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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NATERA, INC.,
Petitioner,

v.

ILLUMINA, INC.,
Patent Owner.

IPR2018-01317
Patent 9,493,831 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and TIMOTHY G. MAJORS, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

INTRODUCTION

Natera, Inc. ("Petitioner") filed a Petition (Paper 1 ("Pet.")), requesting an *inter partes* review of claims 1–10, 12–22, and 24 of U.S. Patent No. 9,493,831 B2 (Ex. 1001, "the '831 patent"). Illumina, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply (Paper 12), and Patent Owner filed a Sur-reply (Paper 13). We review the Petition under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim, we decline to institute an *inter partes* review of claims 1–10, 12–22, and 24 of the '831 patent.

Related Proceeding

According to the parties, Patent Owner asserted the '831 patent against Petitioner in *Illumina, Inc. v. Natera, Inc.*, Case No. 3:18-cv-01662 (N.D. Cal.). Pet. 9; Paper 5, 1.

The '831 Patent

The '831 patent relates to methods for selectively enriching non-random polynucleotide sequences, generating libraries of the selectively enriched sequences, and using the selectively enriched sequences for detection of fetal aneuploidy. Ex. 1001, Abstract.

Aneuploidy is a state where there is an abnormal number of chromosome(s), or parts of a chromosome. *Id.* at 13:42–44. An example of

aneuploidy is Down syndrome, which is caused by the presence of an extra copy of chromosome 21. *Id.* at 13:53.

According to the '831 patent,

> Massively parallel sequencing techniques are used for detection of fetal aneuploidy from samples that comprise fetal and maternal nucleic acids. Fetal DNA often constitutes less than 10% of the total DNA in a sample, for example, a maternal cell-free plasma sample. Sequencing a large number of polynucleotides to generate sufficient data for fetal aneuploidy detection can be expensive.

Id. at 1:24–30. Although prior art described methods for randomly enriching fetal nucleic acids in a cell-free maternal sample, the Specification continues, "[t]here is a need for a means of selectively enriching non-random fetal and maternal polynucleotide sequences in a way that facilitates aneuploidy detection by massively parallel sequencing techniques and increases the sensitivity of aneuploidy detection." *Id.* at 1:30–40.

In one aspect, the '831 patent discloses "methods for generating a library of enriched polynucleotide sequences. A library can be generated by the use of one or more amplification steps, which can introduce functional sequences in polynucleotide sequences that have been selectively enriched." *Id.* at 6:24–29. The examples of sequences introduced include those that serve as hybridization sites for oligonucleotides for sequencing, and those that identify that sample from which the library was generated. *Id.* at 6:30–32.

Illustrative Claims

Among the challenged claims, claims 1 and 14 are independent, and are reproduced below:

1. A method for preparing a sequencing library from a maternal blood sample, the method comprising:

a. obtaining a maternal blood sample comprising fetal and maternal cell-free DNA;

b. selectively enriching a plurality of non-random polynucleotide sequences of genomic DNA from said fetal and maternal cell-free DNA to generate a library of enriched non-random polynucleotide sequences, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from a chromosome tested for being aneuploid, said enriching comprising:

(i) a first amplification step to generate a plurality of first reaction products, said amplification comprising at least 100 first primers configured to amplify at least 100 different non-random polynucleotide sequences;

(ii) a second amplification step to generate a second reaction product, said amplification comprising a second set of primers comprising sequences contained in the first reaction products; and

(iii) a third amplification step to generate a third reaction product comprising said library of enriched non-random polynucleotide sequences, said amplification comprising a third set of primers comprising sequences contained in the second reaction products;

wherein at least one primer of at least one of the second and third sets of primers includes a sequence configured to be added to the different non-random polynucleotide sequences to permit the enriched non-random polynucleotide sequences of the library to anneal to a same sequencing primer for the enriched non-random polynucleotide sequences of the library.

14. A method for preparing a sequencing library from a maternal blood sample, the method comprising:

a. obtaining a maternal blood sample comprising fetal and maternal cell-free DNA;

b. selectively enriching a plurality of non-random polynucleotide sequences of genomic DNA from said fetal and maternal cell-free DNA to generate a library of enriched non-random polynucleotide sequences, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from a chromosome tested for being aneuploid, said enriching comprising:

(i) amplifying said plurality of non-random polynucleotide sequences from said maternal and fetal genomic DNA using a first pair of primers, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from a chromosome tested for being aneuploid;

(ii) amplifying the product of (i) with a second set of primers;

(iii) amplifying the product of (ii) with a third set of primers; and

wherein one of said second or third sets of primers includes an indexing sequence.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Ground	Claim(s)	Basis	Reference(s)
1	1–7, 10, 14–19, 22	§ 103	Fluidigm[1]
2	1–10, 13–22, 24	§ 103	Fluidigm and Sequenom[2]

[1] Mir et al., U.S. Pat. App. Pub. US 2010/0120038 A1, published May 13, 2010 (Ex. 1003, "Fluidigm").

[2] Lee et al., International Publication No. WO 2009/032781 A2, published March 12, 2009 (Ex. 1005, "Sequenom").

Ground	Claim(s)	Basis	Reference(s)
3	12	§ 103	Fluidigm and Harismendy[3]
4	12	§ 103	Fluidigm, Sequenom, and Harismendy

In support of its patentability challenges, Petitioner relies on the Declaration of Dr. Michael L. Metzker (Ex. 1002).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b)[4]; *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

[3] Harismendy et al., *Evaluation of next generation sequencing platforms for population targeted sequencing studies*, 10 GENOME BIOL. R32 (2009) (Ex. 1007).

[4] The Final Rule changing the claim construction standard does not apply here, as the Petition was filed before the effective date of the Final Rule, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,344 (Oct. 11, 2018).

Petitioner proposes that we construe the term "aneuploid." Pet. 18. Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe "aneuploid" or any other claim terms.

Ground 1: Obviousness over Fluidigm

Petitioner contends that claims 1–7, 10, 14–19, and 22 of the '831 patent would have been obvious over Fluidigm in view of the knowledge of a person of ordinary skill. Pet. 19–61. Based on the current record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

Fluidigm

Fluidigm relates generally to the area of high-throughput assays for detection of particular target nucleic acids. Ex. 1003, Abstract, ¶ 2. It teaches four methods for increasing the number of samples and/or targets that can be analyzed in a single assay. *Id.* The first two methods detect a plurality of target nucleic acids in a plurality of samples (*id.* ¶¶ 5, 13) and the last two detect a plurality of target nucleic acids in a sample (*id.* ¶¶ 21, 24). Specifically, the fourth assay method provides a modular approach,

> wherein the target nucleic acids to be detected are divided into sets or "modules," each module of target nucleic acids is tagged with the same set of nucleotide tag pairs. Within each module, the sets of tag pairs differ from one another, but same set of tag pairs is used for each module. Detection can then be carried out by amplifying each module with a set of primer pairs that anneals to the set of tag pairs.

Id. ¶¶ 24, 115.

Fluidigm also teaches that "[i]f desired, tagged target nucleotide sequences generated as described herein may be analyzed by DNA sequencing," using, for example, Solexa DNA sequencing. *Id.* ¶¶ 160, 161.

Claims 1–13

Claim 1 recites a method for "preparing a sequencing library," comprising, among other limitations, three amplification steps. Petitioner argues that the modular approach of Fluidigm "discloses the amplification steps of the '831 patent claims exactly." Pet. 22. Specifically, Petitioner asserts that the pre-preamplification, preamplification, and amplification steps of Fluidigm correlate to the three amplification steps of the challenged claims. *Id.* at 23–27 (citing Ex. 1003 ¶¶ 119–120; Ex. 1002 ¶¶ 98–102); *see also id.* at 42–46 (the same). For the purpose of this Decision, we accept Petitioner's position on this issue.

That, however, does not end our inquiry, because claim 1 also requires "at least one primer of at least one of the second and third sets of primers includes a sequence configured to be added to the different non-random polynucleotide sequences to permit the enriched non-random polynucleotide sequences of the library to anneal to a same sequencing primer for the enriched non-random polynucleotide sequences of the library."

On this limitation, Petitioner argues "Fluidigm teaches that its embodiments (including the Modular Embodiment) can introduce adaptor sequences." Pet. 29 (citing Ex. 1003 ¶¶ 160–161). According to Petitioner, "[a]daptor sequences are typically DNA sequences that will anneal to a sequencing primer," and "[s]uch sequencing primers, in turn, were used by sequencing systems such as the Solexa (later acquired by Illumina) system,

which is also expressly taught by Fluidigm." *Id.* (citing Ex. 1003 ¶ 161; Ex. 1002 ¶ 106). The Petition continues:

> Fluidigm teaches using adaptors in connection with its multi-step amplification-based DNA library preparation methods, followed by Solexa sequencing. (Ex. 1003, ¶0160)(Ex. 1004, ¶0135)(Ex. 1002, ¶106). It would have been obvious to a person of ordinary skill that a sequencing adaptor could be added by the PCR steps in Fluidigm. (Ex. 1002, ¶106). For example, the various amplification steps of Fluidigm's Modular Approach can be used to introduce a tag sequence, and it would have been obvious to include a sequencing adaptor next to the tag sequence, based on Fluidigm's express teaching. (Ex. 1002, ¶106).

Id. at 29–30; *see also id.* at 47–51 (the same).

Patent Owner counters that Fluidigm undermines Petitioner's argument on this issue. Prelim. Resp. 26. According to Patent Owner,

> To satisfy the last limitation of Claim 1, the Petition points to the version of the Modular Approach that involves three PCR amplification steps in combination with a sequencing embodiment from a separate section of Fluidigm. However, the third PCR step in the Modular Approach is used to detect the assay products, not to further amplify the sample prior to detection. The sequencing embodiment only utilizes **two** amplifications steps. The Petition provides no rationale or explanation for combining the PCR-based detection step in the Modular Approach with an additional sequencing detection step.

Id. at 26–27. We find Patent Owner's argument more persuasive.

In Fluidigm, an encoding reaction produces a set of tagged target nucleotide sequences. Ex. 1003 ¶ 24, *see also id.* ¶ 63 ("As used herein an 'encoding reaction' produces a "tagged target nucleotide sequence."). In the modular approach, which Petitioner relies on for teaching the three amplification steps, the encoding reaction is the second step, i.e., the pre-amplification step. *Id.* ¶ 119. Petitioner acknowledges so. *See* Pet. 23

("The Fluidigm Modular Approach next performs a second 'encoding preamplification' step."), *id.* at 24 ("Fluidigm describes the 'encoding pre-amplification' step immediately after describing the 'pre-pre-amplification step[.]'"), *id.* at 27 (stating the "encoding preamplification" step is the "2nd amplification step").

In the modular approach, Fluidigm teaches detecting the "tagged target nucleotide sequences" produced by the "encoding preamplification" step using amplification-based methods. Ex. 1003 ¶ 117 ("Detection of the tagged target nucleotide sequences can be carried out by separately subjecting each aliquot to amplification."). Thus, we agree with Patent Owner that "[t]he **third** PCR step of the Modular Approach is therefore used as a means for **detecting** the tagged target nucleotide sequences produced during the **second** PCR step." Prelim. Resp. 28–29.

Petitioner is correct that Fluidigm also teaches analyzing the tagged target nucleotide sequences by DNA sequencing. Pet. 29, 47; Ex. 1003 ¶ 160. As explained above, however, in the modular approach, the tagged target nucleotide sequences are generated by the second amplification step. Thus, we agree with Patent Owner that "if a POSA had elected to use sequencing as a detection method in Fluidigm's Modular Approach, the sequencing would be used to analyze the PCR products from the **second** (not third) step of the Modular Approach." Prelim. Resp. 29. Petitioner does not sufficiently address why an ordinary artisan would have used sequencing to analyze the products of the third amplification step, which is itself a detection step. As a result, we find Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claim 1 under this Ground. *See In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir.

2000) ("Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference.").

Because each of claims 2–13 depends from claim 1, we similarly find Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any of those claims under this Ground.

Claims 14–24

Claim 14 is also directed to a method for preparing a sequencing library, comprising, among others, three amplification steps. It further requires that "one of said second or third sets of primers includes an indexing sequence."

Petitioner argues that "[i]t would have been obvious to use a primer in the second step of Fluidigm's Modular Approach to also **add an index to the enriched non-random polynucleotide sequences of the library, the index being indicative of the maternal blood sample from which the library was generated**." Pet. 51 (citing Ex. 1002 ¶ 152). As support, Petitioner refers to the following:

> In certain embodiments, the method entails providing **S samples that will be mixed together** prior to assay, where S is an integer greater than 1. Each of these samples can be **separately subjected to an encoding reaction** that produces a set of T tagged target nucleotide sequences, **each tagged target nucleotide sequence comprising a sample-specific nucleotide tag** and a target nucleotide sequence.

Id. at 52 (quoting Ex. 1003 ¶ 5) (emphases added by Petitioner). We are not persuaded.

In determining obviousness, the inquiry is not whether each element existed in the prior art, but whether the prior art made obvious the invention

as a whole. It is not proper to dissect a claim and reconstruct it in piecemeal fashion by picking and choosing from among different methods using the challenged patent as a blueprint.

For claim 14, Petitioner again relies on the modular approach in Fluidigm as teaching the three amplification steps. Pet. 58–59 (stating the analyses on these limitations are the same as those provided in claim 1). The modular approach, which is the fourth assay method in Fluidigm, is for "detecting a plurality target nucleic acids in *a sample*." Ex. 1003 ¶ 24 (emphasis added). In contrast, the excerpt Petitioner relies on for suggesting adding an index sequence describes a different assay. *Id.* ¶ 5 ("The invention provides a *first assay method* for detecting a plurality of target nucleic acids (i.e., T target nucleic acids, where T is an integer greater than one) in *a plurality of samples*.") (emphases added).

The '831 patent discloses that an indexing sequence "allows multiple samples to be pooled without loss of information with respect to which sample a fragment originated." Ex. 1001, 22:26–28. As Patent Owner pointed out, Petitioner "fails to articulate any reason to use an indexing sequence in an assay that has a single sample." Prelim. Resp. 40. Petitioner argues that Fluidigm teaches "samples from different individuals *can* be mixed, and when mixed, the samples *should* be tagged to identify the origin of the sample." Pet. 51 (emphases added). But, "obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Here, Petitioner does not sufficiently explain why an

ordinary artisan would have modified Fluidigm's modular approach from analyzing a single sample to analyzing a plurality of samples.

As a result, we find Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claim 14 under this Ground. Because each of claims 15–24 depends from claim 14, we similarly find Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any of those claims under this Ground.

Other Grounds

In Ground 2, Petitioner argues that claims 1–10, 13–22, 24 would have been obvious over Fluidigm and Sequenom. Pet. 61–69. In Grounds 3 and 4, Petitioner further asserts that claim 12 would have been obvious over Fluidigm and Harismendy, or over Fluidigm, Sequenom, and Harismendy. *Id.* at 70–76. Based on the current record, we determine Petitioner has not established a reasonable likelihood that it would prevail in these assertions.

For Ground 2, Petitioner contends that "Fluidigm and the knowledge of the person of skill in the art are applied in the same manner as in Ground 1, and the discussion from Ground 1 is applied to Ground 2 in the same way." *Id.* at 62. Specifically, Petitioner relies on Sequenom for (1) "document[ing] that fetal DNA in maternal blood samples was known to be of a length that meets the limitations of claims 8, 9, 20 and 21;" and (2) "expressly identifyi[ng] trisomy 13, 18 and 21 as types of chromosomal aneuploidy that are desirably diagnosed using fetal DNA found in maternal blood." *Id.* at 62–63. Because Petitioner does not rely on Sequenom to remedy the deficiencies of Fluidigm as discussed above, Petitioner has not

established a reasonable likelihood that it would prevail in showing the unpatentability of any of the claims under this Ground.

For Ground 3, Petitioner argues that "Fluidigm is applied in the same manner as in Ground 1." Pet. 72. Petitioner relies on Harismendy for "demonstrate[ing] that it would have been obvious to target portions of the genome that sequence at a five-fold faster rate than other sequences on the same chromosome." *Id.* Petitioner also asserts that "Ground 4 is the same as Ground 3, but based on Ground 2 instead of Ground 1." *Id.* at 76. Because Petitioner does not rely on Harismendy to remedy the deficiencies of Fluidigm as discussed above, Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claim 12 under these Grounds.

CONCLUSION

On this record, Petitioner has not demonstrated a reasonable likelihood of prevailing on its challenges to the patentability of any challenged claim of the '831 patent on the grounds asserted in the Petition.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for *inter partes* review of claims 1–10, 12–22, and 24 of the '831 patent is denied and no *inter partes* review is instituted.

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