Petitioner Demonstrative Exhibits

Case IPR2013-00390

August 5, 2014

SEQUENOM EXHIBIT 1106
Sequenom v. Stanford
IPR2013-00390

(12) **United States Patent**
Fan et al.

(10) **Patent No.: US 8,195,415 B2**
(45) **Date of Patent: Jun. 5, 2012**

(54) **NONINVASIVE DIAGNOSIS OF FETAL ANEUPLOIDY BY SEQUENCING**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/696,509**

(22) Filed: **Jan. 29, 2010**

(65) **Prior Publication Data**

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Related U.S. Application Data

(62) Division of application No. 12/560,708, filed on Sep. 16, 2009.

(60) Provisional application No. 61/098,758, filed on Sep. 20, 2008.

(51) **Int. Cl.**
G06F 19/00 (2006.01)

(52) **U.S. Cl.** **702/71**; 435/6.1

(58) **Field of Classification Search** 702/20, 702/182–185, 71; 435/6

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed is a method to achieve digital quantification of DNA (i.e., counting differences between identical sequences) using direct shotgun sequencing followed by mapping to the chromosome of origin and enumeration of fragments per chromosome. The preferred method uses massively parallel sequencing, which can produce tens of millions of short sequence tags in a single run and enabling a sampling that can be statistically evaluated. By counting the number of sequence tags mapped to a predefined window in each chromosome, the over- or under-representation of any chromosome in maternal plasma DNA contributed by an aneuploid fetus can be detected. This method does not require the differentiation of fetal versus maternal DNA. The median count of autosomal values is used as a normalization constant to account for differences in total number of sequence tags is used for comparison between samples and between chromosomes.

17 Claims, 17 Drawing Sheets

Ex. 1001

Grounds of Unpatentability

Ground	Claims	Description
1	1-6, 8-12	Anticipated under 35 U.S.C. § 102(e) by *Lo II*
2	7	Obvious under 35 U.S.C. § 103 over *Lo II*, *Hillier*, and/or *Smith*
3	13, 16	Obvious under 35 U.S.C. § 103 over *Lo II* and *Wang*
4	14	Obvious under 35 U.S.C. § 103 over *Lo II*, *Shimkets*, and/or *Dohm*
5	15	Obvious under 35 U.S.C. § 103 over *Lo II* and *Quake*
6	17	Obvious under 35 U.S.C. § 103 over *Lo II*, *Wang*, *Hillier*, and/or *Smith*

Paper 1, p. 4
Paper 7, pp. 3, 21-22

Claim Construction

Sequenom submits proposed constructions for several claim terms. Pet. 8-12; *see also* Ex. 1010 ¶¶ 29-36. Except for the terms "window" and "sliding window," the claim terms construed by Sequenom are defined either expressly in the '415 patent specification, or are defined expressly in the claims in which they appear. *See* Pet. 8-12.

1. A method of testing for an abnormal distribution of a specified chromosome portion in a mixed sample of normally and abnormally distributed chromosome portions obtained from a subject, comprising:

(a) sequencing DNA from the mixed sample to obtain sequences from multiple chromosome portions, wherein said sequences comprise a number of sequence tags of sufficient length of determined sequence to be assigned to a chromosome location within a genome;

(b) assigning the sequence tags to corresponding chromosome portions including at least the specified chromosome by comparing the determined sequence of the sequence tags to a reference genomic sequence;

(c) determining values for numbers of sequence tags mapping to chromosome portions by using a number of windows of defined length within normally and abnormally distributed chromosome portions to obtain a first value and a second value therefrom; and

(d) using the values from step (c) to determine a differential, between the first value and the second value, which is determinative of whether or not the abnormal distribution exists.

Ex. 1001, Claim 1

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