UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWINSTRAND BIOSCIENCES, INC. Petitioner,

v.

GUARDANT HEALTH Patent Owner.

Inter Partes Review Case No. IPR2022-01116

U.S. Patent No. 10,889,858

DECLARATION OF PAUL T. SPELLMAN, Ph.D.

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TABLE OF CONTENTS

I.	INTRODUCTION 1					
II.	MY BACKGROUND AND QUALIFICATIONS					
III.	SUM	SUMMARY OF OPINIONS				
IV.	LIST	LIST OF DOCUMENTS CONSIDERED 10				
V.	PERSON OF ORDINARY SKILL IN THE ART 16					
VI.	STATE OF THE ART					
	A. The protocols for DNA sequencing were well known in the art17					
		1.	Gene	etic information comprises the building blocks of life 17		
		2.	DNA the o	A sequencing was commonly performed to determine rder of nucleotides in an individual's DNA		
		3.	Next	-generation sequencing involved well-known steps 19		
			a)	Template preparation and tagging 20		
			b)	Amplification		
			c)	Enrichment		
			d)	Sequencing and detection		
			e)	Sequence alignment and assembly		
	B. Prior to December 28, 2013, cell-free DNA in blood had attracted interest for the diagnosis of cancer, fetal gender, many other inherited disorders and was commonly sequer using NGS platforms					
		1.	Cell- biom	free tumor DNA was a well-known cancer arker		
		2.	Circu biom	ulating cell-free fetal DNA was also a well-known arker for prenatal screening and diagnostics		
		3.	Com extra	mercially available kits were routinely used to the stand isolate cfDNA from blood samples		
	C. Prior to December 28, 2013, Duplex Sequencing was developed to dramatically improve the accuracy of next-generation sequencing					

			Inter Partes Review of US Patent 10,88 Declaration of Paul T. Spellman,	9,858 Ph.D.
		1.	Tagging of DNA with adapters comprising molecular	
			barcodes	46
		2.	Amplification	51
		3.	Target enrichment	52
		4.	Sequencing	53
		5.	Mapping the sequence reads to a reference sequence	53
		6.	Grouping the sequenced strands into paired families	53
		7.	Generating a single-strand consensus sequences	56
		8.	Comparing the single strand consensus sequence to its complementary strand-mate (generating a Duplex Consensus)	56
	D	Prior	to December 28, 2013, the art taught that Dupley	50
	D.	Sequ	encing could be used to sequence cfDNA	58
VII.	THE	'858 F	PATENT SPECIFICATION AND CLAIMS	60
VIII.	PRO	SECU	TION HISTORY	69
IX.	THE	MEAN	NING OF CLAIM TERMS	74
Х.	LEG	AL BA	ASIS FOR MY ANALYSIS	75
XI.	KEY	PRIO	R ART	76
	A.	Naray	yan (EX1082)	76
	B.	Schm	nitt (EX1009), Schmitt-623 (EX1083)	77
	C.	Meye	er (EX1005)	83
	D.	Kivic	oja (EX1006)	84
	E.	Craig	g (EX1007)	84
XII.	GRO OBV	UND IOUS	1: CLAIMS 1-7 AND 10-27 WOULD HAVE BEEN OVER NARAYAN, SCHMITT, AND MEYER	85
	A.	Clain	n 1	85
		1.	A method for analyzing sequencing reads of double- stranded cell-free deoxyribonucleic acid (cfDNA) molecules from a sample of a subject, comprising:	85
		2.	(a) tagging a plurality of double-stranded cfDNA molecules from a population of double-stranded cfDNA molecules from the sample with a set of library adaptors	

		<i>Inter Partes</i> Review of US Patent 10,889,858 Declaration of Paul T. Spellman, Ph.D.
		comprising a plurality of molecular barcodes to generate tagged parent polynucleotides,
	3.	wherein the tagging comprises ligating a plurality of library adaptors from the set of library adaptors to the plurality of double-stranded cfDNA molecules from the population using more than a 10× molar excess of library adaptors as compared to the double-stranded cfDNA molecules of the population;
	4.	wherein the tagging produces at least 20% of the double- stranded cfDNA molecules of the populations having library adaptors ligated to both ends of a molecule of the double-stranded cfDNA molecules;
	5.	(b) amplifying a plurality of the tagged parent polynucleotides to produce progeny polynucleotides;
	6.	(c) sequencing a plurality of the progeny polynucleotides to produce a set of sequencing reads; and
	7.	(d) determining, based at least on sequence information from the molecular barcodes, individual double-stranded cfDNA molecules from among the tagged parent polynucleotides for which either (1) both a Watson strand and a Crick strand of the individual double-stranded cfDNA molecule are detected or (2) only one of a Watson strand or a Crick strand of the individual double- stranded cfDNA molecule is detected from a plurality of sequencing reads from the set of sequencing reads
В.	Motiv	vation to combine
	1.	A POSA would have been motivated to use Schmitt's 3- mer hybrid tagging approach to tag a population of cfDNA molecules
	2.	A POSA would have been motivated to use "more than a 10x molar excess" of adaptors 100
	3.	A POSA would also have been motivated to generate "at least 20%" adapter-ligated cfDNA molecules 103
	4.	A POSA would have been motivated to amplify, sequence, and identify paired and unpaired SSCSs as recited in claim 1

		<i>Inter Partes</i> Review of US Patent 10,889,858 Declaration of Paul T. Spellman, Ph.D.		
C.	C. Reasonable expectation of success			
	1.	A POSA would have reasonably expected to successfully sequence cfDNA disclosed in Narayan with Schmitt's Duplex Sequencing method because of knowledge in the art that a routine blood draw contains more than sufficient quantities of cfDNA		
	2.	A POSA would have reasonably expected to successfully tag cfDNA molecules		
	3.	A POSA would have reasonably expected success in using "more than a 10x molar excess" of adapters 111		
	4.	A POSA would also have reasonably expected success in generating "at least 20%" adapter-ligated cfDNA molecules		
D.	Clair	m 16113		
	1.	A method for analyzing double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules from a sample of a subject, comprising:		
	2.	 (a) tagging a plurality of double-stranded cfDNA molecules from a population of double-stranded cfDNA molecules from the sample with a set of library adaptors comprising a plurality of molecular barcodes to generate tagged parent polynucleotides;		
	3.	wherein the tagging comprises ligating a plurality of library adaptors from the set of library adaptors to the plurality of double-stranded cfDNA molecules from the population using more than a 10× molar excess of library adaptors as compared to the double-stranded cfDNA molecules of the population;		
	4.	wherein the tagging produces at least 20% of the double- stranded cfDNA molecules of the population having library adaptors ligated to both ends of a molecule of the double-stranded cfDNA molecules;		
	5.	(b) amplifying a plurality of the tagged parent polynucleotides to progeny polynucleotides;		
	6.	(c) determining nucleotide sequences of a plurality of the progeny polynucleotides; and		

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