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Paper 45
Entered: November 25, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SEQUENOM, INC.,
Petitioner,

v.

THE BOARD OF TRUSTEES OF
THE LELAND STANFORD JUNIOR UNIVERSITY,
Patent Owner.

Case IPR2013-00390
Patent 8,195,415 B2

Before LORA M. GREEN, FRANCISCO C. PRATS, and SCOTT E. KAMHOLZ, *Administrative Patent Judges.*

PRATS, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

A. Statement of the Case

Sequenom, Inc. ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–17, all of the claims, of U.S. Patent No. 8,195,415 B2 (Ex. 1001, "the '415 patent"). Paper 1 ("Pet."). The Board of Trustees of the Leland Stanford Junior University ("Patent Owner") did not file a Preliminary Response. We instituted trial on the following grounds of unpatentability:

Reference[s]	**Basis**	**Claim[s] challenged**
Lo II[1]	§ 102(e)	1–6, 8–12
Lo II, Hillier,[2] Smith[3]	§ 103	7
Lo II, Wang[4]	§ 103	13, 16
Lo II, Shimkets,[5] Dohm[6]	§ 103	14

[1] Lo et al., U.S. Patent App. Pub. No. 2009/0029377 A1 (filed July 23, 2008) (Ex. 1002, "Lo II").
[2] LaDeana W. Hillier et al., *Whole-genome Sequencing and Variant Discovery in C. elegans*, 5 NATURE METHODS 183–88 (published online Jan. 20, 2008) (Ex. 1006).
[3] Andrew D. Smith et al., *Using Quality Scores and Longer Reads Improves Accuracy of Solexa Read Mapping*, 9 BMC BIOINFORMATICS 128 (Feb. 28, 2008) (Ex. 1009).
[4] Tian-Li Wang et al., *Digital Karyotyping*, 99 PNAS 16156–61 (Dec. 10, 2002) (Ex. 1005).
[5] Shimkets et al., U.S. Patent App. Pub. No. 2005/0221341 A1 (published Oct. 6, 2005) (Ex. 1004).
[6] Juliane C. Dohm et al., *Substantial Biases in Ultra-short Read Data Sets from High-throughput DNA Sequencing*, 36 NUCL. ACIDS RES. *e*105 (published online July 26, 2008) (Ex. 1007).

Reference[s]	Basis	Claim[s] challenged
Lo II, Quake[7]	§ 103	15
Lo II, Wang, Hillier, Smith	§ 103	17

Decision to Institute 21–22 (Paper 7, "Dec.").

After the Board instituted trial, Patent Owner filed a Response (Paper 24; "PO Resp.") and Petitioner filed a Reply (Paper 38; "Pet. Reply"). Oral Hearing was held on August 5, 2014, and the Hearing Transcript ("Tr.") has been entered in the record. Paper 44.

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a). We conclude that Petitioner has failed to prove by a preponderance of the evidence that claims 1–17 of the '415 patent are unpatentable.

B. Related Proceedings

The '415 patent is asserted in a co-pending district court case captioned as *Verinata Health, Inc. and the Board of Trustees of the Leland Stanford Junior University v. Sequenom, Inc. and Sequenom Center for Molecular Medicine LLC*, United States District Court for the Northern District of California, Case No. 3:12-cv-00865-SI. Pet. 1. The '415 patent also is involved in Interference No. 105,922, declared on May 3, 2013. *Id.* Petitioner also filed a second petition seeking review of the claims of the '415 patent, Case IPR2014-00337. Paper 32. The Board declined to institute trial on the grounds presented in that petition. *Sequenom, Inc. v. Bd. of Trustees of the Leland Stanford Junior Univ.* ("*Sequenom*

[7] Quake et al., U.S. Patent No. 7,888,017 B2 (filed Feb. 2, 2007,) (Ex. 1008).

II"), Case IPR2014-00337 (PTAB July 16, 2014) (Paper 11); Sequenom II, Paper 14.

C. The '415 Patent

The '415 patent describes prenatal genetic diagnosis methods that allow detection of chromosomal aberrations without the use of invasive techniques, such as amniocentesis or chorionic villus sampling, which pose potentially significant risks to both fetus and mother. *See* Ex. 1001, col. 1, ll. 30–54. The '415 patent explains that, because fetal DNA can constitute nearly ten percent of the cell-free DNA in maternal plasma, fetal aneuploidy can be detected by determining the sequences of the DNA fragments in the maternal plasma. *See id.* at col. 1, l. 55–col. 2, l. 24. More particularly, the '415 patent describes "the successful use of shotgun sequencing and mapping of DNA to detect fetal trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), and trisomy 13 (Patau syndrome), carried out non-invasively using cell-free fetal DNA in maternal plasma." *Id.* at col. 4, ll. 17–21.

Claim 1, reproduced below, illustrates the challenged subject matter:

> 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.

II. ANTEDATING LO II

A. The Parties' Positions

Patent Owner contends that Lo II, which Petitioner relies upon in every instituted ground of unpatentability, does not qualify as prior art under 35 U.S.C. § 102(e) because the invention recited in the '415 patent claims was reduced to practice before Lo II's filing date of July 23, 2008. PO Resp. 31. Patent Owner's contentions in that regard involve a paper published in the Proceedings of the National Academy of Sciences ("the PNAS paper"),[8] which was co-authored by the two inventors of the '415 patent, Drs. Hei-Mun Christina Fan and Stephen R. Quake, along with others. *Id.* at 38–39.

Specifically, Patent Owner contends that two early drafts of the PNAS paper, presented in Exhibits 2111, 2112, and 2113, as well as email

[8] Dr. Hei-Mun Christina Fan et al., *Noninvasive Diagnosis of Fetal Aneuploidy by Shotgun Sequencing DNA from Maternal Blood*, available at www.pnas.org/cgi/doi/10.1073/pnas.0808319105 (2008) (Ex. 2139).

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