapters.

74. (Currently Amended): The method of claim 61, wherein the reducing or tracking redundancy in the set of sequence reads comprises mapping a plurality of the set of sequence reads to a reference sequence.

75. (Previously Presented): The method of claim 61, further comprising:

(f) determining quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads at one or more loci of a reference sequence.

76. (Currently Amended): The method of claim 75, further comprising:

(g) estimating with a programmed computer processor a quantitative measure of tagged parent polynucleotides based at least in part on the quantitative measures of the at least two of (i) the paired reads, (ii) the unpaired reads, (iii) the read depth of the paired reads, and (iv) the read depth of the unpaired reads at ~~each of~~ the one or more loci.

77. (Currently Amended): The method of claim 76, wherein (f) comprises determining quantitative measures of the paired reads and the unpaired reads, and wherein in (g), the quantitative ~~measures~~ measure of the tagged parent polynucleotides is determined based at least in part on the quantitative measures of the paired reads and the unpaired reads.

78. (Previously Presented): A method, comprising:

(a) providing a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) non-uniquely tagging a plurality of the double-stranded cfDNA molecules of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce non-uniquely tagged parent polynucleotides,

wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the double-stranded cfDNA molecules that map to the mappable base position;

(c) amplifying a plurality of the non-uniquely tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads;

(e) reducing or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes;

(f) sorting the set of sequence reads into paired reads and unpaired reads, wherein (i) a paired read corresponds to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides, and (ii) an unpaired read corresponds to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides; and

(g) determining, at one or more loci of a reference sequence, quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads.

79. (Previously Presented): The method of claim 78, wherein the population of double-stranded cfDNA molecules is obtained or derived from a sample from a subject having cancer.

80. (Previously Presented): The method of claim 78, wherein the plurality of double-stranded cfDNA molecules comprises between 1 nanogram (ng) and 100 ng of double-stranded cfDNA molecules.

81. (Previously Presented): The method of claim 78, wherein the non-uniquely tagging comprises ligating the duplex tags to the plurality of the double-stranded cfDNA molecules.

82. (Previously Presented): The method of claim 78, wherein the molecular barcodes of the set of molecular barcodes have between 2 and 10,000 different molecular barcode sequences.

83. (Previously Presented): The method of claim 78, wherein the molecular barcodes of the set of molecular barcodes have between 5 and 10,000 different molecular barcode sequences and have a length of between 5 and 20 base pairs.

84. (Previously Presented): The method of claim 78, further comprising enriching a plurality of the amplified progeny polynucleotides for target regions of interest prior to the sequencing to produce enriched progeny polynucleotides.

85. (Previously Presented): The method of claim 84, wherein the target regions of interest comprise genetic sequences of a plurality of genes selected from the group consisting of ALK, APC, BRAF, CDKN2A, EGFR, ERBB2, FBXW7, KRAS, MYC, NOTCH1, NRAS, PIK3CA, PTEN, RB1, TP53, MET, AR, ABL1, AKT1, ATM, CDH1, CSF1R, CTNNB1, ERBB4, EZH2, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, MLH1, MPL, NPM1, PDGFRA, PROC, PTPN11, RET, SMAD4, SMARCB1, SMO, SRC, STK11, VHL, TERT, CCND1, CDK4, CDKN2B, RAF1, BRCA1, CCND2, CDK6, NF1, TP53, ARID1A, BRCA2, CCNE1, ESR1, RIT1, GATA3, MAP2K1, RHEB, ROS1, ARAF, MAP2K2, NFE2L2, RHOA, and NTRK1.

86. (Previously Presented): The method of claim 84, further comprising amplifying a plurality of the enriched progeny polynucleotides prior to the sequencing.

87. (Currently Amended): The method of claim 78, wherein reducing or tracking the redundancy in the set of sequence reads comprises collapsing a plurality of the set of sequence reads to generate consensus sequences representative of original double-stranded cfDNA molecules from among the non-uniquely tagged parent polynucleotides.

88. (Currently Amended): The method of claim 87, further comprising mapping a plurality of the set of sequence reads ~~and/~~or the consensus sequences to a reference sequence.

89. (Currently Amended): The method of claim 78, further comprising:

(h) estimating with a programmed computer processor a quantitative measure of non-uniquely tagged parent polynucleotides based at least in part on the quantitative measures of the

at least two of (i) the paired reads, (ii) the unpaired reads, (iii) the read depth of the paired reads, and (iv) the read depth of the unpaired reads at ~~each of~~ the one or more loci.

90. (Previously Presented): The method of claim 89, wherein (g) comprises determining quantitative measures of the paired reads and the unpaired reads, and wherein in (h), the quantitative measure of the non-uniquely tagged parent polynucleotides is determined based at least in part on the quantitative measures of the paired reads and the unpaired reads.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16672267
Filing Date	07-Jan-2020
First Named Inventor	AmirAli TALASAZ
Attorney Docket Number	42534-708.304
Title of Invention	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
GUARDANT HEALTH, INC.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16945124 filed on 07/31/2020

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○	I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

○ Small Entity

○ Micro Entity

◉ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 67740

○ A sole inventor

○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

○ A joint inventor; all of whom are signing this request

Signature	/Timothy A. Hott/
Name	Timothy A. Hott

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**170**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16672267

Filing Date: 07-Jan-2020

Applicant/Patent under Reexamination: TALASAZ

Electronic Terminal Disclaimer filed on July 9, 2021

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	43211707
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	09-JUL-2021
Filing Date:	07-JAN-2020
Time Stamp:	15:07:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$170
RAM confirmation Number	E202179F07353077
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00752

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	34017 bb04211d9fbdbd70660e9052d6ec6293b90483ec	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30192 9bdad612eba7e0730c167fa4d6c677fe3cf5954e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64209		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 07/13/2021

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/13/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Applicant-Initiated Interview Summary	**Application No.** 16/672,267	**Applicant(s)** TALASAZ et al.		
	Examiner KENNETH R HORLICK	**Art Unit** 1637	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
KENNETH R HORLICK	Primary Examiner	Telephonic
TIMOTHY HOTT	Attorney of Record	

Date of Interview: 08 July 2021

Issues Discussed:

35 U.S.C. 102

There was a general discussion of the Salk et al. specification and claims. Applicant intends to submit arguments that the instant claims are not anticipated by Salk et al.

35 U.S.C. 103

There was a general discussion of the Salk et al. specification and claims. Applicant intends to submit arguments that the instant claims are not obvious in view of Salk et al.

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

115823 7590 07/21/2021

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER
HORLICK, KENNETH R

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/21/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1000.00	$200	10/21/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

115823 7590 07/21/2021
Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1000.00	$200	10/21/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
HORLICK, KENNETH R	1637	435-006120

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 07/21/2021

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/21/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/672,267	Applicant(s) TALASAZ et al.	
	Examiner KENNETH R HORLICK	Art Unit 1637	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the response filed 07/09/21.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 61-90 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 7/9/21.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

EXAMINER'S COMMENTS AND REASONS FOR ALLOWANCE

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. The terminal disclaimer filed on 07/09/21 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent issuing from the '124 application has been reviewed and is accepted. The terminal disclaimer has been recorded.

3. The following is an examiner's statement of reasons for allowance: regarding claims 66 and 78-90, it has already been noted that no prior art, including Schmitt et al. ('188), has been found teaching or suggesting 'wherein the cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the cfDNA molecules that map to the mappable base position'. Regarding independent claim 61 and its dependent claims 62-65 and 67-77, the response filed 07/09/21 points out that the Salk et al. ('951) priority documents do not support the disclosure of 'cfDNA' as required in these claims, and it is now further noted by the examiner that no prior art, including the '188 and '951 patents, has been found teaching or suggesting step (e) of claim 61, which requires 'reducing or tracking redundancy…wherein the plurality of consensus sequences is generated from (i) paired reads…and (ii) unpaired reads…'.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENNETH R HORLICK whose telephone number is (571)272-0784. The examiner can normally be reached on Mon. - Thurs. 8:30 - 6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

07/14/21

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/03/2020	07/14/2020	08/17/2020	01/11/2021	07/14/2021				
	31	✓	-							
	32	✓	-							
	33	✓	-							
	34	✓	-							
	35	✓	-							
	36	✓	-							
	37	✓	-							
	38	✓	-							
	39	✓	-							
	40	✓	-							
	41	✓	-							
	42	✓	-							
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	45	✓	-							
	46	✓	-							
	47	✓	-							
	48	✓	-							
	49	✓	-							
	50	✓	-							
	51	✓	-							
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	56	✓	-							
	57	✓	-							
	58	✓	-							
	59	✓	-							
	60	✓	-							
1	61		✓	=	✓	=				
2	62		✓	=	✓	=				
3	63		✓	=	✓	=				
4	64		✓	=	✓	=				
5	65		✓	=	✓	=				
6	66		✓	=	✓	=				
7	67		✓	=	✓	=				
8	68		✓	=	✓	=				
9	69		✓	=	✓	=				
10	70		✓	=	✓	=				
11	71		✓	=	✓	=				
12	72		✓	=	✓	=				

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

CLAIM		DATE								
Final	Original	03/03/2020	07/14/2020	08/17/2020	01/11/2021	07/14/2021				
13	73		✓	=	✓	=				
14	74		✓	=	✓	=				
15	75		✓	=	✓	=				
16	76		✓	=	✓	=				
17	77		✓	=	✓	=				
18	78		✓	=	✓	=				
19	79		✓	=	✓	=				
20	80		✓	=	✓	=				
21	81		✓	=	✓	=				
22	82		✓	=	✓	=				
23	83		✓	=	✓	=				
24	84		✓	=	✓	=				
25	85		✓	=	✓	=				
26	86		✓	=	✓	=				
27	87		✓	=	✓	=				
28	88		✓	=	✓	=				
29	89		✓	=	✓	=				
30	90		✓	=	✓	=				

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

CPC - Searched*		
Symbol	Date	Examiner
C12Q 1/6869	07/14/2021	KH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor name search	02/27/2020	KH
updated parent searches in USPAT and PGPUB	02/27/2020	KH
reviewed parent applications and references therein	02/27/2020	KH
updated in USPAT and PGPUB	07/08/2020	KH
updated in USPAT and PGPUB	08/17/2020	KH
updated in USPAT and PGPUB	01/05/2021	KH
updated in USPAT and PGPUB	07/14/2021	KH

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	Art Unit
	KENNETH R HORLICK	1637

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
NONE	NONE	07/14/2021	KH

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

CPC								
Symbol							**Type**	**Version**
C12Q	/	1	/	6869			F	2013-01-01
C12Q	/	1	/	6886			I	2013-01-01
G16B	/	15	/	00			A	2019-02-01
C12Q	/	2600	/	158			A	2013-01-01
C12Q	/	2535	/	122			A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	30	
/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	14 July 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20210714

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12P	/	19	/	34

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	6.12

CROSS REFERENCES(S)							
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**						
435	91.2						

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637 (Primary Examiner)	14 July 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/672,267	TALASAZ et al.
	Examiner	**Art Unit**
	KENNETH R HORLICK	1637

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	61	10	70	19	79	28	88								
2	62	11	71	20	80	29	89								
3	63	12	72	21	81	30	90								
4	64	13	73	22	82										
5	65	14	74	23	83										
6	66	15	75	24	84										
7	67	16	76	25	85										
8	68	17	77	26	86										
9	69	18	78	27	87										

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637 (Primary Examiner)	14 July 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office Part of Paper No.: 20210714

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BIB DATA SHEET

CONFIRMATION NO. 3448

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/672,267	01/07/2020 RULE	435	1637	42534-708.304

APPLICANTS

GUARDANT HEALTH, INC., Redwood City, CA;

INVENTORS

AmirAli TALASAZ, Atherton, CA;
Stefanie Ann Ward Mortimer, Morgan Hill, CA;
Helmy Eltoukhy, Atherton, CA;

**** CONTINUING DATA ***************************

This application is a CON of 16/601,168 10/14/2019 PAT 10801063
which is a CON of 15/892,178 02/08/2018 PAT 10883139
which is a CON of 14/861,989 09/22/2015 PAT 9920366
which is a CON of PCT/US2014/072383 12/24/2014
which claims benefit of 61/948,509 03/05/2014
and claims benefit of 61/921,456 12/28/2013

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

09/21/2020

Foreign Priority claimed	❑ Yes ☑ No	❑ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	❑ Yes ☑ No		CA	11	30	2
Verified and Acknowledged	/KENNETH R HORLICK/ Examiner's Signature	Initials				

ADDRESS

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304
UNITED STATES

TITLE

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

FILING FEE RECEIVED		
2720	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	20140296081	A1	2014-10-02	Diehn et al.	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/K.R.H/	1	2012099832	WO	A2	2012-07-26	Hendricks	Entire Document	

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

/K.R.H/	1	CROWLEY, E. et al. "Liquid biopsy: monitoring cancer-genetics in the blood" Nat Rev Clin Oncology (2013) 8:472-478
/K.R.H/	2	Extended European search report and opinion dated 12/07/2020 for EP Application No. 20183626.9.
/K.R.H/	3	GREAVES, L.C. et al. "Quantification of mitochondrial DNA mutation load" Aging Cell (2009) 8(5): 566–572
/K.R.H/	4	Guardant Health, Inc. Response to Notice of Opposition in EP3378952 filed March 29, 2021.
/K.R.H/	5	Guardant Health, Inc. v. FMI Defendant's Answer and Counter Claims, filed January 14, 2021 (C.A. No. 20-1580 (LPS))
/K.R.H/	6	Guardant Health, Inc. v. FMI Defendant's Answering Brief in Opposition to Plaintiff Guardant Health, Inc's Motion for Preliminary Injunction, filed March 5, 2021 (C.A. No. 20-1580 (LPS))
/K.R.H/	7	Office action dated 06/23/2021 for US Application No. 16/913,965.
/K.R.H/	8	Opposition to EP3524694, dated April 15, 2021 by Foundation Medicine, Inc.
/K.R.H/	9	Opposition to EP3524694, filed April 16, 2021 by Maiwald International

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	07/13/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2021-07-09
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

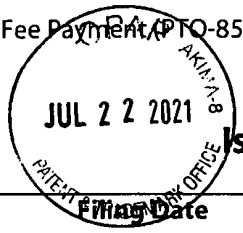
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Document Description: Issue Fee Payment (PTO-85B)



Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
16672267	07-Jan-2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION :

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1637	006120	KENNETH HORLICK

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1200	$0	$1200	21-Oct-2021	$1000

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
115823 Guardant Health / WSGR 650 Page Mill Road Palo Alto CA 94304 UNITED STATES 650-493-9300 Patents@guardanthealth.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☐ Issue Fee	☐ I authorize USPTO to apply my previously paid issue fee to the current fees due
☐ Publication Fee	☒ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number 602231
☐ Advance Order - # of copies _____	☐ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency, or credit any overpayment, to Deposit Account Number _____ . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. Timothy A. Hott
2.
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
GUARDANT HEALTH, INC.	Redwood City	CALIFORNIA	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Timothy A. Hott/	**Date**	07-22-2021
Name	Timothy A Hott	**Registration Number**	67740

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
16672267	07-Jan-2020	AmirAli TALASAZ	42534-708.304	3448

TITLE OF INVENTION :

METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1637	006120	KENNETH HORLICK

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1200	$0	$1200	21-Oct-2021	$1000

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
115823 Guardant Health / WSGR 650 Page Mill Road Palo Alto CA 94304 UNITED STATES 650-493-9300 Patents@guardanthealth.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☐ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☒ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number 602231

☐ Advance Order - # of copies _____

☐ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency, or credit any overpayment, to Deposit Account Number _____ . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. Timothy A. Hott
2.
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
GUARDANT HEALTH, INC.	Redwood City	CALIFORNIA	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Timothy A. Hott/	**Date**	07-22-2021
Name	Timothy A Hott	**Registration Number**	67740

Electronic Acknowledgement Receipt

EFS ID:	43325159
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	22-JUL-2021
Filing Date:	07-JAN-2020
Time Stamp:	23:08:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment after Notice of Allowance (Rule 312)	2021-07-22_GH0004US-CON3_312Amend.pdf	97059 80eedb35cf242d8b55bd55be29c54b4299ea4d5b	no	3
Warnings:		00780			

Information:					
2	Issue Fee Payment (PTO-85B)	Web85b.pdf	46121 af3cf56f9d7fc249a64240b459a238824089dfee	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	143180	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ et al. Serial Number: 16/672,267 Filing Date: November 1, 2019 Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Confirmation No.: 3448 Customer No.: 115823 Group Art Unit: 1637 Examiner: Kenneth R. HORLICK

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER ALLOWANCE UNDER 37 CFR 1.312

Dear Sir:

This communication is in response to the Notice of Allowance mailed July 21, 2021. Entry of the amendments is respectfully requested.

Amendments to the Specification begin on page 2 of this paper.

Remarks begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph [0001] as follows:

[0001] This application is a continuation of U.S. Application No. 16/601,168, filed October 14, 2019 (now U.S. Patent No. 10,801,063, issued October 13, 2020), which is a continuation of U.S. Application No. 15/892,178, filed February 8, 2018 (now U.S. Patent No. 10,883,139, issued January 5, 2021), which is a continuation of U.S. Application No. 14/861,989, filed September 22, 2015 (now U.S. Patent No. 9,920,366, issued March 20, 2018), which is a continuation application of International Application No. PCT/US2014/072383, filed December 24, 2014, which application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 61/921,456, filed December 28, 2013, and U.S. Provisional Application No. 61/948,509, filed March 5, 2014, each of which is entirely incorporated herein by reference.

REMARKS

Applicant amends the specification herein to update the status of the priority applications. No new matter is being introduced.

The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0004US-CON3).

Respectfully submitted,

GUARDANT HEALTH, INC.

Date: July 22, 2021

By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web	PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)**
Application Number	16672267
Filing Date	07-Jan-2020
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	
Attorney Docket Number	42534-708.304
Title	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:
(1) Petition fee; and
(2) One of the following reasons:
(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Petition Fee

- ◯ Small Entity
- ◯ Micro Entity
- ◉ Regular Undiscounted

Reason for withdrawal from issue

◯ One or more claims are unpatentable ◉ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ◯ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).
RCE request,submission, and fee. ☐ I certify, in accordance with 37 CFR 1.4(d)(4) that : The RCE request ,submission, and fee have already been filed in the above-identified application on ☒ Are attached.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ◯ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ◯ A sole inventor ◯ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ◯ A joint inventor; all of whom are signing this e-petition

Signature	/Timothy A. Hott/
Name	Timothy A. Hott
Registration Number	67740

Electronic Patent Application Fee Transmittal

Application Number:	16672267
Filing Date:	07-Jan-2020
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-708.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2140**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Decision Date : July 29, 2021

In re Application of :

AmirAli TALASAZ

DECISION ON PETITION

UNDER CFR 1.313(c)(2)

Application No : 16672267

Filed : 07-Jan-2020

Attorney Docket No : 42534-708.304

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed July 29, 2021 , to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1637 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt

EFS ID:	43380976
Application Number:	16672267
International Application Number:	
Confirmation Number:	3448
Title of Invention:	METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-708.304
Receipt Date:	29-JUL-2021
Filing Date:	07-JAN-2020
Time Stamp:	18:53:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$2140
RAM confirmation Number	E20217SI53294985
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

00790

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Quick Path Information Disclosure Statement	2021-07-29_GH0004US-CON3_QPIDS.pdf	195716 25ebd3d63f2df2f861e07721dd750890cf053c33	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	2021-07-29_GH0004US-CON3_SB08.pdf	1053140 d34fcd9cb9e989eeb09242ae9899aa83dc7c87aa	no	4
Warnings:					
Information:					
3	Request for Continued Examination (RCE)	2021-07-29_GH0004US-CON3_RCETrans.pdf	1364284 fcea181c02f7269ca834d3c5074186a5c72164a1	no	3
Warnings:					
Information:					
4	Petition automatically granted by EFS	petition-request.pdf	39830 c000c967de03b1e03687b83506b300ca46ae5431	no	2
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	40395 6a6000b995b3621d19f9d0f9b1a5beaac923936d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2693365		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20210222243	A1	2021-07-22	Bielas	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

	1	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2021-07-29
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: QPIDS.REQ
Document Description: QuickPath Information Disclosure Statement

PTO/SB/09 (09-18)

CERTIFICATION AND REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM

Non-Provisional Application Number: 16/672,267	Filing Date: 2020-01-07
First Named Inventor: AmirAli TALASAZ	Title of Invention: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS

THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE-IDENTIFIED APPLICATION.

1. Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee.
2. Check the box next to the appropriate selection:

   ☐ Each item of information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(1).

   OR

   ☑ No item of information contained in the IDS was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the IDS was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(2).

   OR

   ☐ See attached certification statement in compliance with 37 CFR 1.97(e).
3. Please charge the IDS fee set forth in 37 CFR 1.17(p) to Deposit Account No. 602231.
4. A Petition to Withdraw from Issue After Payment of the Issue Fee (37 CFR 1.313(c)(2)), including the petition fee set forth in 37 CFR 1.17(h), is submitted herewith as a **Web-based ePetition**. **WARNING:** Do not submit the petition as a follow-on paper via EFS-Web. Submit the petition as a Web-based ePetition by signing on to EFS-Web as a registered user, selecting the radio button next to "Existing application/patent," and then selecting the radio button next to "ePetition (for automatic processing and immediate grant, if all petitions requirements are met)." Failure to use the Web-based ePetition interface will result in automatic entry of the RCE.
5. A request for continued examination (RCE) under 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.
6. The RCE will be treated as a "conditional" RCE. In the event the examiner determines that any item of information contained in the IDS necessitates the reopening of prosecution in the application, the undersigned understands that (i) the RCE will be processed and treated as an RCE under 37 CFR 1.114 and therefore (ii) the IDS fee under 37 CFR 1.17(p) will be returned in accordance with 37 CFR 1.97(b)(4). In the event that no item of information in the IDS necessitates reopening prosecution, the undersigned understands that the RCE will not be processed and the RCE fee under 37 CFR 1.17(e) will be returned.
7. This certification and request is being filed as a **Web-based ePetition** and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE.

Signature /Timothy A. Hott/	Date 07/29/2021
Name (Print/Typed) Timothy A. Hott	Practitioner Registration Number (If applicable) 67740

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below.**

☐ *Total of _____ forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 08/02/2021

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/02/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	16/672,267	TALASAZ et al.	
	Examiner	Art Unit	AIA (FITF) Status
	KENNETH R HORLICK	1637	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 22 July 2021 under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☑ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ et al.	Confirmation No.: 3448
Serial Number: 16/672,267	Customer No.: 115823
Filing Date: November 1, 2019	Group Art Unit: 1637
Title: METHODS AND SYSTEMS FOR DETECTING GENETIC VARIANTS	Examiner: Kenneth R. HORLICK

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER ALLOWANCE UNDER 37 CFR 1.312

Dear Sir:

This communication is in response to the Notice of Allowance mailed July 21, 2021. Entry of the amendments is respectfully requested.

Amendments to the Specification begin on page 2 of this paper.

Remarks begin on page 3 of this paper.

OK TO ENTER: /K.R.H/

/K.R.H/ (07/26/2021)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	01/07/2020	AmirAli TALASAZ	42534-708.304	3448

115823 7590 08/09/2021

Guardant Health / WSGR
650 Page Mill Road
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EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/09/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

CORRECTED ***Notice of Allowability***	**Application No.** 16/672,267	**Applicant(s)** TALASAZ et al.	
	Examiner KENNETH R HORLICK	**Art Unit** 1637	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the submission of 07/29/21.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 61-90 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 7/29/21.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.R.H/	1	20210222243	A1	2021-07-22	Bielas	Entire Document

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16672267
	Filing Date	2020-01-07
	First Named Inventor	AmirAli TALASAZ
	Art Unit	1637
	Examiner Name	Kenneth R. HORLICK
	Attorney Docket Number	42534-708.304

	1	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/KENNETH R HORLICK/	Date Considered	08/03/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16672267
Filing Date	2020-01-07
First Named Inventor	AmirAli TALASAZ
Art Unit	1637
Examiner Name	Kenneth R. HORLICK
Attorney Docket Number	42534-708.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2021-07-29
Name/Print	Timothy A. Hott	Registration Number	67740

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46472

Refund Accounting Date:08/10/2021

Effective Date	Sale Item Reference Number	Refund Total
07/29/2021	16672267	$2,000.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I202180C10504056	1820	RCE- 2ND AND SUBSEQUENT REQUEST	$2,000.00	DA	602231

United States Patent and Trademark Office
Office of the Chief Financial Officer

Document Code:WFEE

User :C46472

Sale Adjustment Accounting Date:08/10/2021

Effective Date	Sale Accounting Date	Sale Item Reference Number
07/29/2021	08/10/2021	16672267

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202180C10504056	1820	RCE- 2ND AND SUBSEQUENT REQUEST	$2,000.00	DA

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/672,267	09/14/2021	11118221	42534-708.304	3448

115823 7590 08/25/2021

Guardant Health / WSGR
650 Page Mill Road
Palo Alto, CA 94304

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

AmirAli TALASAZ, Atherton, CA;
GUARDANT HEALTH, INC., Redwood City, CA;
Stefanie Ann Ward Mortimer, Morgan Hill, CA;
Helmy Eltoukhy, Atherton, CA;