Trials@uspto.gov
Tel: 571-272-7822

Paper 45
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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).

correspondence associated with the drafts, and testimony by Dr. Yair J. Blumenfeld, one of the other PNAS paper co-authors, establish that the inventors had actually reduced to practice the subject matter recited in claims 1–17 of the '415 patent before Lo II's July 23, 2008 filing date. *Id.* Patent Owner presents a chart to support its assertion that the two drafts of the PNAS paper describe all of the subject matter claimed in the '415 patent. *Id.* at 39–59.

Petitioner does not contend that the disclosures in Lo II relied upon to show unpatentability in the instituted grounds are entitled to the benefit of the earlier filing date of Lo II's corresponding provisional application, Lo I.[9] *See* Pet. Reply 7–13. Instead, Petitioner argues that Patent Owner has failed to advance evidence, independent of the inventors' testimony, that sufficiently corroborates the asserted actual reduction to practice before Lo II's filing date. *Id.* at 7–8. Petitioner summarizes its arguments as follows:

> [Inventor] Quake's declaration has been withdrawn, and [inventor] Fan's allegation of a reduction to practice lacks corroboration. Other than the Fan declaration (Ex. 2132), the only evidence of an actual reduction to practice proffered by Patent Owner is an unwitnessed and unsigned laboratory notebook (Ex. 2110), emails between the inventors and various parties that fail to reference the specific steps of the '415 Patent claims, and testimony by third parties who lack specific knowledge of the inventors' alleged activities during the relevant time period ([Dr. J. Chris] Detter) and fail to corroborate a reduction to practice of the steps of the '415 Patent claims (Blumenfeld).

Id.

[9] Lo et al., U.S. Provisional Patent Application 60/951,438 (filed July 23, 2007) (Ex. 1003, "Lo I").

Petitioner argues in particular that Patent Owner has not advanced evidence, independent of the inventors' testimony, corroborating Patent Owner's assertion that the copies of the drafts of the PNAS paper presented in Exhibits 2111 and 2113 are the actual documents communicated by inventor Dr. Christina Fan to the asserted corroborating witness, Dr. Blumenfeld. *Id.* at 9–11. Further, Petitioner argues, the Declaration by Dr. Blumenfeld (Ex. 2134) submitted by Patent Owner is:

> critically deficient because it provides no statement as to what Blumenfeld actually knew and understood about the methods recited in the '415 Patent claims at the time of the alleged reduction to practice, and certainly no evidence that he was aware of all of the steps or that he recognized a complete reduction to practice.

Id. at 12.

B. The Issue

In light of the discussion above, the critical issue in this case is whether Patent Owner has advanced evidence sufficient to corroborate an actual reduction to practice of the subject matter of the '415 patent's claims before the July 23, 2008 filing date of the Lo II reference. *See* 35 U.S.C. § 102(e)(1) (patent-defeating published application must be "filed . . . before the invention by the applicant for patent").[10] For the reasons discussed below, we conclude that Patent Owner has established an actual reduction to practice before the relevant date.

[10] The application which that issued as the '415 patent, serial number 12/696,509, is a divisional application of serial number 12/560,708, which was filed on September 16, 2009. Ex. 1001, 1. Accordingly, the version of § 102(e) in effect before the Leahy-Smith America Invents Act ("AIA") applies to the claims of the '415 patent. *See* AIA, Pub. L. No. 112-29, § 3, 125 Stat. 288 (2011).

C. Analysis

"Generally, the invention of a process is completed, or reduced to practice, when it is successfully performed." *Shurie v. Richmond*, 699 F.2d 1156, 1159 (Fed. Cir. 1983). "In order to establish an actual reduction to practice, an inventor's testimony must be corroborated by independent evidence. . . . [A] 'rule of reason' analysis is applied to determine whether an inventor's testimony regarding reduction to practice has been sufficiently corroborated." *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998) (citation omitted). This "rule of reason" analysis "requires an evaluation of all pertinent evidence when determining the credibility of an inventor's testimony." *Id.* Under that analysis, "to corroborate a reduction to practice, it is not necessary to produce an actual over-the-shoulder observer. Rather, sufficient circumstantial evidence of an independent nature can satisfy the corroboration requirement." *Id.*

Corroborating evidence may be "testimony of a witness, other than an inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor." *Hahn v. Wong*, 892 F.2d 1028, 1032–33 (Fed. Cir. 1989). Corroboration, however, "is not necessary to establish what a physical exhibit before the [B]oard includes. Only the inventor's testimony requires corroboration before it can be considered." *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993) (citation omitted).

In the instant case, as discussed above, Patent Owner advances Exhibits 2111 and 2113, which are essentially identical, to support its contention of reduction to practice. PO Resp. 38–39. Patent Owner asserts that Exhibits 2111 and 2113 include a draft of the PNAS paper, which inventor Dr. Christina Fan forwarded on June 19, 2008, to PNAS paper co-authors Drs. Stephen Quake and

Yair Blumenfeld. *Id.* Patent Owner explains that Dr. Blumenfeld's collaboration with Drs. Fan and Quake consisted of providing patient blood samples for the fetal aneuploidy diagnosis test conducted by Drs. Fan and Quake, and preparing the protocol and consent forms "for the Institutional Review Board ('IRB') in order to collect the samples from patients." *Id.* at 32 (citing Ex. 2134 ¶ 6 (Blumenfeld Decl.)).

We note that Exhibits 2111 and 2113 include a copy of a manuscript entitled "Universal Non-Invasive Diagnosis of Fetal Aneuploidy with Direct Sequencing," listing Drs. Fan, Quake, and Blumenfeld as co-authors. Ex. 2111, 1–14; Ex. 2113, 1–14. Exhibits 2111 and 2113 also include a copy of an email dated June 19, 2008, from Dr. Fan to Drs. Quake and Blumenfeld stating, "[a]ttached is a rough draft of the non-invasive study." Ex. 2111, cover page; Ex. 2113, cover page.

Inventor Dr. Fan testifies that she sent the draft of the PNAS paper in Exhibits 2111 and 2113 to Drs. Quake and Blumenfeld on June 19, 2008. Ex. 2132 ¶ 44.

Dr. Blumenfeld testifies as follows:

> On June 19, 2008, Dr. Fan sent to Stephen Quake and me a "rough draft of the non-invasive study," (**Ex. 2111, 2113**) which was based on their first Solexa sequencing run and was to be submitted to the journal *Proceedings of the National Academy of Sciences, USA*, which ultimately published as the article "Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood," Proc. Natl. Acad. Sci. USA (2008) **105(42)**:16266-16271 ("first draft of the PNAS manuscript"; **Ex. 2113**). I was listed as an author on that paper, along with Christina Fan, Usha Chitkara, Louanne Hudgins and Stephen Quake.

Ex. 2134 ¶ 9. Dr. Blumenfeld also testifies that "[o]n July 7, 2008, Drs. Quake, Fan and I discussed revisions to the PNAS manuscript. (**Ex. 2112, 2131**)." *Id.* at ¶ 11.

Exhibit 2131, which Dr. Blumenfeld cites in his statement immediately above regarding his discussions with Drs. Quake and Fan about revisions to the PNAS manuscript, includes a copy of an email dated July 7, 2008, from Dr. Blumenfeld to Dr. Fan. Ex. 2131, 1.[11] Dr. Blumenfeld also copied Dr. Quake on his July 7, 2008 email. *Id.* Dr. Blumenfeld's email reads as follows:

> Hi Christina,
>
> It looks great. I think I answered most of the comments you directed towards me and I added a little bit about the recent ACOG Practice Bulletin which recommends that invasive testing now be offered to ALL women, regardless of risk factors. I think it will play nicely with the need for a "risk-free" non-invasive diagnostic test.
>
> Thanks,
>
> Yair

Id.

Dr. Blumenfeld's testimony, considered in conjunction with the exhibits he cites, persuades us that Patent Owner has advanced sufficient evidence, independent of the inventors' testimony, to corroborate reduction to practice of the subject matter of claims 1–17 of the '415 patent as of June 19, 2008. In particular, Dr. Blumenfeld's testimony persuades us that the copy of the draft of the PNAS

[11] Exhibit 2131 does not include page numbers. We cite to the first page as page 1 and the remaining pages as if consecutively numbered.

paper presented in identical Exhibits 2111 and 2113 is the document that Dr. Fan sent to Dr. Blumenfeld on June 19, 2008.

Specifically, when referring to the draft of the PNAS paper Dr. Fan sent him on that date, Dr. Blumenfeld expressly identifies Exhibits 2111 and 2113. Ex. 2134 ¶ 9 ("On June 19, 2008, Dr. Fan sent to Stephen Quake and me a 'rough draft of the non-invasive study,' (**Ex. 2111, 2113**) . . . ."). Dr. Blumenfeld's status as a co-author of the paper, as well as his testimony that he reviewed Exhibit 2111 (Ex. 2134 ¶ 5), persuades us that Dr. Blumenfeld was aware of the contents of Exhibit 2111 when he identified it as the document he received from Dr. Fan on June 19, 2008. Moreover, as noted above, in addition to identifying Exhibits 2111 and 2113 as containing the document he received from Dr. Fan on June 19, 2008, Dr. Blumenfeld testifies that, on July 7, 2008, he, Dr. Quake, and Dr. Fan discussed revisions to the PNAS manuscript. Ex. 2134 ¶ 9. In so stating, Dr. Blumenfeld cites to Exhibit 2131, which includes an email from Dr. Blumenfeld explaining his revisions to the draft, and stating that the draft "looks great." *Id.*; *see also* Ex. 2131, 1. Consequently, Petitioner does not persuade us (Pet. Reply 10) that Patent Owner proffers no testimony to verify that the document in Exhibits 2111 and 2113 is a copy of the actual document received by Dr. Blumenfeld on June 19, 2008. To the contrary, Dr. Blumenfeld's testimony that he provided an evaluation of the document in Exhibits 2111 and 2113, as well as proposed revisions to it, shows that he reviewed that document, and corroborates further that the document in Exhibits 2111 and 2113 is in fact a copy of the document Dr. Blumenfeld received from his co-author Dr. Fan on June 19, 2008.

Petitioner gives us no credible reason to doubt that Exhibits 2111 and 2113 are copies of the actual document Dr. Blumenfeld received, nor does Petitioner

direct us to specific evidence that undercuts Dr. Blumenfeld's testimony in that regard, or otherwise supports a contrary finding. Moreover, Petitioner does not explain how the other co-authors and collaborators of the PNAS paper, with the exception of Dr. Quake, were involved in the interchange between Drs. Fan and Blumenfeld described in Dr. Blumenfeld's Declaration. Accordingly, Petitioner does not persuade us that the absence of testimony from those individuals warrants drawing an "adverse inference" against Patent Owner on this issue. *See* Pet. Reply 13. Further, because, under the law, testimony by co-inventor Dr. Quake cannot serve to corroborate evidence that the draft appearing in Exhibits 2111 and 2113 is the document Dr. Fan sent to Dr. Blumenfeld, we decline to draw an adverse inference based on the absence of Dr. Quake's testimony. *See id.*

Regarding the content of the draft of the PNAS paper appearing in Exhibits 2111 and 2113, the fact that Dr. Blumenfeld might not have expressly mentioned the method steps of the '415 patent as being described in those Exhibits, or discussed his understanding of those steps, does not demonstrate that the draft in Exhibits 2111 and 2113 fails to describe an actual reduction to practice of the processes recited in claims 1–17 of the '415 patent. Similarly, the fact that the Declarations of Drs. Blumenfeld and Detter (Exs. 2134, 2138) might not set forth an explanation of the legal standard for actual reduction to practice does not persuade us that the experiments disclosed in Exhibits 2111 and 2113 fail to describe an actual reduction to practice. Specifically, as noted above, "corroboration is not necessary to establish what a physical exhibit before the [B]oard includes. Only the inventor's testimony requires corroboration before it can be considered." *Price*, 988 F.2d at 1195 (internal quotations omitted). As explained in *Price*, "[w]hile evidence as to what the drawing [in the Exhibit at issue] would mean to one of skill in the art may assist the [B]oard in evaluating the

drawing, the content of [the] Exhibit [at issue] does not itself require corroboration." *Id.* at 1195–96; *see also Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577–78 (Fed. Cir. 1996) ("The trier of fact can conclude for itself what documents show, aided by testimony as to what the exhibit would mean to one skilled in the art.").

In reviewing Exhibits 2111 and 2113, claims 1–17 of the '415 patent, and the claim charts presented by Patent Owner, we detect no deficiency in Patent Owner's assertion that the draft of the PNAS paper appearing in those exhibits describes the subject matter of claims 1–17 of the '415 patent. *See* PO Resp. 39–60 (presenting claim charts); Ex. 2138 ¶ 7 (Second Declaration by Dr. J. Chris Detter) (same). Moreover, Petitioner does not allege error in Patent Owner's assertion that the draft of the PNAS paper in Exhibits 2111 and 2113 describes the subject matter of claims 1–17 of the '415 patent. *See* Pet. Reply 7–13. Nor does Petitioner advance expert testimony refuting that assertion or the accuracy of the claim charts. *See id.* Indeed, Petitioner does not point to clear or specific evidence contravening the central assertion in the draft in Exhibits 2111 and 2113, namely that "[w]e demonstrate here the successful use of massively parallel sequencing to detect fetal trisomy 21 (Down Syndrome) and trisomy 18 (Edward Syndrome) non-invasively using cell-free fetal DNA in maternal plasma." Ex. 2111, 2; Ex. 2113, 2. Thus, Petitioner does not advance clear or specific evidence suggesting that the draft of the PNAS paper in Exhibits 2111 and 2113 fails to describe successful performance of the processes recited in the claims of the '415 patent. Accordingly, we are persuaded that the evidence of record not only reasonably supports Patent Owner's assertion that the draft of the PNAS paper appearing in Exhibits 2111 and 2113 is the draft of the PNAS paper that Dr. Fan sent to Dr. Blumenfeld on June 19, 2008, but also reasonably supports Patent Owner's assertion that that document

describes an actual reduction to practice, on that date, of claims 1–17 of the '415 patent, the claims challenged in this proceeding.

Petitioner does not persuade us that the holding in *Hahn v. Wong* mandates a contrary result. In *Hahn*, the Federal Circuit affirmed the Board's conclusion that a patent applicant had not made a prima facie case of prior reduction to practice where the allegedly antedating evidence consisted of spectroscopic graphical data from the inventor's laboratory notebook pages, supplemented with two non-inventor affidavits stating that the affiants had read and understood the notebook pages. 892 F.2d at 1030–31, 1033–34. The court agreed with the Board's conclusion that the applicant had not shown prima facie reduction to practice, because the corroborative affidavits did not explain why the graphical data in the laboratory notebook actually represented the chemical compound in the challenged claims, and because the dates of the alleged reduction to practice were ambiguous. *Id.* at 1033–34.

In the instant case, in contrast, Petitioner has not shown ambiguity in the asserted date of the draft in Exhibits 2111 and 2113. Nor has Petitioner explained convincingly why the draft of the PNAS paper in Exhibits 2111 and 2113, which Petitioner does not dispute describes the processes of the challenged claims, and which is presented in straightforward manuscript form, requires testimony by a technical expert to evaluate whether it describes successful performance of the process recited in the challenged claims.

In sum, for the reasons discussed, non-inventor corroborating evidence reasonably supports Patent Owner's assertion that, on June 19, 2008, inventor Dr. Fan sent to Dr. Blumenfeld the draft of the PNAS paper appearing in Exhibits 2111 and 2113. As also discussed above, the evidence reasonably supports Patent Owner's assertion that that document describes an actual reduction to practice of

the processes recited in claims 1–17 of the '415 patent. We are persuaded, therefore, that Patent Owner has shown that the subject matter of the challenged claims was reduced to practice before Lo II's July 23, 2008 filing date. Accordingly, because the evidence does not support Petitioner's position that Lo II constitutes prior art to the challenged claims under 35 U.S.C. § 102(e), and because Lo II is relied upon in every ground on which trial was instituted, Petitioner has not shown by a preponderance of the evidence that any of the challenged claims is unpatentable, based on any of the asserted grounds of unpatentability.

III. CONCLUSION

For the reasons given, we are not persuaded that Petitioner has shown by a preponderance of the evidence that claims 1–17 of the '415 patent are unpatentable based on the challenges on which trial was instituted.

IV. ORDER

It is ORDERED that claims 1–17 of the '415 patent have not been shown to be unpatentable;

FURTHER ORDERED that because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

For PETITIONER:

Michael Wise
Patrick Morris
PERKINS COIE LLP
mwise@perkinscoie.com
pmorris@perkinscoie.com

For PATENT OWNER:

R. Danny Huntington
Sharon Crane
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
dhuntington@rfem.com
scrane@rfem.com