

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSA DIAGNOSTICS,
Petitioner,

v.

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

Case IPR2013-00308
Patent 8,296,076 B2

Before TONI R. SCHEINER, LORA M. GREEN, and
SCOTT E. KAMHOLZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. *Background*

Petitioner, Ariosa Diagnostics (“Ariosa”), filed a Petition requesting *inter partes* review of claims 1–13 (“the challenged claims”) of U.S. Patent No. 8,296,076 B2 (“the ’076 patent”). Paper 1 (“Pet.”). Patent Owner, The

Board of Trustees of the Leland Stanford Junior University (“Stanford”), did not file a Patent Owner Preliminary Response. We determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–13 as unpatentable under 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted this proceeding on November 20, 2013, as to the challenged claims of the ’076 patent. Paper 7 (“Institution Decision”; “Dec. Inst.”).

Patent Owner filed a Response (Paper 15, “PO Resp.”), but did not file a motion to amend. Petitioner subsequently filed a Reply. Paper 18 (“Reply”). An oral hearing was held on July 11, 2014. The transcript of the hearing has been entered into the record. Paper 39.

We have jurisdiction under 35 U.S.C. § 6(c). This final written decision is issued pursuant to 35 U.S.C. § 318(a). Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of the evidence that the challenged claims of the ’076 patent are unpatentable.

B. Related Proceedings

The ’076 patent is the subject of a civil action, *Verinata Health, Inc. v. Ariosa Diagnostics, Inc.*, No. 3:12-cv-05501-SI (N.D. Cal.), filed October 25, 2012. Paper 6.

C. The ’076 Patent

The ’076 patent issued on October 23, 2012, with Hei-Mun Christina Fan and Stephen R. Quake as the listed co-inventors. The ’076 patent

“relates to the field of molecular diagnostics, and more particularly to the field of prenatal genetic diagnosis.” Ex. 1001, col. 1, ll. 36–38.

The '076 patent teaches that fetal chromosomal aneuploidies may affect 9 out of every 1000 live births. *Id.* at col. 1, ll. 49–50. The discovery of significant amounts of cell-free nucleic acid in the maternal blood stream has led to the development of non-invasive prenatal tests for a variety of traits, but measurement of aneuploidy has presented a challenge due to the high background of maternal DNA, as fetal DNA often constitutes less than 10% of total DNA in maternal cell-free plasma. *Id.* at col. 1, l. 62–col. 2, l. 3. Methods that have been used to detect aneuploidy include detecting an allelic variation between the mother and the fetus, direct shotgun sequencing followed by mapping of fragments to the chromosome of origin, as well as enumeration of the number of fragments per chromosome. *Id.* at col. 2, ll. 4–21.

In a preferred method of the '076 patent, DNA is obtained from maternal serum, wherein the DNA is a mixture of maternal and fetal DNA. *Id.* at col. 3, ll. 40–47. The DNA is sequenced partially to provide a large number of short reads, which act as sequence tags, with a significant number of the short reads being sufficiently unique such that they can be mapped to specific chromosomes or chromosomal locations of the human genome. *Id.* at col. 3, ll. 47–52. “By counting the number of sequence tags mapped to each chromosome (1–22, X and Y), the over- or under-representation of any chromosome or chromosome portion in the mixed DNA contributed by an aneuploid fetus can be detected.” *Id.* at col. 3, ll. 54–58. As taught by the '076 patent, the method does not rely on *a priori* sequence information to distinguish fetal DNA from maternal DNA. *Id.* at col. 3, ll. 64–66.

The '076 patent also discloses a method for correcting for the “nonuniform distribution [of] sequence tags to different chromosomal portions.” *Id.* at col. 4, ll. 54–55. The '076 patent discloses a method in which a large number of windows of defined length are created along chromosomes of interest, such that the windows cover each chromosome of interest, except that non-informative regions of the chromosomes, such as centromere and repetitive regions, are not necessarily included. *Id.* at col. 4, ll. 56–62. As taught by the '076 patent, “[v]arious average numbers, i.e., median values, are calculated for different windows and compared. By counting sequence tags within a series of predefined windows of equal lengths along different chromosomes, more robust and statistically significant results may be obtained.” *Id.* at col. 4, ll. 62–67.

The '076 patent also provides examples that describe “direct sequencing of cell-free DNA from plasma of pregnant women with high throughput shotgun sequencing technology.” *Id.* at col. 20, ll. 30–32. The sequences are mapped to specific chromosomal regions, allowing for the measurement of over- and under-representation of chromosomes from an aneuploid fetus. *Id.* at col. 20, ll. 34–36.

The '076 patent discloses further that “[a]nother method for increasing sensitivity to fetal DNA is to focus on certain regions within the human genome,” such as by using sequencing methods that select sequences that map to a chromosome of interest *a priori*. *Id.* at col. 13, ll. 53–56. An area of focus may be a partial chromosome deletion, such as 22q11 deletion syndrome. *Id.* at col. 13, ll. 57–59. Sequence-based methods that may be used to sequence selected subsequences include sequencing by array, as well

as using capture beads with specific genomic sequences used as capture probes. *Id.* at col. 13, l. 65–col. 14, l. 1.

As taught by the '076 patent:

The subsequencing method is in one aspect contrary to conventional massively parallel sequencing methodologies, which seek to obtain all of the sequence information in a sample. This alternative method selectively ignores certain sequence information by using a sequencing method which selectively captures sample molecules containing certain predefined sequences. One may also use the sequencing steps exactly as exemplified, but in mapping the sequence fragments obtained, give greater weight to sequences which map to areas known to be more reliable in their coverage, such as exons. Otherwise, the method proceeds as described below, where one obtains a large number of sequence reads from one or more reference chromosomes, which are compared to a large number of reads obtained from a chromosome of interest, after accounting for variations arising from chromosomal length, G/C content, repeat sequences and the like.

Id. at col. 14, ll. 21–39.

D. Illustrative Claims

Claim 1 is the only independent challenged claim. Claims 1–3 and 9 are illustrative of the disclosed invention, and are reproduced below (emphases added):

1. A method of testing for an abnormal distribution of a chromosome in a sample comprising a mixture of maternal and fetal DNA, comprising the steps of:

(a) obtaining maternal and fetal DNA from said sample;

(b) *sequencing predefined subsequences* of the maternal and fetal DNA to obtain a plurality of sequence tags aligning to the predefined subsequences, wherein said sequence tags are of

sufficient length to be assigned to a specific predefined subsequence, wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one first chromosome suspected of having an abnormal distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample;

(c) assigning the plurality of sequence tags to their corresponding *predetermined subsequences*;

(d) determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome; and

(e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.

2. The method of claim 1 wherein the sample is a maternal serum or plasma sample, wherein the abnormal distribution of said first chromosome is a fetal aneuploidy, and wherein said second chromosome is a euploid chromosome.

3. The method of claim 2 wherein the sequencing comprises *massively parallel sequencing* of the predefined subsequences.

9. The method of claim 2 wherein said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences.

Ex. 1001, col. 35, ll. 10–41, col. 36, ll. 8–10.

E. Instituted Challenges

Claims	Basis	References
1–5, 7–9, 12, and 13	§ 102(e)	Lo ¹
10 and 11	§ 103(a)	Lo and Brenner ²
1–5 and 7–13	§ 103(a)	Quake ³ and Kapur ⁴
6	§ 103(a)	Lo and Li; ⁵ and Quake, Kapur, and Li

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms also are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer,

¹ Lo et al., Pub. No. US 2009/0029377, published Jan. 29, 2009 (Ex. 1004, “Lo”).

² Brenner, Pub. No. US 2006/0177832 A1, published Aug. 10, 2006 (Ex. 1003, “Brenner”).

³ Quake et al., Pub. No. US 2007/0202525 A1, published Aug. 30, 2007 (Ex. 1006, “Quake”).

⁴ Kapur et al., Pub. No. US 2008/0138809 A1, published Jun. 12, 2008 (Ex. 1005, “Kapur”).

⁵ Heng Li et al., *Mapping Short DNA Sequencing Reads and Calling Variants Using Mapping Quality Scores*, 18 GENOME RESEARCH 1851–1858 (2008) (Ex. 1014, “Li”).

the definition must be set forth in the specification with reasonable clarity, deliberateness, and precision. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). “[A] claim construction that excludes a preferred embodiment . . . is rarely, if ever correct and would require highly persuasive evidentiary support.” *Epos Tech. Ltd. v. Pegasus Tech. Ltd.*, 766 F.3d 1338, 1347 (Fed. Cir. 2014) (alteration in original) (internal citation and quotations omitted). Moreover, “[u]nder the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend.” *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003) (internal citation omitted).

1. “*sequence tag*”

The '076 patent defines “sequence tag” as a “DNA sequence of sufficient length that it may be assigned specifically to one of chromosomes 1–22, X or Y.” Ex. 1001, col. 8, ll. 57–59. We adopt that construction.

2. “*massively parallel sequencing*”

Neither party explicitly requests a construction of this term, which is found in dependent claims 3 and 4, but we set forth the definition provided by the '076 patent, as it informs our construction of other portions of the claim whose construction is at issue. Specifically, the '076 patent defines “massively parallel sequencing” as

techniques for sequencing millions of fragments of nucleic acids, e.g., using attachment of randomly fragmented genomic DNA to a planar, optically transparent surface and solid phase amplification to create a high density sequencing flow cell with millions of clusters, each containing ~1,000 copies of template per sq. cm. These templates are sequenced using four-color DNA sequencing-by-synthesis technology.

Ex. 1001, col. 9, ll. 22–29.

3. “*sequencing predefined subsequences*”

In the Institution Decision, we construed this term as not limited to any particular sequencing technique, and thus encompassing the use of random shotgun sequencing. Dec. Inst. 7–10.

Patent Owner contends that the method claimed by the ’076 patent is limited to “targeted sequencing, *i.e.*, only certain predefined sequences are actually sequenced,” which, Patent Owner asserts, excludes the use of random shotgun sequencing. PO Resp. 7. In particular, Patent Owner argues that the term “predefined” in the claim excludes random sequencing. *Id.* at 8. According to Patent Owner, although the Specification includes embodiments to both random and targeted sequencing, the ordinary artisan would understand that the use of the term “predefined” refers to targeted sequencing. *Id.* at 10–12.

Relying on the Declaration of Dr. J. Chris Detter, Patent Owner asserts that “a person of ordinary skill in the art would understand that the term ‘predefined’ refers to preselecting the nucleic acids to be sequenced prior to sequencing them.” *Id.* at 8–9 (citing Ex. 2008 ¶ 48). Patent Owner argues further that step 1(b) of claim 1 also supports its construction, because the sequence tags are assigned only to predefined subsequences, and thus sequence tags that cannot be assigned to the predefined sequences are not produced. *Id.* at 9. According to Patent Owner, steps 1(c) and 1(d) of claim 1 also support its construction. *Id.* at 10. Specifically, Patent Owner argues that the use of the term “subsequence,” as well as the term “predefined,” “confirms that less than all of the chromosomes of interest are

being sequenced in the claimed method, consistent with targeted sequencing.” *Id.*

Petitioner responds that Patent Owner’s construction excludes the preferred and exemplified embodiments of the ’076 patent, all of which involve the use of random shotgun sequencing. Reply 2.

We have considered Patent Owner’s contentions carefully, as well as the evidence cited by Patent Owner, and we decline to adopt its proffered construction of limiting “sequencing predefined subsequences” to targeted sequencing. As noted by Petitioner, the term “targeted sequencing” nowhere appears in the Specification of the ’076 patent. *Id.* at 1. Moreover, claim terms are not construed in isolation. Rather, claim terms should be construed in the context of the claim as a whole, in light of the teachings of the Specification. *See, e.g., Hockerson-Halberstadt, Inc. v. Converse Inc.*, 183 F.3d 1369, 1374 (Fed. Cir. 1999) (“Proper claim construction . . . demands interpretation of the entire claim in context, not a single element in isolation.”). We find that the rest of claim 1, the dependent claims, and the Specification support our construction.

The portion of step (b) of claim 1 that includes the disputed phrase recites (emphasis added) “*sequencing predefined subsequences* of the maternal and fetal DNA to obtain a plurality of sequence tags aligning to the predefined subsequences.” Thus, the claim language associates “sequencing predefined sequences” with obtaining “sequence tags.” The Specification of the ’076 patent discusses sequence tags in the context of shotgun sequencing. *See, e.g.,* Ex. 1001, col. 14, ll. 56–66. As Petitioner notes, there is no discussion in the Specification of the term “targeted sequencing.” Reply 1. Instead, the ’076 patent also discloses the use of a large number of

windows of defined length created along the chromosome, such that the windows cover each chromosome in question, except for the non-informative regions of the chromosome, such as centromere and repetitive regions, may be omitted. *Id.* at col. 4, ll. 56–62. Thus, “[v]arious average numbers, i.e., median values, are calculated for different windows and compared. By counting sequence tags within a series of *predefined* windows of equal lengths along different chromosomes, more robust and statistically significant results may be obtained.” *Id.* at col. 4, ll. 62–67 (emphasis added). As taught by the ’076 patent, “[e]ach autosome (chr. 1–22) is computationally segmented into contiguous, non-overlapping windows,” although sliding windows could also be used. *Id.* at col. 5, ll. 4–9. In addition, as noted above, the ’076 patent also provides examples that describe “direct sequencing of cell-free DNA from plasma of pregnant women with high throughput shotgun sequencing technology,” wherein sequences were mapped to specific chromosomal regions, allowing for the measurement of over- and under-representation of chromosomes from an aneuploid fetus. *Id.* at col. 20, ll. 30–36. Thus, the Specification does not disclose sequencing *only* the defined sequences as Patent Owner would have us construe this phrase, but instead, it discloses sequencing the predefined sequences along with other sequences, and then using various techniques to locate the predefined sequences in the material that has been sequenced.

Thus, we conclude that the broadest reasonable interpretation of the phrase “sequencing predefined subsequences” is that the subsequences may be predefined through comparison with the predefined windows that are created along the length of the chromosome. The predefined subsequences may walk along the entire length of the chromosome. Thus, although one

predefined subsequence would not include the entire chromosomal sequence, two or more subsequences may include the entire length of the chromosomal sequence. That interpretation encompasses the preferred embodiment of the '076 patent, whereas Patent Owner's proffered construction limiting the method of claim 1 to "targeted" sequencing, as Patent Owner defines that term, would not

Steps (c) and (d) of claim 1 are not inconsistent with our construction. Step (c) requires "assigning the plurality of sequence tags to their corresponding *predetermined subsequences*" (emphasis added), which would encompass matching the sequence tag to its corresponding predefined window. Step (d) requires "determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome," which encompasses counting the number of sequence tags that match the corresponding predefined window.

Moreover, the doctrine of claim differentiation supports our construction. Claim 9 requires that "said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences." Claim 9 depends from claim 2, which depends from claim 1. The claim 9 limitation—that the sequencing step is limited to sequencing only the predefined sequences—further supports our interpretation that "sequencing predetermined sequences" is not limited to sequencing only the predefined sequences, but encompasses sequencing sequences in addition to the predefined sequences. Although we recognize that the doctrine of claim differentiation may be more of a "rebuttable presumption" than a "doctrine," *Retractable Technologies, Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296,

1305 (Fed. Cir. 2011), Patent Owner has not provided evidence or argument sufficient to rebut the presumption. *See also Seachange Intern., Inc. v. C-COR, Inc.*, 413 F.3d 1361, 1368-69 (noting that the “doctrine is at its strongest ‘where the limitation sought to be “read into” an independent claim already appears in a dependent claim’”).

Thus, consistent with the Institution Decision, we decline to limit “sequencing predefined sequences” to any particular sequencing method, but construe the term as encompassing sequencing methods such as random shotgun sequencing, as well as sequencing by hybridization. Dec. Inst. 7–10; *see also* Ex. 1041, 32–34 (District Court claim construction order noting that claim 1 is not limited to selectively capturing sample molecules, that is, molecular preselection).

In sum, we construe “sequencing predefined subsequences” as not limited to targeted sequencing, wherein the sequences are molecularly preselected, such as by hybridization; but as also encompassing informationally predefining the subsequences, such as through the use of the predefined windows taught by the ’076 patent.

4. “predetermined subsequences”

In the Institution Decision, we construed “predetermined subsequences” as “reference sequence information.” Dec. Inst. 10–11. Patent Owner contends that step (d) of claim 1 “states that the ‘predetermined subsequences’ are ‘subsequences of said first chromosome’ and subsequences of the second chromosome.” PO Resp. 15. Thus, Patent Owner argues that “the predetermined subsequences are not just any reference sequence information, but rather are reference sequence information that represent less than all of a chromosome.” *Id.* Specifically,

step (d) of claim 1 recites “determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome.” Given the explicit language of claim 1 that the sequence tags are aligned to a “predetermined subsequence” of a chromosome, to read that limitation as encompassing the entire chromosome would lead the limitation of “subsequence” out of the claim. Thus, we adopt Patent Owner’s proposed construction: That is, we construe “predetermined subsequences” as “reference sequence information that represents less than all of a chromosome.” Similar to our construction of “sequencing predefined subsequences,” however, although one predetermined subsequence would not include the entire chromosomal sequence, two or more predetermined subsequences may include the entire length of the chromosomal sequence.

5. “*polymorphism-independent*”

Although the term “polymorphism-independent” does not appear in claim 1, Patent Owner argues that the claims of the ’076 patent should be construed “as being directed to polymorphism-independent methods of detecting fetal aneuploidy.” PO Resp. 15. Patent Owner contends that the ’076 patent “repeatedly makes reference to the fact that the invention is polymorphism-independent.” *Id.* Patent Owner does not point us to any claim language, however, that would limit the claim only to detecting fetal aneuploidies that are polymorphism-independent. Moreover, Patent Owner has not explained how the references to “polymorphism-independent” in the specification amount to a “clear disclaimer” of polymorphism dependent methods. *In re Am. Acad. Of Sci. Tech. Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004). Thus, we determine that the broadest reasonable interpretation of the

method of claim 1 is that it encompasses methods of testing for both polymorphism dependent, and polymorphism-independent, abnormal distributions of a chromosome.

B. Patentability

To prevail on its challenges to the patentability of claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

1. Principles of Law

a. Anticipation

In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). We must analyze prior art references as a skilled artisan would. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009) (to anticipate, “[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention”).

b. Obviousness

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Moreover, a determination of unpatentability on the ground of obviousness must include “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis “should be made explicit” and it “can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR*, 550 U.S. at 418.

2. *Patent Owner’s Contention that Petitioner’s Arguments are Legally Deficient*

Patent Owner contends that the expert testimony relied upon by Petitioner “is legally deficient and does not reflect a proper anticipation or obviousness analysis.” PO Resp. 16–17. According to Patent Owner, both of Petitioner’s experts, Dr. Cynthia Casson Morton and Dr. Robert Nussbaum, “acknowledged that they applied an incorrect and overly broad understanding of the legal standard for anticipation,” and Dr. Morton could not “accurately identify a distinction between obviousness and anticipation.” *Id.* Patent Owner argues further that the testimony of Dr. Morton and Dr. Nussbaum is unreliable. PO Resp. 18–19. For example, Patent Owner argues that Dr. Nussbaum admitted in his deposition that he had not read the entirety of the ’076 patent, and Dr. Morton admitted that

she did not review all of the materials cited in her Declaration. *Id.* at 18-19 (citing Ex. 1038, 9:23–24; Ex. 1037, 37:3–6). We note, however, that it is within our discretion to assign the appropriate weight to be accorded to the testimonial evidence of Dr. Morton and Dr. Nausbaum. Thus, we decline to dismiss testimony of Petitioner’s experts out-of-hand and will give it the weight we find to be appropriate.

3. *Anticipation under 35 U.S.C. § 102(e) of claims 1–5, 7–9, 12, and 13 by Lo*

Petitioner contends that Lo anticipates the challenged claims to the extent that they encompass shotgun sequencing, and also anticipates the claims to the extent they encompass sequencing of selected targeted subsequences. Pet. 20. Petitioner also sets forth a claim chart demonstrating where each element of the claims is taught by the reference, and relies, initially, on the Declaration of Dr. Morton (Ex. 1008), as well as the Declaration of Dr. Nussbaum (Ex. 1009). *Id.* at 21–27; *see also* Dec. Inst. 11–16 (applying the teaching of Lo to the challenged claims). Patent Owner disagrees with Petitioner’s assertions (PO Resp. 4–55), and relies on the Declaration of Dr. Detter (Ex. 2008) as evidence that Lo does not anticipate the challenged claims.

a. *Lo (Ex. 1004)*

Lo is drawn to “the diagnostic testing of fetal chromosomal aneuploidy by determining imbalances between different nucleic acid sequences, and more particularly to the identification of trisomy 21 (Down syndrome) and other chromosomal aneuploidies via testing a maternal sample (e.g., blood).” Ex. 1004 ¶ 3; *see also* ¶ 46 (defining “chromosomal aneuploidy” as “a variation in the quantitative amount of a chromosome from that of a diploid genome”). According to Lo, a number of sequences

are randomly sequenced, wherein the number is based on the desired accuracy. *Id.* ¶ 18. Lo defines “random sequencing” as

sequencing whereby the nucleic acid fragments sequenced have not been specifically identified or targeted before the sequencing procedure. Sequence-specific primers to target specific gene loci are not required. The pools of nucleic acids sequenced vary from sample to sample and even from analysis to analysis for the same sample. The identities of the sequenced nucleic acids are only revealed from the sequencing output generated.

Id. ¶ 47. Lo notes, however, that “the random sequencing may be preceded by procedures to enrich a biological sample with particular populations of nucleic acid molecules sharing certain common features.” *Id.*

Lo teaches that a biological sample, such as plasma or serum, is obtained from a pregnant female, wherein the sample contains nucleic acid fragments from both the fetus and the mother. *Id.* ¶ 54. The nucleic acid fragments may then be sequenced, for example, by using massively parallel sequencing methods. *Id.* ¶¶ 55–56. Bioinformatics analysis may then be used to identify those sequence reads which map to a chromosome of interest. *Id.* ¶¶ 57–58; *see also id.* ¶ 70 (noting that sequencing from “Illumina Genome Analyzer” results in “short sequence tags,” which “were aligned to the human reference genome sequence[,] and the chromosomal original was noted”). A second amount of one or more of a second chromosome is also determined. *Id.* ¶ 59. By taking into account the relative amount of the first chromosome to the second chromosome, a normalized frequency is obtained, which allows for the detection of an aneuploidy, such as a trisomy. *Id.* ¶ 69. Lo teaches generating sequence tags, which may be aligned to each chromosome, and compared to a

reference chromosome, to allow for the identification of chromosomal gains or losses. *Id.* ¶ 70.

Lo teaches that “the number of aligned sequenced tags were counted and sorted according to chromosomal location.” *Id.* ¶ 71. As taught by Lo, “[g]ains or losses of chromosomal regions or whole chromosomes were determined by comparing the tag counts with the expected chromosome size in the reference genome or that of a non-disease representative specimen.” *Id.*

Lo teaches another embodiment, wherein:

the fraction of the nucleic acid pool that is sequenced in a run is further sub-selected prior to sequencing. For example, hybridization based techniques such as oligonucleotide array could be used to first sub-select for nucleic acid sequences from certain chromosomes, e.g.,] a potentially aneuploid chromosome and other chromosome(s) not involved in the aneuploidy tested. Another example is that a certain sub-population of nucleic acid sequences from the sample pool is sub-selected or enriched prior to sequencing.

Id. ¶ 72.

In particular, Lo teaches that “sequences originating from a potentially aneuploid chromosome and one or more chromosomes not involved in the aneuploidy could be enriched by hybridization techniques for example onto oligonucleotide microarrays,” which sequences would then be subject to random sequencing. *Id.* ¶ 79. Lo teaches further that one aspect of this massively parallel sequencing approach is that representative data from all of the chromosomes may be generated at the same time. *Id.* ¶ 80. Lo explains that although the sequencing is done at random, a database search may be performed to identify the chromosome from which a particular fragment originates. *Id.*

b. Analysis

Lo teaches a method of testing for an abnormal distribution of a chromosome, using genomic material obtained from maternal blood. Lo ¶ 3. Thus, Lo is drawn to a “method of testing for an abnormal distribution of a chromosome in a sample comprising a mixture of maternal and fetal DNA,” as well as the step of “obtaining maternal and fetal DNA from said sample” as required by challenged claim 1.

Lo teaches also that the DNA fragments obtained from the sample may then be sequenced, for example, by using massively parallel sequencing methods. *Id.* ¶¶ 55–56. As taught by Lo, sequence tags are generated, aligned to each chromosome, and tags identified as originating from a potentially aneuploid chromosome are compared quantitatively to tags originating from a reference chromosome, to allow for the identification of chromosomal gains or losses. *Id.* ¶ 70. That falls within the scope of the limitation of step (b) of claim 1 of “sequencing predefined subsequences of the maternal and fetal DNA to obtain a plurality of sequence tags aligning to the predefined subsequences, wherein said sequence tags are of sufficient length to be assigned to a specific predefined subsequence.” That is, as construed above, the sequencing step is not limited to sequencing only the predefined subsequences, but encompasses sequencing other portions of the genome. And, as Lo teaches that the sequence tags are aligned to a chromosome to allow for the identification of chromosomal gains or losses (*id.* ¶ 70), the tags generated must necessarily be of sufficient length to be assigned to a specific predefined subsequence. *See, e.g.*, Ex. 1008 ¶ 60 (noting that although Lo “does not describe specifically that the sequence tags were of sufficient length to be assigned to a specific region of the

genome, one skilled in the art would understand this to be the case, because the sequence tags used to identify chromosomal origin must have been of sufficient length to allow assignment to a particular genomic region”).

Moreover, to the extent that the claim encompasses preselecting sequences, Lo teaches that a fraction of the nucleic acid pool may be further sub-selected prior to sequencing. Ex. 1004 ¶ 72. As taught by Lo, hybridization based techniques, such as the use of an oligonucleotide array, may be used to first sub-select for nucleic acid sequences from certain chromosomes, such as a potentially aneuploid chromosome, as well as a second chromosome not involved in the aneuploidy being tested. *Id.* Thus, although claim 1 does not specify a pre-selection step, Lo teaches a pre-selection step, wherein only certain subsequences of the total fraction of genomic material obtained from the maternal sample is sequenced, wherein the subsequences are selected for using a hybridization reaction, *e.g.*, such as hybridization to a DNA array.

In addition, Lo teaches that the sequencing data can be used to determine an amount of a “first chromosome,” such as the chromosome being tested for aneuploidy, as well as one or more second chromosomes in the sample. *Id.* ¶ 58. As taught by Lo, gains or losses of chromosomal regions or whole chromosomes may then be determined by comparing the tag counts with the expected chromosome size in the reference genome to that of the reference chromosome. *Id.* ¶ 71. Thus, Lo teaches the limitation of step (b) of claim 1: “the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one first chromosome suspected of having an abnormal

distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample.”

Lo teaches that the sequence tags that are generated are aligned to the human reference genome sequence in order to determine their chromosomal origin (*id.* ¶ 70), and thus discloses a step of “assigning the plurality of sequence tags to their corresponding predetermined subsequences,” as set forth in step (c) of claim 1. Although Lo states that the sequences are aligned with the reference genome sequence to determine their chromosomal origin, the sequence tags are nucleic acid fragments obtained from the maternal sample. Ex. 1004 ¶ 54. Thus, as the nucleic sample obtained from the pregnant female only contains chromosomal fragments, the fragments necessarily can only be aligned to the subsequence of the chromosome that corresponds to the sequence of the fragment.

As for step (d) of claim 1, which requires “determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome,” Lo discloses tabulating the total number of individual sequence tags aligned to each chromosome of the human reference genome sequence. Lo ¶ 70. Finally, Lo also teaches that “[g]ains or losses of chromosomal regions or whole chromosomes were determined by comparing the tag counts with the expected chromosome size in the reference genome or that of a non-disease representative specimen” (*id.* ¶ 71), and thus teaches step (e) of claim 1: “comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.”

Patent Owner argues that Lo cannot anticipate the challenged claims as “it does not teach at least the claimed element ‘sequencing predefined subsequences.’” PO Resp. 20. Patent Owner asserts that Lo teaches only random sequencing, and that even Petitioner’s expert, Dr. Morton, agrees that Lo does not teach how to pre-select nucleic acids for sequencing. *Id.* (citing Ex. 1037, 71–72). The random sequencing of Lo, Patent Owner argues, does not anticipate the claims when the claim term “predefined” is given the meaning of “targeted sequencing.” *Id.* at 24. That is, the claim requires “the pre-selection of sequences prior to the sequencing step.” *Id.* at 25.

Patent Owner asserts further that paragraph 72 of Lo does not teach “sequencing predefined subsequences,” and that the Declarations of Dr. Morten and Dr. Nussbaum do not provide any analysis as to why that paragraph of Lo teaches that limitation. *Id.* at 20. According to Patent Owner, Lo at paragraph 72 discloses that hybridization is used to select the entire chromosome for sequencing. *Id.* at 22 (citing Ex. 2008 ¶ 66).

Patent Owner contends further that we erred in instituting the challenge based on Lo. That is, in the Institution Decision, we construed “sequencing predefined subsequences” as requiring that the subsequences should uniquely map to a chromosome region of interest (Dec. Inst. 10), but Lo uses hybridization to select an entire chromosome for sequencing, and not just a selected subsequence or region of the chromosome. PO Resp. 21–22. Patent Owner contends that although Lo teaches that sequences from a potentially aneuploid chromosome, as well as one or more chromosomes not involved in the aneuploidy, could be enriched by hybridization techniques, and then subjected to random sequencing, “[a] person of ordinary skill in the

art would understand that enriching a pool of nucleic acids for sequences originating from a chromosome is not the same as sequencing only particular predefined subsequences of the chromosome.” *Id.* at 23 (citing Ex. 1004 ¶ 79; Ex. 2008 ¶ 68). We disagree.

Patent Owner’s arguments are premised primarily on a narrow construction of “sequencing predefined subsequences” as being drawn to “targeted sequencing,” wherein “only certain predefined sequences are actually sequenced”—a construction we have declined to adopt, as discussed above. *See* section II.A.3.

Moreover, to the extent that the claim requires preselecting sequences for sequencing, we do not find convincing Patent Owner’s argument that paragraph 72 of Lo does not teach a pre-selection step. Specifically, Patent Owner relies on the Declaration of Dr. Detter, who states that “using an array to select all fragments associated with an entire chromosome[] is not the same concept as predefining subsequences for sequencing as required by the claims of the Fan ’076 patent.” Ex. 2008 ¶ 66; *see also id.* ¶ 68 (noting that “a person of ordinary skill in the art would understand that enriching a pool of nucleic acids for sequences originating from a chromosome is not the same as sequencing only particular predefined subsequences of the chromosome as in a targeted sequencing approach”).

As noted above, the Specification of the ’076 patent nowhere uses the term “targeted sequencing.” In addition, although claim 1 uses the term “predefined subsequences,” neither the language of the claim, nor the remainder of the Specification, defines how the subsequence is predefined or predetermined. As discussed above in section II.A.3, although we construed a single subsequence as not encompassing an entire chromosomal sequence,

we noted that two or more subsequences can encompass the entire length of the chromosome.

As taught by Lo (¶ 72), and acknowledged in the Specification of the '076 patent (Ex. 1001, col. 4, ll. 41–44), the fetal nucleic acids present in maternal plasma are short fragments. Lo teaches the use of an *oligonucleotide* (i.e., a short nucleotide molecule) array to sub-select for sequences from certain chromosomes. Thus, although Lo may in fact be using the oligonucleotide array to sub-select for sequences along the entire length of a desired chromosome, the oligonucleotides that make up the array are selecting for subsequences of the chromosome, which subsequences may then be analyzed using massively parallel sequencing. Lo thus teaches sequencing of predefined subsequences of a chromosome.

Also, our finding that Lo anticipates the method of challenged claim 1 is not inconsistent with our construing “sequencing predefined subsequences” to mean “sequencing predefined nucleic acid molecules that uniquely map to a chromosome region of interest in a reference genome.” Specifically, as discussed above, the fetal nucleic acids that are present in plasma are short fragments. Lo teaches that the short sequence tags are aligned to a human reference sequence, and that the chromosomal origin is noted. Lo ¶ 70. Thus, in the alignment, the sequence tags are necessarily aligned with a region of the longer chromosome, given that the sequence tags are short fragments derived from chromosomal DNA.

For similar reasons, Patent Owner contends also that Lo does not disclose step (d) of claim 1, as “Lo makes it clear that predetermined sequences are not used in its method.” PO Resp. 28. Lo teaches that after massively parallel sequencing, the chromosomal location of the sequenced

tags was determined. Patent Owner argues that Petitioner does not explain how that “involves determining a number of sequence tags aligning to predetermined subsequences of chromosomes.” *Id.* That is, Patent Owner argues, “the Lo Publication makes clear that ‘massively parallel sequencing is not dependent on the detection or analysis of predetermined or a predefined set of DNA sequences.’” *Id.* at 29 (emphasis omitted) (citing Ex. 1004 ¶ 108).

Again, Patent Owner’s contentions are based, in large part, on a narrow construction of the term “sequencing predefined subsequences,” a construction we decline to adopt for the reasons set forth above. Moreover, to the extent that the claims requires sequencing predefined subsequences, wherein the sequences are molecularly selected, paragraph 72 of Lo discusses the use of an *oligonucleotide* array to sub-select for sequences from certain chromosomes. In addition, Lo teaches tabulating the total number of individual sequence tags aligned to each chromosome of the human reference genome sequence. *Id.* ¶ 70. Thus, when a potential aneuploid chromosome and a reference chromosome are preselected using a DNA array, only those fragments that hybridize to the array are sequenced and aligned with chromosomal sequences, i.e., the sequence of a potentially aneuploid chromosome, as well as the sequence of a selected reference chromosome. Ex. 1043 ¶ 15. That method would meet the limitation of “determining a number of sequence tags aligning to the predetermined subsequences” of challenged claim 1.

Patent Owner does not present separate argument as to claims 2, 5, 7–9, 12, and 13. As to claims 3 and 4, Patent Owner argues that “Lo does not

disclose the use of a massively parallel sequencing system that sequences predefined subsequences.” PO Resp. 29–30.

Lo teaches that “the fraction of the nucleic acid pool that is sequenced in a run is further sub-selected *prior* to sequencing.” Lo ¶ 72 (emphasis added). Thus, the sub-selection occurs prior to sequencing. Lo also teaches that nucleic acid fragments may be sequenced, for example, by using massively parallel sequencing methods. *Id.* ¶¶ 55–56. The ordinary artisan would understand that the sub-selection described by paragraph 72 of Lo could be performed before performing any of the sequencing methods disclosed by Lo, including massively parallel sequencing.

c. Conclusion

After considering Petitioner’s and Patent Owner’s positions, as well as their supporting evidence, we determine that Petitioner has shown by a preponderance of the evidence that claims 1, 3, and 4 are unpatentable under 35 U.S.C. § 102(e) as anticipated by Lo. In addition, we have reviewed Petitioner’s position and evidence as to claims 2, 5, 7–9, 12, and 13, and determine that Petitioner has also shown by a preponderance of the evidence that those claims are unpatentable under 35 U.S.C. § 102(e) as anticipated by Lo.

4. Obviousness of Claims 10 and 11 over the Combination of Lo and Brenner (Ex. 1003)

Petitioner contends that claims 10 and 11 are rendered obvious by the combination of Lo and Brenner (Pet. 28–29). Patent Owner presents no evidence or argument demonstrating how Petitioner’s contentions are incorrect. Upon review of claims 10 and 11, as well as the contentions and evidence relied upon by Petitioner, we determine that the preponderance of

the evidence of record demonstrates that those claims are rendered unpatentable by the combination of Lo and Brenner.

5. Obviousness of Claims 1–5 and 7–13 over the combination of Quake (Ex. 1006) and Kapur (Ex. 1005)

Petitioner contends that the combination of Quake and Kapur teaches all the limitations of the challenged claims (Pet. 29–39), and relies, initially, on the Declaration of Dr. Morton (Ex. 1008), as well as the Declaration of Dr. Nussbaum (Ex. 1009), for a rationale to combine those elements. Patent Owner disagrees with Petitioner’s assertions (PO Resp. 30–60) and relies on the Declaration of Dr. Detter (Ex. 2008) as evidence that it would not have been obvious for one of ordinary skill in the art to combine the teachings of the references in the manner set forth by Petitioner.

a. Quake (Ex. 1006)

Quake is drawn to the use of “digital PCR” to detect fetal aneuploidies, such as Down’s syndrome, which is a chromosomal trisomy. Ex. 1006 ¶ 9. In the method of Quake, a sample is obtained from the mother, wherein the sample is preferably maternal peripheral blood of blood plasma or serum, wherein the sample contains a mixture of maternal and fetal genetic material. *Id.* ¶ 26. The genetic material is then distributed into discrete samples, such that each sample does not contain, on average, more than one target sequence per sample. *Id.* ¶ 27. Quake teaches that “[t]he presence or absence of different target sequences in the discrete samples is detected; and the results are analyzed whereby the number of results from the discrete sample will provide data sufficient to obtain results distinguishing different target sequences.” *Id.* In addition, Quake uses a

control sequence to detect an abnormal increase in the target sequence, such as a trisomy. *Id.* ¶ 54.

Quake teaches further the quantitative analysis of the detection of maternal and fetal nucleic acid target sequences, which may “include targets to different regions such as probes to a target on a chromosome suspected of being present in an abnormal copy number (trisomy) compared to a normal diploid chromosome, which is used as a control.” *Id.* ¶ 61. Specifically, Quake teaches that detection may “be conveniently . . . carried out by a sequence specific probe,” or by “directly sequencing a region of interest to determine if it is the target sequence of interest.” *Id.* ¶ 84.

Quake teaches that the “method of differential detection of target sequences may involve direct sequencing of target sequences,” wherein the sequencing may be of a single molecule, or of an amplified derivative of the target molecule. *Id.* ¶ 33. Additionally, Quake teaches the use of massively parallel sequencing to detect the target sequence. *Id.* ¶ 120. Quake describes the use of microfluidics to achieve the digital PCR conditions, but notes that the sample need not be separated into separate wells, but may be isolated on different beads, or by adhering to different areas of a substrate. *Id.* ¶¶ 112, 116. As taught by Quake, “[o]nly about 30 [base pairs] of random sequence information are needed to identify a sequence as belonging to a specific human chromosome,” and teaches that software methods to identify a sequence to a known genome sequence are known. *Id.* ¶ 121.

b. Kapur (Ex. 1005)

Kapur discloses a method of enriching a rare cell population, such as fetal cells from a maternal peripheral blood sample, for the detection and diagnosis of fetal abnormalities. Ex. 1005 ¶ 5. Kapur teaches that genetic

conditions that can be determined include trisomy 13, trisomy 18, trisomy 21, Klinefelter Syndrome, dup(17)(11. 2p11. 2) syndrome, as well as Down syndrome. *Id.* ¶ 7. Specifically, according to Kapur, a sample from a pregnant female, such as a blood sample, is enriched for fetal cells. *Id.* ¶ 11. Genetic analysis is then performed on the cells, such as by SNP detection or RNA expression detection. *Id.* In some embodiments, the genetic analysis of SNP detection or RNA expression can be done using a microarray, wherein up to 100,000 SNPs may be detected in parallel, or 10,000 transcripts may be detected in parallel for detecting RNA expression. *Id.* ¶ 13. According to Kapur, the genetic analysis may be performed on DNA from chromosomes X, Y, 13, 18, or 21, and may also be performed on a control sample or reference sample, such as a maternal sample. *Id.* ¶ 114.

As taught by Kapur, the target cells can be selected and binned, resulting in the reduction of complexity and/or the total cell number of the output of the enriched cells. *Id.* ¶¶ 87–88. In order to analyze the genetic material, Kapur teaches that “target nucleic acids from a test sample are amplified and optionally results are compared with amplification of similar target nucleic acids from a non-rare cell population (reference sample).” *Id.* ¶ 109. According to Kapur, the nucleic acid of interest may also be preamplified, such as by amplification of outer primers in a nested PCR approach. *Id.* ¶ 111. The amplified nucleic acids may then be quantified, for example for determining gene or allele number, such as by using microarrays. *Id.* ¶ 112–113.

Kapur teaches:

In some embodiments, analysis involves detecting one or more mutations or SNPs in DNA from e.g., enriched rare cells or enriched rare DNA. Such detection can be performed using,

for example, DNA microarrays. Examples of DNA microarrays include those commercially available from Affymetrix, Inc. (Santa Clara, Calif.), including the Gene-Chip™ Mapping Arrays including Mapping 100K Set, Mapping 10K 2.0 Array, Mapping 10K Array, Mapping 500K Array Set, and GeneChip™ Human Mitochondrial Resequencing Array 2.0. The Mapping 10K array, Mapping 100K array set, and Mapping 500K array set analyze more than 10,000, 100,000 and 500,000 different human SNPs, respectively. . . . In some embodiments, a microarray is used to detect at least 5, 10, 20, 50, 100, 200, 500, 1,000, 2,000, 5,000[,] 10,000, 20,000, 50,000, 1,00[0],000, 200,000, or 500, 000 different nucleic acid target(s) (e.g., SNPs, mutations or STRs) in a sample.

Id. ¶ 114. Kapur also notes that computer implemented methods for estimating copy number based on hybridization intensity are known.

Id. ¶ 115.

Kapur provides an exemplary method in Figure 6, which is an overview of a process of using a SNP detection microarray. *Id.* ¶ 117.

Figure 7 is an overview of another method of detecting mutations or SNPs using bead arrays. *Id.* ¶ 123.

c. Analysis

Petitioner contends that “[i]t would have been obvious to use the sequencing by array methods taught by *Kapur* in combination with analysis of targeted gene loci taught by *Quake* to identify fetal abnormalities.” Pet. 30. Patent Owner responds that the combination of *Quake* and *Kapur* would not have rendered the method of the challenged claims obvious, as *Kapur* does not teach a method of sequencing by array, but in fact teaches a method of genotyping by single nucleotide polymorphism (“SNP”) analysis via a hybridization array. PO Resp. 32, 44. Thus, Patent Owner contends,

the ordinary artisan would not have used the SNP detection array as taught by Kapur as the sequencing method of Quake. *Id.* at 51.

According to Patent Owner, in a method of sequencing by array, the probes on the array “will contain all or most of the possible nucleotide combinations within a given length,” and the method is thus not sequence-dependent. *Id.* at 44; *see also id.* at 45–46 (describing a method of sequencing by hybridization). Arrays that are used for SNP detection, Patent Owner contends, are not the same as those used for sequencing by hybridization, as the SNP arrays do not contain every possible combination of nucleotides. *Id.* at 47–48; *see also id.* at 46–47 (describing a method of SNP detection). Patent Owner argues that the ordinary artisan also would have understood that sequencing by array, and the use of arrays to detect SNPs, are two separate fields. *Id.* at 48.

We agree with Patent Owner that, based on the record currently before us, Petitioner has not demonstrated that the ordinary artisan would have combined Quake and Kapur as set forth in the Petition (29–39) to arrive at the method of challenged claim 1.

In particular, Petitioner relies on Figures 6 and 7 of Kapur as teaching “a method for sequence determination of randomly generated DNA fragments using arrays having oligonucleotides of known sequence. Sequencing of a randomly generated genomic fragment via binding to a predefined sequence on an array aligns a random sequence to a probe indicative of a specific genomic region.” Pet. 31. The evidence relied upon by Petitioner does not explain, however, why one would have used a method for detecting SNPs as taught by Kapur to perform the sequencing of Quake. That is, what is lacking in the Petition and accompanying

Declarations is an “articulated reason[] with some rational underpinning to support the legal conclusion of obviousness.” *Kahn*, 441 F.3d at 988.

Petitioner responds that the “sequencing by array technology of Balasubramanian (US 2003/0022207 A1, published Jan. 30, 2003, Ex. 1040) is cited in all of Kapur (Ex. 1005 ¶ 163), Quake (Ex. 1006 ¶ 120), and the ‘076 patent (Ex. 1001 at col. 10, lines 50–56).” Paper 34 ¶ 19. Figures 6 and 7 relied upon by Petitioner, however, are drawn to methods of detecting SNPs, and not to the sequencing array technology of Balasubramanian. In fact, Petitioner first relies on paragraph 163 of Kapur, which it contends cites the sequencing array technology of Balasubramanian, in its challenge of claim 3, which is drawn to the use of massively parallel sequencing. Petitioner cannot rely upon Balasubramanian in its Reply to make up for the deficiencies in its Petition. *See, e.g.*, 37 C.F.R. § 42.23(b) (noting that “[a]ll arguments for the relief requested in a motion must be made in the motion,” and that a “reply may only respond to arguments raised in the corresponding opposition or patent owner response”).

Petitioner contends further that “Dr. Detter conceded on cross-examination that sequencing is detection and Prof. Morton concurs with that view.” Reply 14 (citing Ex. 2023, 59, ll. 20–23; Ex. 1043 ¶ 50). Specifically, in response to the question of whether you can detect nucleic acid by sequencing, Dr. Detter testified “[t]hat is what you detect by sequencing, is a nucleic acid.” Ex. 2023, 59, ll. 20–23. We do not disagree with Petitioner that, by virtue of the ability of the nucleic acid to hybridize to a sequence on the SNP array, the ordinary artisan would have understood that if the sequence of the sequence on the array is known, one can determine the sequence of the nucleic acid that hybridized to it. This

reasoning does not explain, however, why the ordinary artisan would have used the arrays for detecting SNPs as taught by Kapur in the method of Quake.

Moreover, in its observations of the cross-examination of Dr. Morton, Patent Owner argues that “Dr. Morton testified that people of ordinary skill in the art would not use or understand the term ‘sequencing’ to refer to the use of SNP detection arrays,” which is consistent with Dr. Nussbaum’s testimony. Paper 31, 8 (citing Ex. 1051, 139–141; Ex. 1038, 17–18); *see also id.* at 10 (noting that Dr. Morton stated on cross-examination that SNP detection as shown in Figure 6 of Kapur is not a sequencing method, but a genotyping method (citing Ex. 1051, 143–145)).

Specifically, Dr. Morton testified that SNP detection is “in some ways . . . sequencing, but not the way we would typically think of determining perhaps a sequence.” Ex. 1051, 139. According to Dr. Morton, it would be referred to as genotyping, noting, however, that the genotype is obtained from the sequence. *Id.* at 139. When asked whether “[u]sing these methods for genotyping would not be considered sequencing as you believe people skilled in the art use the term ‘sequencing,’” Dr. Morton responded:

I think using BeadChips and the Affy chips, people would typically refer to as genotyping and not sequencing. If I was going to tell somebody I was going to genotype a sample, they wouldn't necessarily -- if I was going to -- there wouldn't be a confusion between -- if I said I was going to sequence a sample, they'd think I'm going to get a different output than the genotyping, because the genotyping, you're looking for a specific SNP or to -- to classify that individual. But it is sequenced. It is nucleotide.

Id. at 141. Dr. Morton's testimony further supports our determination that the ordinary artisan would not have used the method of genotyping using SNP detection for the sequencing required by the method of Quake.

d. Conclusion

After considering Petitioner's and Patent Owner's positions, as well as their supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–5 and 7–13 are unpatentable under 35 U.S.C. § 103(a) as obvious over Quake and Kapur.

6. Obviousness of Claim 6 over the combination of Lo and Li (Ex. 1014), and Over Quake, Kapur, and Li

Petitioner contends that claim 6 is rendered obvious by the combination of Lo and Li, or the combination of Quake, Kapur, and Li (Pet. 58–59). Patent Owner presents no evidence or argument demonstrating how Petitioner's contentions are incorrect. Upon review of claim 6, as well as the contentions and evidence relied upon by Petitioner as to the combination of Lo and Li, we determine that the preponderance of the evidence of record demonstrates that the claim is rendered obvious by that combination.

As to the challenge based on the combination of Quake, Kapur, and Li, we have already determined that Petitioner has not established by a preponderance of the evidence that the combination of Quake and Kapur renders independent claim 1 obvious. For the same reasons, we conclude that Petitioner has not established by a preponderance of the evidence that the combination of Quake, Kapur, and Li renders claim 6, which is dependent on claim 1, obvious.

C. Patent Owner's Motion to Exclude Evidence (Paper 30)

Patent Owner asks us to exclude the Second Declaration of Dr. Morton (Ex. 1043), Exhibits 1044–1049, as well as the portions of Petitioner's Reply that rely on Exhibit 1043.

We relied only on paragraph 15 of Exhibit 1043, and did not rely on the remainder of that Declaration, nor did we rely on Exhibits 1044–1049 in making our final determination. We conclude, therefore, that it is unnecessary to consider Patent Owner's objections to the admissibility of those Exhibits, except to the extent that Patent Owner objects to the admissibility of paragraph 15 of Exhibit 1043.

As to paragraph 15 of Exhibit 1043, Patent Owner contends that the figure at the end of the paragraph contains an error. Paper 30, 7. That is, according to Patent Owner, “[w]hile most of the figure shows the life cycle of a single strand, the last element of the figure shows obtaining six sequence tags.” *Id.* Dr. Morton admitted, however, “that using the sequencing techniques described in Lo, one would only get a single sequence tag from a single strand.” *Id.* Patent Owner contends, therefore, that “the figure is both irrelevant under FRE 402 and misleading under FRE 403.” *Id.*

Patent Owner's objections go more to the weight that paragraph 15 of Exhibit 1043 should be afforded, rather than to its admissibility. It is within our discretion to assign the appropriate weight to be accorded to Dr. Morton's testimonial evidence. The Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented. *Gnosis S.P.A. v. S. Alabama Medical Science Foundation*, IPR2013-00118, slip op. at 43 (PTAB June 20,

2014) (Paper 64). *See also Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941) (“One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received.”). We thus decline to exclude paragraph 15 of Exhibit 1043.

III. CONCLUSION

Petitioner has shown by a preponderance of the evidence that claims 1–5, 7–9, 12, and 13 are unpatentable under 35 U.S.C. § 102(e) as anticipated by Lo;

Petitioner has shown by a preponderance of the evidence that claims 10 and 11 are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Lo and Brenner;

Petitioner has shown by a preponderance of the evidence that claim 6 is unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Lo and Li;

Petitioner has not shown by a preponderance of the evidence that claims 1–5 and 7–13 are unpatentable under 35 U.S.C. § 103(a) over the combination of Quake and Kapur; and

Petitioner has not shown by a preponderance of the evidence that claim 6 is unpatentable under 35 U.S.C. § 103(a) over the combination of Quake, Kapur, and Li.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 1–13 of the '076 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *denied* to the extent it seeks to exclude paragraph 15 of Exhibit 1043, and *dismissed* as moot as to the extent it seeks the exclusion of the remainder of Exhibit 1043, as well as Exhibits 1044–1049, as well as the portions of Petitioner's Reply that rely on Exhibit 1043; and

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.

IPR2013-00308
Patent 8,296,076 B2

For PETITIONER:

Greg Gardella
Scott McKeown
Kevin Laurence
OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, L.L.P.
cpdocketgardella@oblon.com
cpdocketmckeown@oblon.com
cpdocketlaurence@oblon.com

Dianna DeVore
ARIOSADIAGNOSTICS
ddevore@ariosadx.com

Sarah Brashears
CONVERGENT LAW GROUP LLP
sbrashears@covergentlaw.com

For PATENT OWNER:

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