

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

IPR2019-00634
Patent 9,840,743 B2

Before TINA E. HULSE, JOHN E. SCHNEIDER,
and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

JUDGMENT

Final Written Decision

Determining Some Challenged Claims Unpatentable

Denying Patent Owner's Motion to Amend

Denying Patent Owner's Motion to Exclude

Denying Petitioner's Motion to Exclude

35 U.S.C. § 318(a)

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–26 of U.S. Patent 9,840,743 B2 (“the ’743 patent,” Ex. 1001). We have jurisdiction under 35 U.S.C. § 6, and enter this decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Foundation Medicine, Inc., (“Petitioner”) has shown by a preponderance of the evidence that claims 1–9, 20, and 22–26 are unpatentable, but has not shown that claims 10–19 or 21 are unpatentable. Additionally, we deny the contingent Motion to Amend filed by Guardant Health, Inc. (“Patent Owner”).

A. Procedural History

Petitioner filed a petition for *inter partes* review of the challenged claims under 35 U.S.C. § 311. Paper 2 (“Pet.”). Petitioner supported the Petition with the Declaration of Dr. Stacy Gabriel. Ex. 1002. Patent Owner filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). Petitioner submitted an authorized Reply to the Preliminary Response. Paper 9

On August 19, 2019, pursuant to 35 U.S.C. § 314(a), we instituted trial to determine whether any of the challenged claims are unpatentable on the grounds raised in the Petition. Paper 10. (“Inst. Dec.”). In our Decision, we declined to exercise our discretion to deny the Petition under 35 U.S.C. § 314(a). Inst. Dec. 33–42.

Patent Owner filed a Response to the Petition. Paper 25 (“PO Resp.”). Patent Owner supported the Response with the Declaration of Carlos D. Bustamante, Ph.D. (Ex. 2023) and the Declaration of Dr. John Quackenbush (Ex. 2026). Petitioner filed a Reply to the Patent Owner Response. Paper 33 (“Pet. Reply”). Patent Owner filed a Sur-Reply. Paper 37 (“PO Sur-Reply”).

Patent Owner filed a Contingent Motion to Amend. Paper 26 (“MTA”). Patent Owner supported the Motion to Amend with the Declaration of Carlos D. Bustamante, Ph.D. (Ex. 2024). Petitioner filed an Opposition to the Motion to Amend. Paper 34 (“MTA Opp.”). Petitioner supported the Opposition with the Declaration of Dr. Stacy Gabriel (Ex. 1060). Patent Owner filed a Reply to Petitioner’s opposition to the motion. Paper 36 (“MTA Reply”). Petitioner filed a Sur-Reply. Paper 44 (“MTA Sur-Reply”).

On May 13, 2020, the parties presented argument at an oral hearing. Paper 41. The hearing transcript has been entered into the record. Paper 51 (“Tr.”).

B. Real Parties in Interest

Petitioner identifies the real parties in interest as Foundation Medicine, Inc. and Roche Holdings, Inc., Roche Finance Ltd., and Roche Holding Ltd. Pet. 73. Patent Owner identifies Guardant Health, Inc. as the real party in interest.

C. Related Matters

Petitioner represents that the ’743 patent has been asserted in two infringement actions, *Guardant Health, Inc. v. Foundation Medicine, Inc.*, C.A. No. 17-cv-1616-LPS-CJB (D. Del.) and *Guardant Health, Inc. v. Personal Genome Diagnostics, Inc.*, C.A. No. 17-cv-1623-LPS-CJB (D. Del.). Pet. 73–74.

Petitioner has also filed petitions challenging Patent Owner’s related patents as follows: IPR2019-00636 (challenging U.S. Patent No. 9,902,992); IPR2019-00637 (also challenging U.S. Patent No. 9,902,992); IPR2019-00652 (challenging U.S. Patent No. 9,834,822); IPR2019-00653 (also

challenging U.S. Patent No. 9,834,822); and IPR209-00130 (challenging U.S. Patent 9,598,731). Paper 3.

Personal Genome Diagnostics, Inc. (“PGDx”) also filed a petition seeking post-grant review of the ’743 patent, designated PGR2018-00057. That proceeding was terminated without final decision on July 5, 2018. PGR2018-00057, Paper 9.

D. The ’743 Patent

The ’743 patent, titled “Systems and Methods to Detect Rare Mutations and Copy Number Variation,” issued on December 12, 2017, from U.S. Patent Application No. 15/467,570, filed on March 23, 2017. Ex. 1001, codes (54), (45), (21), (22). The ’743 patent is a continuation of U.S. Patent Application No. 14/425,189, filed on September 4, 2013. The ’743 patent claims priority to U.S. Provisional Application No. 61/845,987, filed on July 13, 2013; U.S. Provisional Application No. 61/793,997, filed on March 15, 2013; U.S. Provisional Application 61/704,400, filed on September 12, 2012; and U.S. Provisional Application No. 61/696,734, filed on September 4, 2012. *Id.*, code (60).

The ’743 patent involves a system and method for detecting rare mutations and copy number variations in cell free polynucleotides. Ex. 1001, code (57). The ’743 patent teaches that cell-free DNA (“cfDNA”) found in different types of bodily fluids may be used to detect and monitor disease. For instance, cfDNA may contain genetic aberrations like a change in copy number variation and/or single or multiple nucleic acid sequence variation associated with a particular disease that may be used to detect or monitor such disease. *Id.* at col. 1, ll. 29–45, col. 30, ll. 9–12.

The ’743 patent states that the disclosed system and method generally “comprise sample preparation, or the extraction and isolation of cell free

polynucleotide sequences from a bodily fluid; subsequent sequencing of cell free polynucleotides by techniques known in the art; and application of bioinformatics tools to detect rare mutations and copy number variations as compared to a reference.” *Id.* at col. 30, ll. 11–20.

E. Illustrative Claims

Of the challenged claims, claims 1 and 10 are independent. Claims 2–9, 20, and 22–26 depend, directly or indirectly, from claim 1. Claims 11–19 and 21 depend, directly or indirectly, from claim 10. Claims 1 and 10 read as follows:

1. A method for detecting copy number variation, comprising:
 - a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads;
 - b) filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold;
 - c) mapping the plurality of sequence reads to a reference sequence;
 - d) quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence; and
 - e) determining copy number variation in one or more of the plurality of predefined regions by:
 - i) normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or
 - ii) processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample.

10. A method for detecting a rare mutation in a cell-free or substantially cell-free sample obtained from a subject, comprising:

- a) sequencing extracellular polynucleotides from a bodily sample from the subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads;
- b) filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold;
- c) mapping sequence reads derived from the sequencing onto a reference sequence;
- d) determining unique sequence reads corresponding to the extracellular polynucleotides from among the sequence reads;
- e) identifying a subset of mapped unique sequence reads that include a variant as compared to the reference sequence at each mappable base position;
- f) for each mappable base position, calculating a ratio of (a) a number of mapped unique sequence reads that include a variant as compared to the reference sequence, to (b) a number of total unique sequence reads for each mappable base position; and
- g) processing the ratio with a similarly derived number from a reference sample.

Ex. 1001, col. 62, ll. 43–65, col. 63, ll. 26–49.

F. Evidence

Petitioner relies on the following references:

Chiu et al., *Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma*, 105 PROC. NAT. ACAD. SCI. 20458 (2008) (“Chiu”) Ex. 1022.

Kinde et al., *Detection and quantification of rare mutations with massively parallel sequencing*, 108 PROC. NAT. ACAD. SCI. 9539 (2011) (“Kinde 2011”) Ex. 1023.

Kinde et al., *FAST-SeqS: A Simple and Efficient Method for the Detection of Aneuploidy by Massively Parallel Sequencing*, 7 PLOS ONE e41162 (2012) (“Kinde 2012”) Ex. 1041.

Forsheew et al., *Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA*, 4 SCI. TRANSL. MED. 1 (2012) (“Forsheew”) Ex. 1035.

G. Asserted Grounds

Petitioner asserts that claims 1–26 would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–3, 22–26	102(a) ¹	Chiu
1–9, 20, 22–26	103	Kinde 2011, Kinde 2012
10–13, 15–19, 21	103	Kinde 2011, Forsheew
14	103	Kinde 2011, Kinde 2012, Forsheew

II. ANALYSIS

A. Legal Standards

To prevail in this *inter partes* review, Petitioner must demonstrate by a preponderance of the evidence that the claims of the ’743 patent are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d) (2017). “In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”). That burden of persuasion never shifts to Patent Owner.

¹ The provisions of the America Invents Act regarding novelty and obviousness apply to patents containing at least one claim having an effective filing date on or after March 16, 2013. Pub L. 112–29. The ’743 patent is subject to the novelty and obviousness provisions of the AIA. Ex. 1036, 4.

Dynamic Drinkware, LLC v. Nat'l Graphics, Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

“Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference.” *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). “[U]nless a [prior art] reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, “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 before the effective filing date of the invention.” 35 U.S.C. § 103 (2013); *see also 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 the scope and content of the prior art, any differences between the claimed subject matter and the prior art, the level of ordinary skill in the art, and objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing “mere conclusory statements.” *Magnum Oil*, 829 F.3d at 1380. Moreover, a decision on the ground of obviousness must include “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988

(Fed. Cir. 2006)). “An obviousness determination requires finding both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016)). “The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention.” *Intelligent Bio-Sys., Inc.*, 821 F.3d at 1367. A reasonable expectation of success “does not require absolute predictability of success . . . all that is required is a reasonable expectation of success.” *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)).

We analyze Petitioner’s asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int’l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner contends that a person of ordinary skill in the art at the time the ’743 patent was filed would have had “a Ph.D. in genetics, molecular biology, bioinformatics or a related field, and at least five years of research in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics.” Pet. 16 (citing Ex. 1002 ¶ 66). Petitioner also contends that the person of ordinary skill in

the art would “have had knowledge of DNA sequencing, including next generation sequencing (NGS) and related sequencing methods, and related sample preparation techniques; bioinformatics methods for grouping and comparing sequence reads and mapping sequence reads onto genomes; and methods for identifying genetic variants in a sample.” *Id.*

Patent Owner has not proposed a definition of a person of ordinary skill in the art although Dr. Bustamante testified that the definition above describes “a person of exceptional skill, not a person of ordinary skill in the art.” Ex. 2023 ¶ 28. Nevertheless, Dr. Bustamante adopted Petitioner’s definition in his analysis of the claims. *Id.* ¶ 29.

Accordingly, for this Decision, we adopt Petitioner’s definition, while maintaining that the prior art demonstrates the appropriate level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect appropriate level of ordinary skill in art). Moreover, we have reviewed the credentials of Drs. Gabriel, Bustamante, and Quackenbush, and consider each of them to be qualified to provide their opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention.

C. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.* Furthermore, we only need to construe terms that are in controversy, and to the extent necessary to resolve the controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868

F.3d 1013, 1017 (Fed. Cir. 2017); *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

While Petitioner contends that all the claim terms should be given their ordinary meaning and that no claim construction is needed, Patent Owner has identified three terms that require construction: “predefined regions,” “copy number variation,” and “unique sequence read.” PO Resp. 9–22. We will address each of these terms in turn.

1. Predefined Regions

In our Decision to Institute, we determined that the term “predefined regions” is not limited to any specific number of base pairs, but encompasses any predefined region of a genome, including an entire chromosome. Inst. Dec. 8.

Patent Owner contends that the construction we adopted is in error as it does not make sense in the context of the claims. PO Resp. 11. Patent Owner contends that the term in step (e) of claim 1 calling for normalizing the number of reads “in the plurality of predefined regions” does not make sense if the predefined region is a chromosome. *Id.* According to Patent Owner, step (e) excludes reading the term to include chromosomes as the term calls for looking for copy number variation *within* the chromosome, not *between* chromosomes. *Id.* at 11–12. Patent Owner contends that the step of normalizing the reads within a chromosome would yield information about the relative size of the chromosomes, but would not yield information about the number of chromosomes. *Id.* at 12–13 (citing Ex. 2023 ¶ 43).

Patent Owner also contends that the Specification supports a narrower construction of the term “predefined regions.” PO Resp. 12–13. Patent Owner points to the passage in the Specification where it states that “[i]n some embodiments the predefined regions are uniform or substantially

uniform in size. In some embodiments, the predefined regions are at least about 10 kb, 20 kb, 30 kb[,] 40 kb, 50 kb, 60 kb, 70 kb, 80 kb, 90 kb, or 100 kb in size. In some embodiments, at least 50, 100, 200, 500, 1000, 2000, 5000, 10,000, 20,000, or 50,000 regions are analyzed.” PO Resp. 13; Ex. 1001, col. 16, ll. 7–12. Patent Owner acknowledges that the Specification refers to these kilobase ranges as specific embodiments but contends that, when read in context, the Specification supports Patent Owner’s construction. PO Resp. 14.

Patent Owner contends that while the portions of the Specification cited in our Decision to Institute refer to regions in the genome without any limitation on the number of base pairs, those portions of the Specification do not support interpreting the term to embrace entire chromosomes. *Id.* at 14–15.

Petitioner responds by contending that Patent Owner’s proposed construction would result in reading a limitation from a specific embodiment into the claim, something our reviewing court has held to be improper. Pet. Reply 10 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005); *Cont’l Circuits LLC v. Intel Corp.*, 915 F.3d 788, 796–96 (Fed. Cir. 2019)).

Petitioner also contends that the Board’s preliminary construction was proper and supported by the Specification. Pet. Reply 10–11. Petitioner contends that the definition adopted by the Board is consistent with a person of ordinary skill in the art’s understanding of the term. *Id.* at 11 (citing Ex. 1002 ¶¶ 88, 96; Ex. 2022, 71–72).

Petitioner contends that the language of the claims does not support Patent Owner’s contention that “predefined region” cannot be a complete chromosome. Pet. Reply 11–12. Petitioner points out that the actual

language of the claims refers to normalizing reads “in a plurality of predefined regions” and that this would include a set of chromosomes. *Id.* Petitioner contends that Dr. Bustamante testified that step (e)(i) does not require normalization to a single region but includes determining copy number variation among the plurality of regions. *Id.* (citing Ex 1050, 168).

We have considered the arguments advanced by the parties and the evidence of record and we conclude that we did not err in our original construction of the term “predefined regions.” The portions cited by Patent Owner in support of its construction make clear that the base pair discussion is directed to specific embodiments and not the invention as a whole. *See, e.g.,* Ex. 1001, col. 16, ll. 9–10 (stating “[i]n some embodiments” the predefined regions are specific sizes). Patent Owner does not point to, nor do we discern, anything in the intrinsic evidence to support a conclusion that Patent Owner intended this narrow definition to apply to all embodiments. Rather, as we found in our Decision to Institute, the Specification teaches that predefined regions can be any region in a genome. Inst. Dec. 7–8 (citing Ex. 1001, col. 5, l. 22, col. 10, l. 50; col. 17, l. 32, col. 25, ll. 2–3). And Patent Owner acknowledges that a chromosome is a part of a genome. PO Resp. 14–15.

We are unpersuaded by Patent Owner’s argument that interpreting the term “predefined regions” would not make sense in the context of step (e)(i), which calls for normalization of the reads in the plurality of predefined regions to each other. PO Resp. 11–12. As Petitioner points out, Patent Owner’s argument is premised on normalizing reads in each of the predefined regions to each other, i.e., on the same chromosome. Pet. Reply 12; PO Resp. 11–13. Claim 1, however, reads normalizing “a number of reads in the plurality of predefined regions to each other,” which includes

normalizing among multiple predefined regions, such as a set of chromosomes. Indeed, Dr. Bustamante admits that step (e)(i) is not limited to normalizing in a single region but includes determining copy number variation among a plurality of regions. Ex. 1050, 168.

2. *Copy Number Variation*

In our Decision to Institute, we construed the term “copy number variation” (CNV) to include aneuploidy. Inst. Dec. 11.

Patent Owner contends that we erred in construing the term to include aneuploidy, because the Specification teaches that CNV and aneuploidy are two separate and distinct genetic variations. PO Resp. 17. Patent Owner also contends that construing the term to exclude aneuploidy is consistent with Patent Owner’s proposed construction of predefined region being a region smaller than a chromosome. *Id.*

Patent Owner contends that its proposed construction is consistent with how the term is defined in the art. *Id.* at 20–21. Patent Owner contends that the COSMIC² database teaches that copy number variations occur on a chromosome. *Id.* at 20 (citing Ex. 2035, 1). Patent Owner argues that Loo³ distinguishes between ploidy and copy number variation. *Id.* at 21.

We have considered the arguments of the parties and the evidence of record and conclude that we did not err in construing the term “copy number variation” to include aneuploidy.

² The Catalogue of Somatic Mutations in Cancer (COSMIC) is a database containing information on somatic mutations in human cancer. Ex. 1058, 1.

³ Loo et al., *Allele-specific copy number analysis of tumors*, 107 PROC. NAT. ACAD. SCI. 16910 (2010) (Ex. 2036, “Loo”).

The Specification refers to aneuploidy as a type of copy number variation that can be detected by the disclosed method. The '743 patent states:

For example, for quantitative analysis, a measure, e.g., a count, of the amount of tagged parent molecules mapping to a reference sequence is determined. This measure can be compared with a measure of tagged parent molecules mapping to a different genomic region. That is, the amount of tagged parent molecules mapping to a first location or mappable position in a reference sequence, such as the human genome, can be compared with a measure of tagged parent molecules mapping to a second location or mappable position in a reference sequence. This comparison can reveal, for example, the relative amounts of parent molecules mapping to each region. *This, in turn, provides an indication of copy number variation for molecules mapping to a particular region.* For example, if the measure of polynucleotides mapping to a first reference sequence is greater than the measure of polynucleotides mapping to a second reference sequence, *this may indicate that the parent population, and by extension the original sample, included polynucleotides from cells exhibiting aneuploidy.*

Ex. 1001, col. 35, ll. 8–31 (emphases added).

During oral argument counsel for Patent Owner was asked about whether this passage taught that aneuploidy fell within the definition of copy number variation as the term is used in the '743 patent. Tr. 47–49. Counsel for Patent Owner responded that this section of the '743 patent actually distinguishes between aneuploidy and copy number variation. Tr. 72–73. Specifically, Patent Owner explained:

[I]t's a comparison. So, the reasoning is that if you have two chromosomes and you have a predefined region of 50 being mapped to Chromosome A and you have counts for 100 being mapped to Chromosome B, you don't know if it's a predefined region or if it's simply because Chromosome B is duplicated or

aneuploidy. So that is what that is trying to do, is a comparison of the relative amounts of the parent molecules, which provides the copy number variation for the molecules mapping to a particular region. And then, it goes on to measure the polynucleotides. They're comparing, then, to the referenced sequences. And I think the goal there is, by extension, the original sample included polynucleotides from cells exhibiting aneuploidy. So, that's the point, is to exclude that possibility.

Id.

We are unpersuaded by this argument. We find that the Specification teaches that the method described in the '743 patent can be used to detect aneuploidy, which is an example of copy number variation. The Specification explains that comparing the relative amounts of parent molecules mapping to two different locations can “provide[] an indication of copy number variation for molecules mapping to a particular region.” Ex. 1001, col. 35, ll. 20–22. The Specification then provides an example of this, where the amount of polynucleotides mapping to a first reference sequence is greater than the amount of polynucleotides mapping to a second reference sequence. *Id.* at col. 35, ll. 22–25. According to the Specification, “this may indicate that the parent population, and by extension the original sample, included polynucleotides from cells exhibiting aneuploidy.” *Id.* at col. 35, ll. 25–27. Thus, we read this paragraph as teaching that comparing relative amounts of parent molecules can provide an indication of copy number variation, and an example of this may indicate that the parent population includes cells with aneuploidy. In other words, the Specification teaches that aneuploidy is a type of copy number variation.

Patent Owner argues that the Specification teaches that copy number variation and aneuploidy are distinct types of mutations. PO Resp. 18. In support of this contention, Patent Owner cites to the passages in the

Specification that list various genetic aberrations that can be detected by the disclosed method. *Id.* (citing Ex. 1001, col. 52, ll. 15–20). Patent Owner contends that, because copy number variation and aneuploidy are listed separately, one skilled in the art would consider them to be two distinct disorders. *Id.*

We are not persuaded by this argument. While the Specification lists copy number variation and aneuploidy separately, as we noted in our Decision to Institute, many of the terms listed in the cited paragraph are synonyms or subsets of each other. Inst. Dec. 9–11. The Specification states that the method disclosed therein may detect any number of genetic aberrations, including, but not limited to:

mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer.

Ex. 1001, 52:17–26. Arguably, most, if not all, of the genetic aberrations listed after “mutations” are types of mutations. And Patent Owner admitted that copy number variations are a type of rare mutation. Prelim. Resp. 16 (“Claims 1 and 10 . . . are directed to methods for detecting rare mutation, such as copy number variation . . .”). Thus, Patent Owner’s argument that the Specification distinguishes between aneuploidy and copy number variation because it lists them as separate genetic aberrations is not persuasive.

The extrinsic evidence cited by Patent Owner does not compel a different interpretation. The page from the COSMIC database is an explanation of a specific tab used in the COSMIC system and is not a definition of the term CNV. Ex. 2035, 1 (“This tab shows an overview of the data for the specified CNV.”). Loo discusses an analysis of a subset of copy number events—allele-specific copy number variation which include aneuploidy. Ex. 2036, 1; *see also* Ex. 1050, 39–40. We agree with Petitioner that neither of these references excludes aneuploidy from the definition of copy number variation. Pet. Reply 9.

Moreover, the evidence of record shows that those skilled in the art interpret the term copy number variation to include aneuploidy. For example, Sehnert⁴ teaches, “Because we are collecting information across the entire genome, this method is capable of detecting any aneuploidy or other copy number variation including insertions and deletions.” Ex. 1026, 1048. Similarly, Casbon⁵ states, “Copy number variations can include genomic rearrangements such as deletions, duplications, inversions, and translocations or whole chromosome aneuploidies.” Ex. 1056, 24. For these reasons, we find that the intrinsic and extrinsic evidence support our construction of “copy number variation” as including aneuploidy.

3. *Unique Sequence Read*

While neither party initially proposed a construction for the term “unique sequence read,” in its Preliminary Response, Patent Owner argued

⁴ Sehnert et al., *Optimal Detection of Fetal Chromosomal Abnormalities by Massively Parallel DNA sequencing of Cell-Free Fetal DAN from maternal Blood*, 57 CLIN CHEM 1042 (2011) (Ex. 1026 “Sehnert”).

⁵ Casbon et al., WO 2012/038839 A2, published March 29, 2012, (Ex. 1056 “Casbon”).

that the terms “sequence reads” and “unique sequence reads,” as used in the claims, are directed to two separate embodiments. Prelim. Resp. 23–28. In the Decision to Institute, we agreed with Patent Owner and construed the term “unique sequence read” to refer to “a sequence read that contains unique sequences, such that the sequences can be identified without the need for a barcode.” Inst. Dec. 12.

Petitioner contends that we erred in our construction, specifically the requirement that the term excludes the use of a barcode to identify the sequence. Pet. Reply. 12–15. Petitioner contends that the term should be construed to mean a sequence that can be mapped to just one location. *Id.* at 14.

We have considered Petitioner’s argument and the evidence of record and conclude that we did not err in our construction of the term “unique sequence read.”

As we noted in our Decision to Institute, while the Specification does not define “unique sequence reads,” the Specification teaches:

Additionally, individual sequences may be identified based upon characteristics of sequence data for the read themselves. For example, the detection of unique sequence data at the beginning (start) and end (stop) portions of individual sequencing reads may be used, alone or in combination, with the length, or number of base pairs of each sequence read unique sequence to assign unique identities to individual molecules. Fragments from a single strand of nucleic acid, having been assigned a unique identity, may thereby permit subsequent identification of fragments from the parent strand. This can be used in conjunction with bottlenecking the initial starting genetic material to limit diversity.

Further, using unique sequence data at the beginning (start) and end (stop) portions of individual sequencing reads

and sequencing read length may be used, alone or [in] combination, with the use of barcodes.

Ex. 1001, col. 37, ll. 37–53. The discussion above, that the unique sequence data can be used alone or with barcodes, supports our conclusion that a unique sequence read is distinct from a sequence with a barcode.

Based on the foregoing we conclude that our initial construction of the term “unique sequence reads” was correct. “Unique sequence reads” as used in the ’743 patent means a sequence read that contains unique sequences, such that the sequences can be identified without the need for a barcode.

D. Ground 1 – Anticipation by Chiu

Petitioner contends that claims 1–3 and 22–26 are unpatentable under 35 U.S.C. § 102(a) as anticipated by Chiu. Pet. 20–31.

1. Chiu

Chiu discloses the use of “massively parallel genomic sequencing to quantify maternal plasma DNA sequences for noninvasive prenatal detection of fetal trisomy 21.” Ex. 1022, Abst. Chiu discloses a method comprising the steps of: obtaining a sample of human DNA from maternal plasma; sequencing the isolated DNA; aligning the DNA sequences to the human genome; counting the number of unique sequences; calculating the percentage of unique sequences; and calculating the Z-score for each chromosome and test sample. Ex. 1022, Fig. 1.

2. Analysis of Claim 1

Claim 1 is directed to a method for detecting copy number variation. Petitioner contends that each of the method steps is disclosed by Chiu. Pet. 20. Petitioner points to the chart shown in Figure 1 of Chiu as showing the steps recited in claim 1. *Id.*

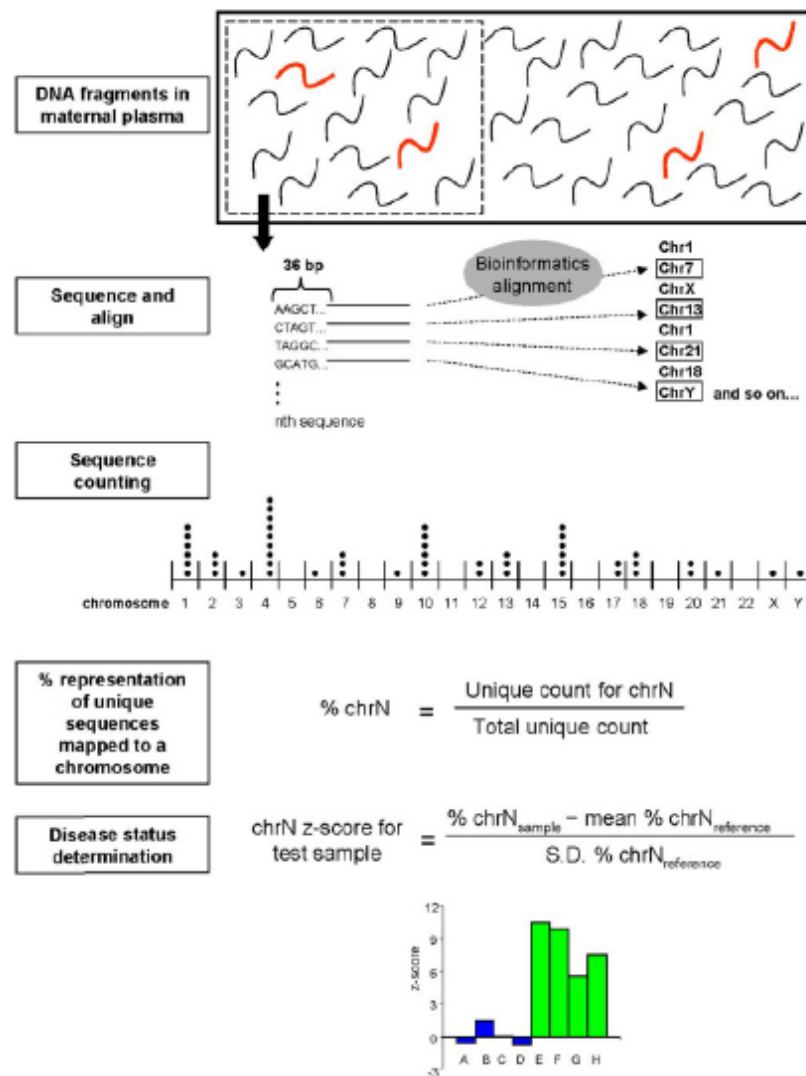


Figure 1 of Chiu outlines the method described therein. Ex. 1022, Fig. 1.

a) Method for detecting copy number variation

Petitioner contends that this limitation is met in that Chiu discloses a method for detecting aneuploidy. Pet. 17, 22.

Patent Owner contends that this limitation has not been met because the term copy number variation, as used in the '743 patent, does not include aneuploidy. PO Resp. 22–24. Patent Owner reiterates the arguments made with respect to the construction of the term copy number variation discussed above. *Id.*

As discussed above, we have construed the term copy number variation to include aneuploidy. Section II.C.2 *supra*. Chiu discloses a method for detecting fetal chromosomal aneuploidy. Ex. 1022, 1. We find that Chiu discloses the recited limitation.

b) Sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads

Petitioner contends that Chiu discloses this limitation as Chiu discloses amplifying the DNA fragments prior to sequencing such that multiple copies of the fragments are generated. Pet. 23 (citing Ex. 1002 ¶ 80; Ex. 1022, SI1).

Patent Owner does not contest that Chiu discloses this limitation. *See* PO Resp. 23–25.

We find that Chiu discloses this limitation. Chiu discloses extraction of DNA from plasma, which is an extracellular polynucleotide. Ex. 1022, SI1; Ex. 1002 ¶ 80. Chiu goes on to disclose that the DNA was then amplified using 15-cycle PCR and that the DNA was sequenced. Ex. 1022, SI1; Ex. 1002 ¶ 80.

c) Filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold

Petitioner contends that Chiu discloses this limitation. Pet. 23–24. Petitioner argues that Chiu discloses that only sequences that could be mapped to just one location were counted and that this meets the criteria for the filtering step. *Id.* (citing Ex. 1002, 20459; Ex. 1002 ¶¶ 83–84).

Patent Owner does not contest that Chiu discloses this limitation. *See* PO Resp. 23–25.

We find that Chiu discloses this limitation. As Dr. Gabriel testifies and we agree, one skilled in the art would have understood that a mapping score is “a metric used to indicate whether a sequence read maps to a single

location in the genome or multiple locations in the genome” and that this definition is consistent with the teachings of the ’743 patent. Ex. 1002 ¶ 82.

As Chiu discloses

In this study, we counted only sequences that could be mapped to just one location in the repeat-masked reference genome with no mismatch, i.e., deemed as a “unique” sequence in the human genome. We termed these sequences as U0-1-0-0 on the basis of values in a number of fields in the data output files of the ELAND sequence alignment software (Illumina).

Ex. 1022, 20459. Dr. Gabriel testifies, and we agree, that one skilled in the art would have understood this passage of Chiu to describe the filtering step recited in claim 1. *See* Ex. 1002 ¶ 84.

d) Mapping the plurality of sequence reads to a reference sequence

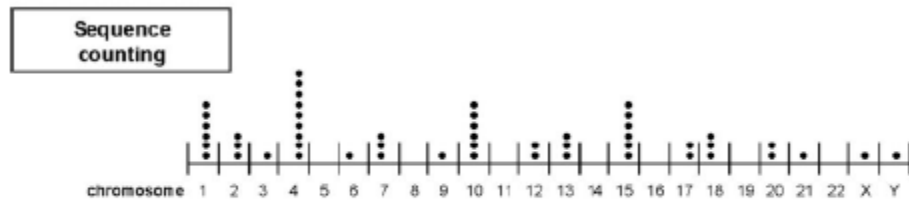
Petitioner contends that Chiu discloses this limitation. Petitioner contends that Chiu discloses identifying the chromosomal origin of each sequence through mapping to a human reference genome. Pet. 31 (citing Ex. 1022, Fig. 1).

Patent Owner does not contest that Chiu discloses this limitation. *See* PO Resp. 23–25.

We find that Chiu discloses this limitation. Chiu states, “the chromosomal origin of each 36-bp sequence was identified through mapping to the human reference genome by bioinformatics analysis.” Ex. 1022, 20459, Fig. 1. Dr. Gabriel testifies, and we agree, that this disclosure meets the claim limitation calling for mapping the sequence reads to a reference sequence. Ex. 1002 ¶ 85.

e) Quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence

Petitioner contends that Chiu discloses this limitation. Pet. 25–26. Referring to part of Figure 1 reproduced below, Petitioner contends that Chiu teaches “the number of sequence reads originating from any particular chromosome was then counted and tabulated for each human chromosome.” *Id.* (quoting Ex. 1022, 20459.)



Portion of Fig. 1 of Chiu showing Sequence Counting.

Patent Owner contends that Chiu does not disclose this step, arguing that Petitioner has improperly equated a predefined region with an entire chromosome. PO Resp. 23–24.

We have considered the arguments presented by the parties and the evidence of record and find that Chiu discloses quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence. Chiu teaches that the sequence reads, which originate from a particular chromosome, are counted and tabulated. Ex. 1022, 20459. Chiu also states that the method described in the article is designed to “quantify the amount of chr21 sequences in maternal plasma.” *Id.* We agree with Dr. Gabriel that the counting and tabulating procedure described in Chiu meets the claim limitation calling for quantifying mapped regions in a plurality of predefined regions of the reference sequence. Ex. 1002 ¶¶ 86–88.

With respect to Patent Owner's contention that a predefined region does not include whole chromosomes, as discussed above we do not find that the term is so limited.

f) Determining copy number variation in one or more of the plurality of predefined regions by:

Petitioner contends that Chiu discloses this limitation in that Chiu is directed to a method of diagnosing aneuploidy using both a normalizing step and a processing step. Pet. 26. Petitioner refers back to its discussion of the construction of the term "predefined regions". *Id.*

Patent Owner contends that this limitation is not disclosed by Chiu because Chiu does not determine copy number variation in one or more of the plurality of predefined regions. PO Resp. 24. Patent Owner contends that the term "in one or more of the plurality of predefined regions" limits the claim to copy number variations within a region and thus excludes copy number variation based on an entire chromosome. *Id.*

We have considered the arguments advanced by the parties and the evidence of record and find that Chiu discloses this limitation. The limitation at issue reads "determining copy number variation in one *or* more of the plurality of predefined regions." Ex. 1001, 62:56–57 (emphasis added). As discussed above, we have construed the term "predefined regions" to include whole chromosomes. See Section II.C.1, *supra*. Thus, the limitation at issue embraces determining copy number variation both within a chromosome and between or among chromosomes. Chiu discloses determining copy number variation among chromosomes, e.g., aneuploidy. Ex. 1022, 20459; *see* Ex. 1002 ¶ 89.

- g) *Normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or*

Petitioner contends that Chiu discloses this limitation. Petitioner contends that Chiu discloses:

We then determined the percentage contribution of unique sequences mapped to each chromosome by dividing the U0-1-0-0 count of a specific chromosome by the total number of U0-1-0-0 sequence reads generated in the sequencing run for the tested sample to generate a value termed % chrN, when the chromosome of interest is chrN.

Pet. 27 (quoting Ex. 1022, 20459). Petitioner contends that this represents a normalization of the data so that unique sequence reads can be compared to one another. *Id.*

Patent Owner contends that Chiu does not disclose this limitation. PO Resp. 25–26. Patent Owner contends:

When different chromosomes are normalized to each other (each being a “predefined region” according to the petition), even with Z-score processing, information relates to the population of chromosomes in general, and not to any one specific chromosome. Thus, meaningful information regarding aneuploidy would not be obtained. EX2023, ¶61. Petitioner has not demonstrated otherwise.

Id.

We have considered the arguments advanced by the parties and the evidence of record and conclude that Chiu discloses the normalization step of claim 1. Chiu discloses calculating a % chrN value for each chromosome by comparing the number of sequence reads for a given chromosome to the total number of sequence reads. Ex. 1022, 20459. This allows the sequence reads for each chromosome to be compared with each other as well as allowing comparison to the total sequence reads. Ex. 1002 ¶ 92. This

comparison step meets the requirement of normalization. *See* Ex. 1050, 52–53, 151.

Patent Owner’s argument that Chiu does not teach the normalization step is unpersuasive. Patent Owner contends that if chromosomes were the predefined regions, the normalization step would not yield any meaningful data regarding aneuploidy. PO Resp. 25. However, Chiu specifically teaches that the data from the normalization step can be used to determine if aneuploidy is present. *See* Ex. 1022, 29459 (stating normalization data was then used to calculate a z-score, which is then used to determine aneuploidy). We find that this disclosure adequately teaches the “normalizing” step.

h) Processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample

Petitioner contends that Chiu discloses this limitation. Pet. 28–30. Petitioner contends that Chiu discloses calculating the z-score of % chr21 of a test sample, which represents the number of standard deviations from the mean of a reference data set. *Id.* at 29. Petitioner contends that this is equivalent to processing a number of unique reads in a plurality of predefined regions with the numbers obtained from a control sample. *Id.* (citing Ex. 1002 ¶ 96).

Patent Owner contends that Chiu does not disclose this limitation. PO Resp. 25–26. Patent Owner reiterates the arguments made with respect to step (e)(i) (the “normalizing” step) above. *Id.*

We have considered the arguments advanced by the parties and the evidence of record and find that Chiu discloses the processing step of claim 1. Chiu discloses:

To determine if a tested maternal plasma sample belonged to a T21 pregnancy, we calculated the z-score of % chr21 of the tested sample. The z-score refers to the number of standard deviations from the mean of a reference data set. Hence, for a T21 fetus, a high z-score for % chr21 was expected when compared with the mean and standard deviation of % chr21 values obtained from maternal plasma of euploid pregnancies.

Ex. 1022, 20459. We agree with Dr. Gabriel that “[b]y comparing that value in a tested sample to that value in a control sample, Chiu describes ‘processing a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample.’” Ex. 1002 ¶ 96.

Patent Owner’s arguments regarding the processing step are unpersuasive for the reasons stated above regarding the normalization step.

3. *Claim 2*

Claim 2 reads:

The method of claim 1, further comprising isolating extracellular polynucleotides from the bodily sample.

Ex. 1001, col. 62, ll. 66–67.

Petitioner contends that Chiu discloses this limitation. Pet. 30.

Patent Owner offers no separate argument regarding the patentability of claim 2. *See* PO Resp. 22–28.

We find that Chiu discloses the step of claim 2. Chiu states, “DNA from maternal plasma was extracted with the blood and bodily fluid protocol of the QIAmp DSP DNA blood mini kit (Qiagen).” Ex. 1022, SI1; Ex. 1002 ¶ 97. We find that this disclosure adequately teaches the claimed limitation of “isolating extracellular polynucleotides from the bodily sample.”

4. *Claim 3*

Claim 3 reads:

The method of claim 1, further comprising generating copies of the extracellular polynucleotides prior to sequencing.

Ex. 1001, col. 63, ll. 1–3.

Petitioner contends that Chiu discloses this step. Pet. 30.

Patent Owner offers no separate argument regarding the patentability of claim 3. *See* PO Resp. 22–28.

We find that Chiu discloses the step of claim 3. Chiu discloses that the selected DNA libraries were amplified, followed by sequencing. Ex. 1022, SII, 20459 Figure 1; Ex. 1002 ¶ 98. Thus, we find that this disclosure adequately teaches “generating copies of the extracellular polynucleotides prior to sequencing.”

5. *Claim 22*

Claim 22 reads:

The method of claim 1, wherein e) comprises i) and ii).

Ex. 1001, col. 64, ll. 33–34.

Petitioner contends that Chiu discloses the method of claim 22 in that Chiu discloses both steps i) and ii).

Patent Owner offers no separate argument regarding the patentability of claim 22. *See* PO Resp. 22–28.

We find that Chiu discloses the method of claim 22. As discussed above, Chiu discloses normalization of the sequence reads followed by processing the reads with numbers from a reference sample. Ex. 1022, 20459.

6. *Claims 23–26*

Claims 23 through 26 read:

23. The method of claim 1, wherein e) comprises i) normalizing the number of reads in the plurality of predefined regions to each other.

24. The method of claim 1, wherein e) comprises i) normalizing the number of unique sequence reads in the plurality of predefined regions to each other.

25. The method of claim 1, wherein e) comprises ii) processing the number of reads in the plurality of predefined regions with numbers obtained from the control sample.

26. The method of claim 1, wherein e) comprises ii) processing the number of unique sequence reads in the plurality of predefined regions with numbers obtained from the control sample.

Ex. 1001, col. 64, ll. 38–47.

Petitioner contends that Chiu discloses the elements of claims 23–26 in that Chiu teaches the use of sequence reads and unique sequence reads. Pet. 31.

Patent Owner offers no separate argument regarding the patentability of claims 23–26. *See* PO Resp. 22–28.

We find that Chiu discloses the elements of claims 23–26. Chiu discloses that the method described uses only sequences that could be mapped to a single location and describes these sequences as unique. Ex. 1022, 20459, Fig. 1. Dr. Gabriel testifies, and we agree, that the filtering process used in Chiu produces unique sequences. Ex. 1002 ¶ 84. Unique sequence reads are a subset of reads, and thus the sequence reads used in Chiu satisfy both the requirement for sequence reads and unique sequence reads. *See* Ex. 1002 ¶ 96 (unique sequence reads are reads in the plurality of predefined regions).

7. *Summary*

For all the above reasons, we determine that Petitioner has shown by a preponderance of the evidence that Chiu discloses each and every limitation of claims 1–3 and 22–26. Thus, we find claims 1–3 and 22–26 unpatentable for anticipation by Chiu.

E. Ground 2 – Obviousness based on Kinde 2012 and Kinde 2011

Petitioner contends that the subject matter of claims 1–9, 20, and 22–26 would have been obvious to a person of ordinary skill in the art at the time the invention was made over Kinde 2012 combined with Kinde 2011.

1. Kinde 2012

Kinde 2012 teaches a method for detecting fetal aneuploidy using cell-free DNA from a sample of maternal plasma. Ex. 1041, Abst. The method of Kinde 2012 includes selecting DNA fragments from chromosomal regions, amplifying and sequencing the DNA fragments to generate multiple sequence reads for each fragment, filtering the reads for quality, mapping the reads to the human genome, counting the reads that map to each chromosomal region, normalizing the reads across regions, and comparing the normalized figures to a control sample. Ex. 1041, 2–5.

2. Kinde 2011

Kinde 2011 teaches a method for “identif[ying] mutations that are present in a small fraction of DNA templates.” Ex. 1023, Abst. In the method of Kinde 2011, each DNA fragment to be analyzed is assigned a unique sequence identifier. *Id.* at 9530. The tagged DNA fragments are then amplified to create a number of daughter fragments. *Id.* The daughter fragments are then sequenced. *Id.*

3. *Analysis of Claim 1*

Claim 1 is directed to a method for detecting copy number variations. Petitioner contends that Kinde 2012 combined with Kinde 2011 teach or suggest all of the steps of the method recited in claim 1.

a) A method for detecting copy number variation comprising:

Petitioner contends that Kinde 2012 teaches a method for detecting fetal aneuploidy, which is a type of copy number variation. Pet. 34. Petitioner also contends that it would have been obvious to one skilled in the art to use the method of Kinde 2012 to detect other forms of copy number variation. *Id.*

Patent Owner contends that Kinde 2012 is not directed to detecting copy number variation because the term copy number variation, as used in the context of the '743 patent, does not encompass aneuploidy. PO Resp. 33–35. Patent Owner reiterates the same arguments presented concerning construction of the term copy number variation. *Id.*

We have considered the argument presented by the parties and the evidence of record and conclude that Kinde 2012 teaches a method for determining copy number variation. Kinde 2012 teaches an improved sequencing method that can be used as part of a “safe and effective screening method for fetal aneuploidies.” Ex. 1041, Abstr. As discussed above, for purposes of this Decision, we have construed the term “copy number variation” to include aneuploidy. Therefore, Kinde 2012 teaches a method for determining copy number variation. Ex. 1002 ¶ 107.

- b) Sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads*

Petitioner contends that Kinde 2012 combined with Kinde 2011 teaches this step of the claim. Pet. 34–35. Petitioner contends that Kinde 2012 teaches an improved method for sequencing cell-free, maternal DNA. *Id.* at 34. Petitioner contends that Kinde 2012 uses the amplification technique disclosed in Kinde 2011. *Id.* at 34–35.

Patent Owner does not present a separate argument concerning this step of the claim. *See* PO Resp. 28–46.

We find that Kinde 2012 combined with Kinde 2011 teaches this step of the claimed method. Kinde 2012 teaches a method for sequencing cell-free, maternal plasma DNA, which is an extracellular polynucleotide. Ex. 1041, Abst.; Ex. 1002 ¶ 108. Kinde 2012 teaches that the DNA fragments were amplified using the method described in Kinde 2011. Ex. 1041, 2.

As shown below, Figure 1 of Kinde 2011 teaches that the fragments were first assigned a unique identification DNA sequence followed by amplifying each unique fragment to create a plurality of fragments. Ex. 1023, 9530, Fig. 1.

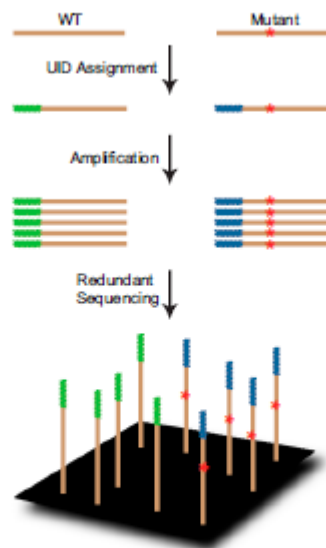


Fig. 1. Essential elements of Safe-SeqS. In the first step, each fragment to be analyzed is assigned a unique identification (UID) DNA sequence (green or blue bars). In the second step, the uniquely tagged fragments are amplified, producing UID families, each member of which has the same UID. A supermutant is defined as a UID family in which $\geq 95\%$ of family members have the same mutation.

Figure 1 from Kinde 2011, Ex. 1023 showing the tagging, amplification and filtering steps.

Based on the foregoing, we agree with Dr. Gabriel that Kinde 2012 combined with Kinde 2011 teaches the step of “sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads.”

Ex. 1002 ¶¶ 108–110.

c) Filtering out reads that fail to meet a set accuracy, quality score, or a mapping score threshold

Petitioner contends that the disclosure of Kinde 2011 satisfies this limitation because Kinde 2011 teaches that only high quality reads that meet a set criteria are used in the analysis. Pet. 43 (citing Ex. 1009, SI2).

Patent Owner does not present a separate argument concerning this step of the claim. See PO Resp. 28–46.

We find that Kinde 2011 teaches this step of claim 1. Kinde 2011 teaches:

Only high-quality reads meeting the following criteria were used for subsequent analysis: (i) the first 25 bases passed the standard Illumina chastity filter; (ii) every base in the read had a quality score ≥ 20 ; and (iii) ≤ 3 mismatches to expected sequences. For the exogenous UID libraries, we additionally required the UIDs to have a quality score ≥ 30 .

Ex. 1009, SI2. We agree with Dr. Gabriel that this passage describes filtering out reads that fail to meet a set quality score threshold. Ex. 1002 ¶ 111.

d) Mapping the plurality of sequence reads to a reference sequence

Petitioner contends that Kinde 2012 teaches this step of the method of claim 1 in that Kinde 2012 teaches that the distinct sequences were mapped to the human genome. Pet. 37–38.

Patent Owner contends that Kinde 2012 does not teach or suggest this step of the claimed method. PO Resp. 36–38. Patent Owner contends that Kinde 2012 teaches that it does not map the sequences to the human genome but instead maps the sequences to a discrete set of chromosomal positions. *Id.* at 37. Patent Owner contends that this is mapping the sequences to predefined regions and not mapping to a reference sequence. *Id.*

We have considered the arguments of the parties and the evidence of record and conclude that Kinde 2012 teaches the step of mapping the plurality of sequences to a reference sequence. While we agree with Patent Owner that Kinde 2012 does not map the sequences against the entire human genome, claim 1 only requires mapping to “a reference sequence.” Ex. 1001, col. 62, ll. 51–52. The Specification of the ’743 patent refers to “the human genome” as an example of “a reference sequence,” and states that reads can

be mapped to particular locations or positions in the reference sequence. Ex. 1001, col. 35, ll. 14–22. Thus, nothing in claim 1 or the Specification requires the “reference sequence” to be the entire human genome. Similarly, Kinde 2012 teaches that the sequences are aligned against a discrete set of chromosomal positions within the reference sequence. Ex. 1041, 2. Thus, we find Kinde 2012 teaches mapping a plurality of sequence reads to the reference sequence (i.e., the human genome) by aligning reads to a discrete set of chromosomal positions within the genome. Ex. 1042, 2.

e) Quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence

Petitioner contends that Kinde 2012 teaches this step of the method claimed. Pet. 38. Petitioner contends that Kinde 2012 teaches generating counts for each chromosomal position. *Id.*

Patent Owner contends that Petitioner’s argument concerning the definition of a reference sequence is inconsistent with its position of a predefined region used in other steps of Kinde 2012’s method. PO Resp. 29. Patent Owner contends that, for this step, Petitioner relies on the L1 retrotransposon regions as the plurality of predefined regions, but with respect to the normalizing and processing steps, Petitioner relies on entire chromosomes as the predefined regions. *Id.* at 29–34. Patent Owner contends that this inconsistency precludes a finding that Kinde 2012 teaches the claimed method. *Id.*

We have considered the arguments advanced by the parties and the evidence of record and find that Kinde 2012 teaches the quantification step of claim 1. Kinde 2012 teaches “generating a table of tag counts for each sample where each row represents a unique position (note that all tables will be of equal length as only the shared positions in each experiment were

analyzed).” Ex. 1041, 4. The generation of tag counts is the same as quantifying mapped reads in a plurality of predefined regions of the reference sequence. Ex. 1002 ¶ 118.

We have considered Patent Owner’s argument regarding the alleged inconsistency of Petitioner’s analysis and are unpersuaded. As discussed above, the Specification teaches that mapping can be performed using only a portion of the reference sequence. Ex. 1001, col. 35, ll. 14–22 (teaching measuring the amount of polynucleotides mapping to a first and second location in a particular region of a human genome). Similarly, Kinde 2012 teaches mapping sequences to the retrotransposon regions, i.e., a portion of the chromosomes, because mapping sequences to a discrete set of chromosomal positions is simpler than aligning to the entire genome. Ex. 1041, 2; Ex. 1002 ¶ 115. Kinde 2012, therefore, uses portions of the reference sequence or predefined region to determine copy number variation. Ex.1041, 5. Thus, we find Kinde 2012 teaches quantifying mapped reads of unique sequence reads in a plurality of predefined regions of the reference sequence.

- f) Determining copy number variation in one or more of the plurality of predefined regions by: i) normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or ii) processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with number obtained from a control sample*

Petitioner contends that Kinde 2012 teaches these steps. Pet. 37–42. Petitioner contends that Kinde 2012 teaches both normalization and processing of the sequence read counts. *Id.*

Patent Owner contends that Kinde 2012 does not teach either of the steps. PO Resp. 29–33, 36–39. Patent Owner contends that Kinde 2012 does

not teach normalizing a plurality of predefined regions to each other but teaches normalizing the tag count across samples. PO Resp. 29–30.

We have considered the arguments presented by the parties and the evidence of record and find that Kinde 2012 teaches both the normalization and processing steps of claim 1. Kinde 2012 teaches that normalization was performed using the following steps:

- 1) generating a table of tag counts for each sample where each row represents a unique position (note that all tables will be of equal length as only the shared positions in each experiment were analyzed);
- 2) sorting the rows in each table based on tag counts, resulting in each table having a different order of positions;
- 3) determining the mean tag count for each row across all samples;
- 4) replacing an individual sample's tag count with the mean tag count for all samples at each row; and
- 5) sorting the tag counts for each sample's table back to their original order based on position.

Ex. 1041, 4. As stated above, each row used in the normalization process represents a unique position and mean tag counts are determined for each row or unique position. *Id.* We agree with Dr. Gabriel that normalizing tag counts for each position is the same as normalizing a number of reads in a plurality of defined regions to each other. Ex. 1002 ¶¶ 117–119. This conclusion is also supported by the testimony of Dr. Bustamante. Ex. 1050, 123–125 (testifying that Kinde 2012 teaches comparing tag counts within each sample, which is the same as normalizing the number of reads in the plurality of defined regions to each other).

Kinde 2012 goes on to teach

A common method of determining the aneuploidy status of a particular sample in Digital Karyotyping-based assays is by comparison of z-scores. Through this method, one determines

the mean and standard deviation of tag counts lying within a chromosome of interest in a group of reference samples (e.g., samples with known euploid content), and then creates a standardized score (i.e., z-score) for a chromosome of interest for each sample.

Ex. 1041, 4–5 (citations omitted). We agree with Dr. Gabriel that by teaching the steps of calculating z-scores for both the test sample and the control sample and then comparing the z-scores, Kinde 2012 teaches processing a number of reads or unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample. Ex. 1002 ¶¶ 120–123.

We are unpersuaded by Patent Owner’s argument that Kinde 2012 does not teach normalizing tag counts to each other but instead teaches normalizing the counts across samples. PO Resp. 29–30. As seen from the passage of Kinde 2012 quoted above, normalization is done for rows, which represent a unique sequence. Ex. 1041, 4. Dr. Gabriel testifies, and we agree, that normalizing tag counts for each position is the same as normalizing a number of reads in a plurality of predefined regions to each other. Ex. 1002 ¶¶ 117–119.

We are also unpersuaded by Patent Owner’s argument that Petitioner has failed to show that Kinde 2012 teaches steps c), d), and e) of claim 1. As shown by the analysis discussed above, Kinde 2012 teaches all three steps. *See* Section II.E. 3.d–f, *supra*.

g) Motivation to combine/Reasonable expectation of success

Petitioner contends that one skilled in the art would have been motivated to combine the teachings of Kinde 2012 with those of Kinde 2011. Pet. 31–34. Petitioner contends that both Kinde references have the same authors and teach similar methods for detecting rare mutations and

copy number variations using massively parallel sequencing. *Id.* at 31.

Petitioner also contends that Kinde 2012 incorporates the teachings of Kinde 2011. *Id.* at 32.

Patent Owner contends that Petitioner has failed to establish a motivation to combine the references. PO Resp. 39–41. Patent Owner contends that Petitioner has not shown why one skilled in the art would use the filtering technique of Kinde 2011 in the method of Kinde 2012. *Id.* at 40. Patent Owner also contends that Kinde 2011 discloses several different embodiments and there is nothing in either reference to teach or suggest which embodiment of Kinde 2011 to use. *Id.* at 41.

We have considered the arguments advanced by the parties and the evidence of record and we find that one skilled in the art would have been motivated to incorporate the teachings of Kinde 2011 into the method of Kinde 2012. Both Kinde 2011 and Kinde 2012 teach methods for detecting rare mutations and copy number variations using massively parallel sequencing. Ex. 1023, 9530; Ex. 1041, Abstract. Kinde 2012 specifically teaches using the library preparation techniques of Kinde 2011, including Kinde 2011's amplification and sequencing techniques. Ex. 1041, 2, 7. We also find that a person of ordinary skill in the art would have had a reasonable expectation of success. Specifically, Kinde 2012 successfully incorporated certain steps of Kinde 2011 into the method taught in Kinde 2012. Ex. 1002 ¶ 106. We find that this teaching of the successful incorporation of Kinde 2011 into Kinde 2012 would lead one skilled in the art to have a reasonable expectation of successfully accomplishing the same incorporation of Kinde 2011 into Kinde 2012 with respect to the steps of amplifying and tagging the polynucleotides.

h) Conclusion

Based on the foregoing, we conclude that Petitioner has demonstrated by a preponderance of the evidence that the subject matter of claim 1 would have been obvious to one of ordinary skill in the art at the time of the invention and is therefore unpatentable.

4. Claim 2

Claim 2 reads

The method of claim 1, further comprising isolating extracellular polynucleotides from the bodily sample.

Ex. 1001, col. 62, ll. 66–67

Petitioner contends that Kinde 2012 teaches this claim element. Pet. 42. Petitioner contends that Kinde 2012 teaches obtaining plasma samples from patients followed by preparing DNA for sequencing and that preparing the DNA for sequencing necessarily involves isolating the DNA from the plasma. *Id.*

Patent Owner offers no separate argument regarding the patentability of claim 2. *See* PO Resp. 41–46.

We find that Kinde 2012 teaches the step of isolating extracellular polynucleotides from a bodily sample. Kinde 2012 refers to testing maternal plasma DNA for aneuploidy. Ex. 1041, 2. Dr. Gabriel testifies, and we agree, that plasma is a bodily sample and one skilled in the art would have understood that in order to sequence the DNA in the plasma, the DNA would need to be isolated from the plasma. Ex. 1002 ¶ 127.

As discussed above, Petitioner has demonstrated a motivation to combine the Kinde references with a reasonable expectation of success. We, therefore, conclude that Petitioner has shown by a preponderance of the

evidence that the subject matter of claim 2 would have been unpatentable for obviousness.

5. *Claim 3.*

Claim 3 reads:

The method of claim 1, further comprising generating copies of the extracellular polynucleotides prior to sequencing.

Ex. 1001, col. 63, ll. 1–3.

Petitioner contends that Kinde 2011 discloses this step in that it teaches making copies of the DNA fragments before sequencing. Pet. 42.

Patent Owner contends that Kinde 2011 does not teach or suggest generating copies of extracellular DNA prior to sequencing. PO Resp. 42. Patent Owner contends that Kinde 2011 relates to cellular DNA and not extracellular DNA. *Id.*

We have considered the arguments advanced by the parties and the evidence of record and conclude that Kinde 2012 in combination with Kinde 2011 teaches or suggests the step recited in claim 3. As shown in Figure 1 of Kinde 2011 reproduced above, Kinde 2011 teaches amplifying the DNA fragment prior to sequencing. Ex. 1023, 9531.

While we agree with Patent Owner that Kinde 2011 is directed to cellular DNA, Kinde 2012 is directed to extracellular DNA. *See* Ex. 1041, 1. Thus, it is the combination of the Kinde references that teaches or suggests the subject matter of claim 3.

As discussed above, Petitioner has demonstrated a motivation to combine the Kinde references with a reasonable expectation of success.

We conclude that Petitioner has established by a preponderance of the evidence that claim 3 is unpatentable for obviousness.

6. *Claim 4*

Claim 4 reads:

The method of claim 1, further comprising determining a percent of sequences having copy number variation or rare mutation or variant in the bodily sample.

Ex. 1001, col. 63, ll. 4–6.

Petitioner contends that this step is taught by Kinde 2011. Pet. 43. Petitioner contends that Kinde 2011 teaches creating oligonucleotide mixtures with predetermined percentages of mutant and normal fractions and then using the method of Kinde 2011 to analyze the mixtures. *Id.* The resulting ratios were reported in a percent of the mutant present in the mixture. *Id.*

Patent Owner contends that Petitioner has not explained why one skilled in the art would have used the percentage calculation disclosed in Kinde 2011 in the method disclosed in Kinde 2012. PO Resp. 43. Patent Owner also contends that Kinde 2012 does not relate to either copy number variations or rare mutations. *Id.*

We have considered the arguments presented by the parties and the evidence of record, and find that the combination of the Kinde references teaches the step recited in claim 4.

Kinde 2011 teaches:

Does Safe-SeqS preserve the ratio of mutant:normal sequences in the original templates? To address this question, we synthesized two 31- base oligonucleotides of identical sequence with the exception of nucleotide 15 . . . and mixed them at nominal mutant/normal fractions of 3.3% and 0.33%. Through Safe-SeqS analysis of the oligonucleotide mixtures, we found that the ratios were 2.8% and 0.27%, respectively. We conclude that the UID assignment and amplification procedures used in Safe-SeqS do not greatly alter the proportion of variant

sequences and thereby provide a reliable estimate of that proportion when unknown.

Ex. 1021, 9533. Dr. Gabriel testifies that one skilled in the art would have known that mutation frequency can be expressed as a percentage of the sequences containing a mutation. Ex. 1002 ¶ 133. Dr. Gabriel testifies, and we agree, that the percentage of mutations can be easily calculated from the data in Kinde 2011 “simply by dividing the number of ‘total supermutants identified’ by the number of ‘UID families.’” Ex. 1002 ¶ 134.

With respect to the motivation to use the percentage calculation of Kinde 2011 in the method of Kinde 2012, as explained above, the Kinde articles address the same problem and Kinde 2012 specifically teaches using the method of Kinde 2011. Moreover, as Dr. Gabriel testifies and we agree, calculating the percentage of sequences containing a mutation was a common way of expressing mutation frequency at the time the invention was made. Ex. 1002 ¶¶ 133–135.

As to Patent Owner’s argument regarding “a rare mutation,” we note that the language of claim 4 recites “copy number variation or rare mutation or variant.” Ex. 1001, col. 63, ll. 5–6. The method of claim 4 need only determine the percentage of sequences having one of these types of mutations to satisfy the claim step. As discussed above, Kinde 2012 determines aneuploidy, a form of copy number variation. Section II, E, 3 *supra*. Also, Kinde 2011 determines the percentage of mutant (or variant) sequences. Ex. 1021, 9533.

Based on the foregoing, we conclude that Petitioner has established by a preponderance of the evidence that the subject matter of claim 4 would have been obvious over Kinde 2012 combined with Kinde 2011.

7. *Claims 5, 6, and 9*

Claims 5, 6, and 9 read:

5. The method of claim 1, further comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to sequencing.

6. The method of claim 5, wherein each barcode attached to the extracellular polynucleotides or fragments thereof prior to sequencing is not unique.

9. The method of claim 1, further comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to an amplification or enrichment step.

Ex. 1001, col. 63, ll. 7–12 and 21–25.

Petitioner contends that Kinde 2011 teaches the steps recited in claims 5, 6, and 9 in that Kinde 2011 teaches attaching barcodes to DNA fragments prior to sequencing and amplification, and that the barcodes are not unique. Pet. 44.

Patent Owner contends that Kinde 2011 does not teach the steps of claim 5, 6, and 9 because the claims call for the barcodes to be attached to extracellular DNA and Kinde 2011 is directed to cellular DNA. PO Resp. 43–44. Patent Owner also contends that the embodiment of Kinde 2011 that teaches non-unique barcodes is not applicable to the DNA of Kinde 2012, because the embodiment of Kinde 2011 requires the presence of sheared ends and the extracellular DNA of Kinde 2012 does not possess sheared ends. *Id.* at 44–45 (citing Ex. 2020 ¶ 36).

We have considered the arguments presented by the parties and the evidence of record and find that Kinde 2012 combined with Kinde 2011 teach the steps of claims 5, 6, and 9.

Kinde 2012 relates to analysis of extracellular DNA to determine aneuploidy. Ex. 1041, Abstr. Kinde 2012 also teaches that the DNA

fragments were “tagged with a unique identifier DNA sequence” and that amplification was done using the method of Kinde 2011. Ex. 1041, 2. Kinde 2011 teaches that tagging was done before amplification. Ex. 1023, Figure 1. Kinde 2011 also teaches that the unique identifier DNA is also known as a barcode. *Id.* at 9531. Thus, the combination of Kinde references teaches attaching a barcode to extracellular sequences or fragments prior to amplification as recited in claims 5 and 9.

Claim 6 calls for the use of non-unique barcodes. We agree with Petitioner that Kinde 2011 teaches this limitation. In the inverse PCR experiment reported in Kinde 2011, Kinde analyzed over 1000 different polynucleotides using just 12 different sequences for the UUIDs of barcodes. Ex. 1012, 9531, SI10, table 4. Given the number of barcodes used in the analysis was significantly less than the number of polynucleotides analyzed, the barcodes used were not unique. Ex. 1002 ¶ 145.

Patent Owner contends that one skilled in the art would not have been motivated to combine the teachings of Kinde 2011 with those of Kinde 2012 to produce the method of claim 6 because Kinde 2011 requires that the polynucleotides have sheared ends to create a UUID and the method of Kinde 2012 does not produce sheared ends. PO Resp. (citing Ex. 2026 ¶ 36).

We are not persuaded by Patent Owner’s argument with respect to claim 6. Kinde 2012 teaches that the amplification and tagging process of Kinde 2011 was used in the method disclosed in Kinde 2011. Ex. 1041, 4. As discussed above, Kinde 2011 discloses using a set of UUIDs that are not unique.

We conclude that Petitioner has shown that the subject matter of claims 5, 6, and 9 would have been obvious over Kinde 2012 combined with Kinde 2011.

8. *Claim 7*

Claim 7 reads

The method of claim 5, wherein each barcode comprises a fixed or semi-random oligonucleotide sequence that in combination with a diversity of molecules sequenced from a selected region enables identification of unique molecules.

Ex. 1001, col. 63, ll. 13–17.

Petitioner contends that the step recited in claim 7 is taught by the combination of Kinde 2011 and Kinde 2012. Pet. 47–50. Petitioner contends that the index sequences used in one embodiment of Kinde 2011 comprise fixed sequences as the term is used in the '743 patent. Pet. 48–49. Petitioner contends that Kinde 2011 teaches that the index sequences can be used to create unique identifier DNA. *Id.* Petitioner contends that the combination of Kinde 2012 and Kinde 2011 teaches the use of the index sequences in combination with a diversity of molecules sequenced from a selected region for the identification of unique molecules. Pet. 50.

Patent Owner contends that like claim 6, claim 7 calls for the use of a non-unique barcode and that Kinde 2011 does not teach the use of a non-unique barcode. PO Resp. 44–45. Patent Owner also contends that Petitioner has not explained why one skilled in the art would use the specific embodiment in Kinde 2011 of using index sequences in the method disclosed in Kinde 2012. *Id.*

We have considered the arguments presented by the parties and the evidence of record and conclude that Petitioner has shown that the subject matter of claim 7 would have been obvious over Kinde 2012 combined with Kinde 2011. We agree with Petitioner that Kinde 2011 teaches the use of a

non-unique barcode. Further, Kinde 2012 teaches using the UIDs of Kinde 2011 in the method of Kinde 2012. Ex. 1041, 4.

9. *Claim 8*

Claim 8 reads

The method of claim 1, further comprising selectively enriching regions from a genome or transcriptome of the subject prior to sequencing.

Ex. 1001, col. 63, ll. 18–20.

Petitioner contends that the step of claim 8 is taught by Kinde 2012 in that Kinde 2012 teaches the use of specific primers that anneal to a subset of repeated regions dispersed throughout the genome prior to sequencing. Pet. 51 (citing Ex. 1041, 5). Petitioner contends that this step is the same as selective enrichment required by claim 8. *Id.*; Ex. 1002 ¶¶ 156–158.

Patent Owner does not present a separate argument regarding the patentability of claim 8. *See* PO Resp. 41–46.

We find that Petitioner has shown by a preponderance of the evidence that the subject matter of claim 8 would have been obvious to one skilled in the art over Kinde 2012 combined with Kinde 2011. Kinde 2012 teaches “the use of specific primers that anneal to a subset of repeated regions dispersed throughout the genome” prior to sequencing. EX1041, 5. Dr. Gabriel testifies, and we agree, that one skilled in the art would have understood selective enrichment to mean “selecting and/or enriching particular portions of genomic regions of interest for analysis.” Ex. 1002 ¶ 156 (citing Ex. 1031, 374–375). Dr. Gabriel also testifies, and we agree, that using that definition of selective enhancement, the subject step of selective enhancement would have been obvious to one skilled in the art based on the teachings of Kinde 2012. Ex. 1002 ¶ 158.

10. Claim 20

Claim 20 reads

The method of claim 1, wherein each of the plurality of predefined regions is a single base.

Ex. 1001, col. 64, ll. 29–30.

Petitioner contends that Kinde 2011 teaches this limitation. Pet. 51–52. Petitioner contends that Kinde 2011 teaches identifying mutations in the CTNNB1 gene wherein each mutation is identified as a single mutation. *Id.* (citing Ex. 1023, 9533, Table S1). Petitioner also contends that one skilled in the art would have understood that next generation sequencing methods such as those taught in Kinde 2011 and Kinde 2012 “offer substantial benefits for copy number analysis, including higher resolution (up to the level of the single-base insertion or deletion).” *Id.* (quoting Ex. 1042, 690–691).

Petitioner contends that based on the teaching of Kinde 2011 and the general knowledge in the art, it would have been obvious to one skilled in the art to analyze a plurality of regions each consisting of a single base pair. *Id.* at 52 (citing Ex. 1002 ¶ 161).

Patent Owner does not present a separate argument regarding the patentability of claim 20. *See* PO Resp. 41–46

We find that Petitioner has shown by a preponderance of the evidence that the subject matter of claim 20 would have been obvious to one of ordinary skill in the art over Kinde 2012 combined with Kinde 2011. Kinde 2011 teaches that the disclosed method can be used to detect single point mutations. Ex. 1023, 9533; Ex. 1002 ¶ 159. Dr. Gabriel testifies, and we agree, that given the state of the art and the teachings of Kinde 2011, it would have been obvious to analyze a plurality of regions each consisting of

a single base pair. Ex. 1002 ¶ 161. For example, Meyerson⁶ teaches “[n]ucleotide substitution mutations are the most common known somatic genomic alteration in cancer” and that next-generation sequencing methods “offer substantial benefits for copy number analysis, including higher resolution (up to the level of the single base insertion or deletion).” Ex. 1042, 690–691. Thus, we agree with Dr. Gabriel that it would have been routine for person of ordinary skill in the art to analyze a plurality of regions.

11. Claim 22

Claim 22 reads

The method of claim 1, wherein e) comprises i) and ii).

Ex. 1001, col. 64, ll. 33-34.

Petitioner contends that Kinde 2012 combined with Kinde 2011 teach the method of claim 22 as the combination of references teach performing both the normalization step and the processing step recited in step e). Pet. 52.

Patent Owner does not present a separate argument regarding the patentability of claim 22. *See* PO Resp. 41–46.

As discussed above, we find that Kinde 2012 combined with Kinde 2011 teach the steps of normalization followed by processing. Section II.E. 3.f. We conclude that Petitioner has shown by a preponderance of evidence that the subject matter of claim 22 would have been obvious to one skilled in the art over Kinde 2012 combined with Kinde 2011.

12. Claims 23–26

Claims 23 to 26 read

⁶ Meyerson et al., *Advanced in understanding cancer genome through second-generation sequencing*, 11 NATURE REVIEWS 685 (2010) (Ex. 1042, “Meyerson”).

23. The method of claim 1, wherein e) comprises i) normalizing the number of reads in the plurality of predefined regions to each other.

24. The method of claim 1, wherein e) comprises i) normalizing the number of unique sequence reads in the plurality of predefined regions to each other.

25. The method of claim 1, wherein e) comprises ii) processing the number of reads in the plurality of predefined regions with numbers obtained from the control sample.

26. The method of claim 1, wherein e) comprises ii) processing the number of unique sequence reads in the plurality of predefined regions with numbers obtained from the control sample.

Ex. 1001, col. 64, ll. 36–48.

Petitioner contends that it would have been obvious to apply the normalization and processing steps of step e) to both reads and unique sequence reads in view of the teachings of Kinde 2012 and Kinde 2011. Pet. 52.

Patent Owner does not present a separate argument regarding the patentability of claims 23–26. *See* PO Resp. 41–46.

While we agree with Petitioner that Kinde 2011 and Kinde 2012 teach the application of both normalization and processing to “reads” as recited in claims 23 and 25, we do not agree that they teach the application of those steps to “unique sequence reads” as recited in claims 24 and 26. As discussed above, we have construed the term “unique sequence reads” to exclude the use of barcodes. Both Kinde 2012 and Kinde 2011 teach the use of barcodes as a part of their process. Ex. 1023, 9531; Ex. 1041, 2. Petitioner has not pointed to, nor have we discerned, any teaching in the record to show that one skilled in the art would have applied the methods of Kinde 2012 or Kinde 2011 to sequences lacking a barcode.

We conclude that Petitioner has shown by a preponderance of the evidence that the subject matter of claims 23 and 25 would have been obvious over Kinde 2012 combined with Kinde 2011, but that Petitioner has not shown that the subject matter of claims 24 and 26 would have been obvious.

13. Conclusion

Based on the foregoing we conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 1–9, 20, 22, 23, and 25 are unpatentable as obvious over Kinde 2011 combined with Kinde 2012. We also conclude that Petitioner has not demonstrated by a preponderance of the evidence that claims 24 and 26 are unpatentable as obvious over Kinde 2011 combined with Kinde 2012.

F. Ground 3 – Obviousness based on Kinde 2011 and Forshew.

Petitioner contends that claims 10–13, 15–19, and 21 would have been obvious over the teachings of Kinde 2011 combined with Forshew.

1. Forshew

Forshew teaches a method for detecting rare “cancer mutations present in circulating [cell-free] DNA.” Ex. 1035, Abstract. Forshew teaches targeting DNA fragments from genomic regions, amplifying and sequencing the fragments, and then aligning the sequences to a reference sequence to identify mutations. *Id.*, Fig. 1, Supplement 1–4. The method can be used to monitor mutation frequencies over time using samples from a patient and to compare mutation frequencies in a sample to a reference sample. *Id.* at 8–9, Fig. 4.

2. Analysis

Petitioner contends that Kinde 2011 combined with Forshew teaches the step in claim 10 calling for the detection of a rare mutation in a “cell-free

or substantially cell-free sample obtained from a subject.” Pet. 56. In support of this contention, Petitioner points to the statement in Kinde 2011 that the method can be used “to determine the prevalence of rare mutations in a small region of the CTNNB1 gene,” and that the method can be used to identify rare mutations. Pet. 56 (citing Ex. 1023, 9533). Petitioner also relies on Forsheew, which describes a method of detecting rare mutations in cell-free tumor DNA. *Id.* (citing Ex. 1035, 1).

Petitioner contends that Kinde 2011 also teaches the filtering step of claim 10. Petitioner cites to Kinde 2011 as follows:

Only high-quality reads meeting the following criteria were used for subsequent analysis: (i) the first 25 bases passed the standard Illumina chastity filter; (ii) every base in the read had a quality score ≥ 20 ; and (iii) ≤ 3 mismatches to expected sequences. For the exogenous UID libraries, we additionally required the UIDs to have a quality score ≥ 30 .

Ex. 1023, SI2; Ex. 1002 ¶ 181.

Petitioner contends that Kinde 2011 teaches the step of mapping the sequence reads in claim 10. Pet. 57. In support of this contention, Petitioner cites to the teaching in Kinde 2011 where the sequences are aligned using the Eland pipeline, as well as the testimony of Dr. Gabriel. Pet. 57 (citing Ex. 1023, SI2; Ex. 1002 ¶ 183). Dr. Gabriel also testified that it would have been obvious to map the sequences against a human reference. Ex. 1002 ¶¶ 188–189.

Petitioner contends that Kinde 2011 teaches the step of determining unique sequence reads corresponding to the extracellular polynucleotides from among the sequence reads. Pet. 58. In support of this contention Petitioner cites to the portion of Kinde 2011 that teaches that the DNA molecules to be analyzed are assigned unique identifiers that are used to

group similar DNA fragments after amplification. Pet. 85; Ex. 1023, 9530, 9535. Petitioner contends that Kinde 2011 combined with Forshew teaches the step of claim 10 calling for “identifying a subset of mapped unique sequence reads that include a variant as compared to the reference sequence at each mappable base position.” Pet. 59.

Petitioner contends that Kinde 2011 teaches identifying a daughter fragment that includes a variant. Pet 59; Ex. 1023, 9530. Petitioner also contends that Forshew teaches a method that includes identifying subsets of reads that include a variant for each of multiple mappable base positions. Pet. 59. Petitioner contends that Forshew teaches the step for each mappable base position, calculating a ratio of (a) a number of mapped unique sequence reads that include a variant as compared to the reference sequence, to (b) a number of total unique sequence reads for each mappable base position. In support of this contention, Petitioner cites to Forshew where it teaches calculating an allele frequency for each specific genomic location. Pet. 60; Ex. 1035, 1, Fig 2; Ex. 1002 ¶ 197. Forshew teaches that an allele frequency is “calculated as the fraction of reads with the mutant.” Ex. 1035, Fig 2. Dr. Gabriel testifies that this calculation would require knowing the number of reads with the mutation and the total number of reads. Ex. 1002 ¶ 202. Petitioner contends that one skilled in the art would have understood that by teaching allele frequency, Forshew was also teaching “calculating a ratio of mapped sequence reads that include a variant as compared to the reference sequence to a number of total sequence reads.” Pet. 61.

Petitioner contends that Forshew teaches the step in claim 10 calling for “processing the ratio with a similarly derived number from a reference sample.” Pet. 63. Petitioner contends that the processing step simply means “comparing a ratio from a test sample to a ratio from a reference sample.”

Pet. 64; Ex. 1002 ¶ 208. Petitioner contends that the term “reference sample” is not defined in the Specification, but that one skilled in the art would understand the term to mean a sample that is “similar to the test sample and can be readily compared to the test sample.” Pet. 64; Ex. 1002 ¶ 209. Petitioner contends that Forshew teaches comparing the ratios determined to the test samples with ratios of reference samples, particularly samples with normal DNA. Pet. 65; Ex. 1035, 8, Fig. 4A; Ex. 1002 ¶¶ 211–215.

Petitioner contends that one skilled in the art would have been motivated to combine the teachings of Kinde 2011 and Forshew because they both relate to using similar technology to detect rare mutations. Pet. 54. Petitioner also contends that one skilled in the art would have been motivated to combine the references, because Forshew teaches the desirability to increase the accuracy of the method and reduce false positives and Kinde 2011 teaches an improved method to achieve that goal. Pet. 54; Ex. 1002 ¶ 170. Petitioner contends that one skilled in the art would have had a reasonable expectation of success because “the method of Kinde 2011 was capable of detecting mutations at precisely the mutation frequencies that were likely to occur in cell-free DNA.” Pet. 55.

In its Preliminary Response, Patent Owner contended that the references do not teach or suggest all elements of the claimed method. Prelim Resp. 42. Specifically, Patent Owner contended that Forshew fails to teach the analysis of unique sequence reads as required by claim 10. *Id.* at 44. Patent Owner contended that although Forshew refers to mapped sequence reads, nothing in Forshew teaches or suggests the use of unique sequence reads as required by claim 10. *Id.*

Patent Owner contended that Petitioner has not shown why one skilled in the art would have been motivated to combine Kinde 2011 and Forshew.

Id. at 44–49. Patent Owner contended that, other than a general allegation that the references are in the same field, Petitioner did not provide any specific reason why one skilled in the art would apply the teachings of Kinde 2001 to Forshew. *Id.* at 445. Patent Owner contended this is particularity important because Petitioner has not shown that Kinde 2011 is relevant to the cell-free DNA analysis described in Forshew. *Id.* Patent Owner also contended that Petitioner fails to describe with particularity how the references are to be combined. *Id.* at 48–49.

In our Decision to Institute, we concluded that Petitioner had failed to demonstrate a reasonable likelihood of showing that claims 10–13, 15–19 and 21 were unpatentable over Kinde 2011 combined with Forshew. Inst. Dec. 31. In the Decision to Institute, we found that Petitioner had failed to show that either Kinde 2011 or Forshew disclosed the use of unique sequence reads, i.e., a sequence read that contains unique sequences, such that the sequence reads can be identified without the need for a barcode or other added identifier. *Id.* In its Response, Patent Owner reiterates that the references fail to teach or suggest using a unique sequence read and that Petitioner failed to articulate a motivation to combine the references. PO Resp. 46–49.

As discussed above, our construction of the term “unique sequence reads” has not changed from the construction we gave the term in our Decision to Institute. As we found in the Decision to Institute, there is nothing in the teachings of either Kinde 2011 or Forshew that teach the use of unique sequence reads. Inst. Dec. 31.

In its Reply, Petitioner contends that the construction we gave to the term is in error and that Kinde 2011 specifically references unique identifiers to determine unique reads. Pet. Reply 26.

As discussed above, we do not find our original construction of the term “unique sequence reads” to be in error. Thus, the term excludes the use of barcodes or other added identifier.

While Kinde 2011 refers to unique identifiers, that term refers to the barcodes attached to the isolated sequences to aid in sorting the sequences. Ex. 1021, 9532, Figure 1. Thus, Kinde 2011 teaches the use of barcodes, which are excluded from the definition of unique sequence reads.

Claims 11–13, 15–19, and 21 depend, either directly or indirectly, on claim 10 and thus also require the use of “unique sequence reads,” which Petitioner fails to establish is taught by the prior art. Thus, based on the foregoing we conclude that Petitioner has failed to establish by a preponderance of the evidence that claims 10–13, 15–19, and 21 are unpatentable over Kinde 2011 combined with Forshew.

G. Ground 4 – Obviousness based on Kinde 2011, Forshew, and Kinde 2012.

Petitioner contends that the subject matter of claim 14 would have been obvious over Kinde 2011 combined with Kinde 2012 and Forshew. Pet. 69–70.

Claim 14 depends indirectly from claim 10, and adds the step of determining a percent of sequences having copy number variation or rare mutation or variant in the bodily sample by calculating a percent of predefined regions with an amount of polynucleotides above or below a threshold. Ex. 1001, col. 64, ll. 6–11.

Petitioner contends that Kinde 2012 teaches this additional step. Pet. 70. Petitioner supports this contention by pointing to the teaching in Kinde 2012 that when the z-score for the samples were calculated, “no autosome in any sample has a z-score outside the range of -3.0 and 3.0.” Pet. 70; Ex.

1041, Fig. 2. Petitioner contends that this passage teaches identifying the amount of nucleotides above and below a certain threshold.

Patent Owner contends that Petitioner has failed to show that claim 14 would have been obvious for the same reasons as discussed for claim 10 above. PO Resp. 51. Patent Owner also contends that Petitioner has failed to show how the cited portion of Kinde 2012 teaches the limitation of claim 14. *Id.*

In its Reply, Patent Owner contends claim 14 is not unpatentable for the reasons argued with respect to Ground 3 above. PO Resp. 51. Patent Owner also contends that none of the references teaches the limitation calling for “calculating a percentage of predefined regions with an amount of polynucleotides above or below a threshold.” *Id.*

For the reasons stated above with respect to Ground 3, we conclude that Petitioner has failed to demonstrate by a preponderance of the evidence that claim 14 is unpatentable over Kinde 2011 combined with Forshew and Kinde 2012.

III. PATENT OWNER’S MOTION TO AMEND

Patent Owner’s motion to amend is contingent on the Board’s finding of unpatentability of the challenged claims 1–9, 20, and 22–26. MTA 1. Because we conclude that Petitioner has demonstrated that the challenged claims are unpatentable, we proceed to consider Patent Owner’s motion to substitute claims 27–41 for claims 1–9, 20, and 22–26. For the reasons discussed below, Patent Owner’s motion to amend is denied.

A. Threshold Requirements

In an *inter partes* review, claims may be added as part of a proposed motion to amend. 35 U.S.C. § 316(d). The Board must assess the

patentability of the proposed substitute claims “without placing the burden of persuasion on the patent owner.” *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1328 (Fed. Cir. 2017) (en banc); *see also Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-001129, Paper 15 at 3–4 (PTAB Feb. 25, 2019) (precedential). Subsequent to the issuance of *Aqua Products*, the Federal Circuit issued a decision in *Bosch Automotive Service Solutions, LLC v. Matal*, 878 F.3d 1027 (Fed. Cir. 2017) (“*Bosch*”), as well as a follow-up Order amending that decision on rehearing. *See Bosch Auto. Serv. Sols., LLC v. Iancu*, No. 2015-1928 (Fed. Cir. Mar. 15, 2018) (Order on Petition for Panel Rehearing).

In accordance with *Aqua Products*, *Bosch*, and *Lectrosonics*, a patent owner does not bear the burden of persuasion to demonstrate the patentability of the substitute claims presented in the motion to amend. Rather, ordinarily, “the petitioner bears the burden of proving that the proposed amended claims are unpatentable by a preponderance of the evidence.” *Bosch*, 878 F.3d at 1040 (as amended on rehearing); *see Lectrosonics*, Paper 15 at 3–4. In determining whether a petitioner has proven unpatentability of the substitute claims, the Board focuses on “arguments and theories raised by the petitioner in its petition or opposition to the motion to amend.” *Nike, Inc. v. Adidas AG*, 955 F.3d 45, 51 (Fed. Cir. 2020).

Patent Owner’s proposed substitute claims, however, must still meet the statutory requirements of 35 U.S.C. § 316(d) and the procedural requirements of 37 C.F.R. § 42.121 as a threshold matter. *Lectrosonics*, Paper 15 at 4–8.. Accordingly, Patent Owner must demonstrate: (1) the amendment proposes a reasonable number of substitute claims; (2) the amendment does not seek to enlarge the scope of the claims of the patent or

introduce new subject matter; (3) the amendment responds to a ground of unpatentability involved in the trial; and (4) the original disclosure sets forth written description support for each proposed claim. *See* 35 U.S.C. § 316(d)(1)(B), (3); 37 C.F.R. § 42.121;

B. Proposed Substitute Claims

Proposed substitute claims 27–41 are reproduced below with markings showing proposed changes from claims 1–9, 20, and 22–26 respectively. Underlining indicates inserted text and double brackets indicates deletions.

27. (Substitute for claim 1, if found unpatentable) A method for detecting sub-chromosomal copy number variation, comprising:
- a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads;
 - b) filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold;
 - c) mapping the plurality of sequence reads to a reference sequence;
 - d) quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence; and
 - e) determining sub-chromosomal copy number variation in one or more of the plurality of predefined regions by:
 - i) normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or
 - ii) processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample,
- wherein each of the predefined regions is up to 100 kb.

28. (Substitute for claim 2, if found unpatentable) The method of claim [[1]] 27, further comprising isolating extracellular polynucleotides from the bodily sample.

29. (Substitute for claim 3, if found unpatentable) The method of claim [[1]] 27, further comprising generating copies of the extracellular polynucleotides prior to sequencing.

30. (Substitute for claim 4, if found unpatentable) The method of claim [[1]] 27, further comprising determining a percent of sequences having copy number variation or rare mutation or variant in the bodily sample.

31. (Substitute for claim 5, if found unpatentable) The method of claim [[1]] 27, further comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to sequencing.

32. (Substitute for claim 6, if found unpatentable) The method of claim [[5]] 31, wherein each barcode attached to the extracellular polynucleotides or fragments thereof prior to sequencing is not unique.

33. (Substitute for claim 7, if found unpatentable) The method of claim [[5]] 31, wherein each barcode comprises a fixed or semi-random oligonucleotide sequence that in combination with a diversity of molecules sequenced from a selected region enables identification of unique molecules.

34. (Substitute for claim 8, if found unpatentable) The method of claim [[1]] 27, further comprising selectively enriching regions from a genome or transcriptome of the subject prior to sequencing.

35. (Substitute for claim 9, if found unpatentable) The method of claim [[1]] 27, further comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to an amplification or enrichment step.

36. (Substitute for claim 20, if found unpatentable) The method of claim [[1]] 27, wherein each of the plurality of predefined regions is a single base.

37. (Substitute for claim 22, if found unpatentable) The method of claim [[1]] 27, wherein e) comprises i) and ii).

38. (Substitute for claim 23, if found unpatentable) The method of claim [[1]] 27, wherein e) comprises i) normalizing the number of reads in the plurality of predefined regions to each other.

39. (Substitute for claim 24, if found unpatentable) The method of claim [[1]] 27, wherein e) comprises i) normalizing the number of unique sequence reads in the plurality of predefined regions to each other.

40. (Substitute for claim 25, if found unpatentable) The method of claim [[1]] 27, wherein e) comprises ii) processing the number of reads in the plurality of predefined regions with numbers obtained from the control sample.

41. (Substitute for claim 26, if found unpatentable) The method of claim [[1]] 27, wherein e) comprises ii) processing the number of unique sequence reads in the plurality of predefined regions with numbers obtained from the control sample.

MTA, App'x A.

C. Statutory Requirements for a Motion to Amend

We construe only those terms that are in controversy, and only to the extent necessary to resolve the controversy. *See Vivid Techs.*, 200 F.3d at 803; *see also Nidec Motor Corp.*, 868 F.3d at 1017 (applying *Vivid Techs.* in the context of an *inter partes* review). None of the newly added claim terms are in controversy, so no claim construction is required.

The number of substitute claims is also deemed to be reasonable. Patent Owner proposed 15 substitute claims to replace an equal number of original claims. *See* MTA, App’x. A.

Moreover, for the reasons discussed below, we determine that the proposed substitute claims do not broaden the invention and that substitute claims 27–41 are definite and have adequate written description support and that a reasonable number of claims have been proposed..

1. The Proposed Substitute Claims Do Not Broaden the Scope of the Claims

Proposed substitute claim 27 adds limitations limiting copy number variations to sub-chromosomal variations and limits the predefined regions to 100 kb or less. MTA 4. The amendments narrow the types of mutations detected by the claimed method and narrow the predefined regions analyzed by the method. The amendments do not broaden the scope of the claims.

2. The Proposed Substitute Claims Are Supported by the Specification

Patent Owner contends that the added limitation limiting the copy number variations to sub-chromosomal variations is supported by the Specification and by the prior applications. MTA 5–11. Patent Owner contends that one skilled in the art reading the present Specification and the prior applications would understand that the Specification teaches detecting copy number variation at the sub-chromosomal level. *Id.* Patent Owner points to the teaching in the Specification that detection is performed with “sub-chromosomal resolution: e.g., at least 100 megabase resolution, at least 10 megabase resolution, at least 1 megabase resolution, at least 100 kilobase resolution, at least 10 kilobase resolution or at least 1 kilobase resolution.” MTA 6–7 (emphasis omitted); Ex. 1001, col. 7, ll. 38–45.

Patent Owner contends that the Specification also supports the limitation limiting the predefined regions to up to 100 kb. MTA 10–11. Patent Owner supports this contention by pointing to the teaching in the Specification where it states “In some embodiments, predefined regions are uniform or substantially uniform in size, about 10 kb, 20 kb, 30 kb 40 kb, 50 kb, 60 kb, 70 kb, 80 kb, 90 kb, or 100 kb in size.” *Id.*; Ex. 1001, col. 3, ll. 61–63.

Petitioner contends that the term “sub-chromosomal copy number variation” is not supported by the Specification. MTA Opp. 2–4. Petitioner argues that while the term sub-chromosomal is used in the Specification, the term is used in connection with the resolution achieved by the claimed method and not the size of the copy number variation. *Id.* at 3. Petitioner also contends that the discussion of genetic aberrations in the Specification does not support the term sub-chromosomal copy number variations. *Id.* at 4.

Petitioner does not appear to contend that the limitation restricting the predefined region to up to 100 kb is not supported by the Specification. *See* MTA Opp. 4.

We have considered the arguments presented by the parties and the evidence of record and conclude that the proposed substitute claims are supported by the present disclosure. While we agree with Petitioner that the Specification does not specifically use the term “sub-chromosomal copy number variation” that does not mean that the term is unsupported by the Specification. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (finding support “‘need not be used *in haec verba*’”). As Dr. Bustamante testifies, and we agree, one skilled in the art, reading the present specification, would have understood that the Specification discloses a

method for detecting sub-chromosomal copy number variations. Ex. 2024 ¶¶ 35–44.

Specifically, the Specification refers to performing the claimed method at a sub-chromosomal resolution of “at least 100 megabase resolution, at least 10 megabase resolution, at least 1 megabase resolution, at least 100 kilobase resolution, at least 10 kilobase resolution or at least 1 kilobase resolution.” Ex. 1001, col. 7, ll. 38–45. While this passage refers to sub-chromosomal resolution and not sub-chromosomal copy number variation, we are persuaded by Dr. Quackenbush’s testimony that the level of resolution speaks to the size of the aberration detected. Ex. 1051, 104–107. We agree with Dr. Bustamante that one skilled in the art would have understood that this passage teaches detecting copy number variation at the sub-chromosomal level. Ex. 2024 ¶¶ 34–45.

3. The Proposed Substitute Claims Address a Ground of Unpatentability Raised in the Petition

The proposed substitute claims address two issues of patentability raised in the Petition, namely anticipation by Chiu and obviousness based on Kinde 2012 combined with Kinde 2011. In those grounds, we found that the references disclosed detecting copy number variation in that the references disclosed detection of aneuploidy, which is a type of copy number variation involving entire chromosomes. *See* Section II.E.3, *supra*. We also found that predefined regions included whole chromosomes and that the references disclosed or taught predefined regions that include whole chromosomes.

The amendments introduced in the proposed substitute claims address both of these issues by limiting copy number variations to sub-chromosomal copy number variations and by limiting predefined regions to a maximum of 100 kb, which is smaller than a whole chromosome.

D. Unpatentability of the Proposed Substitute Claims

Petitioner asserts that the proposed substitute claims are unpatentable under 35 U.S.C. §§ 102 or 103. MTA Opp. 1. Petitioner contends that claims 27 and 37–41 are anticipated by Rava.⁷ *Id.* at 7–15. Petitioner also contends that the subject matter of claims 28–36 would have been obvious over Rava. *Id.* at 15–21. Petitioner also contends that the subject matter of claims 27 and 38–41 would have been obvious over Hyland.⁸ *Id.* at 21–25. Petitioner supports its contentions with the declaration of Dr. Gabriel. Ex. 1060 Patent Owner disagrees. MTA Reply 1–12. Patent Owner relies on the declaration of Dr. Bustamante. Ex. 2037.

E. Anticipation by Rava

Petitioner contends that proposed substitute claims 27 and 37–41 are anticipated by Rava. MTA Opp. 7–15.

1. Rava

U.S. Patent No. 9,323,888 (“Rava”), entitled “Detecting and Classifying Copy Number Variation,” was filed as U.S. Patent Application No. 13/600,043 on August 30, 2012. Ex. 1055, codes (10), (54), (21), (22).). Rava describes methods “for determining copy number variations (CNV) of a sequence of interest in a test sample that comprises a mixture of nucleic acids that are known or are suspected to differ in the amount of one or more sequence [sic] of interest.” *Id.* at col. 2, ll. 31–35; Ex. 1060 ¶¶ 19–23. “Sequences of interest include genomic segment sequences ranging from, e.g., kilobases (kb) to megabases (Mb) to entire chromosomes that are known or are suspected to be associated with a genetic or a disease

⁷ Rava et al., US 9,323,888 B2, issued April 26, 2016 (Ex. 1055) (“Rava”).

⁸ Hyland et al., US 2012/0046877 A1, published February 23, 2012 (Ex. 1061) (“Hyland”).

condition.” Ex. 1055, col. 27, l. 65–col. 28, l. 1; *see also id.* at col. 2, ll. 40–45; Ex. 1060 ¶ 21.

Rava applies its methods to analyze nucleic acid molecules in test samples, such as “maternal sample[s],” which include “a mixture of fetal and maternal cell-free DNA molecules.” Ex. 1055, col. 9, ll. 8–10; Ex. 1060 ¶ 22. Rava’s methods “may employ next generation sequencing technology (NGS)” to obtain quantitative information, e.g., “each sequence read is a countable ‘sequence tag’ representing an individual clonal DNA template or a single DNA molecule.” Ex. 1055, col. 38, ll. 62–64, col. 39, ll. 2–16; Ex. 1002 ¶ 23. Rava uses generated sequencing data, *inter alia*, to:

align the reads to portions of a reference sequence/genome and determine the amount of DNA (e.g., the number of reads) that map to defined portions [of] the reference sequence (e.g., to defined chromosomes or chromosome segments); calculate a dose of one or more of the defined portions by normalizing the amount of DNA mapping to the defined portions with an amount of DNA mapping to one or more normalizing chromosomes or chromosome segments selected for the defined portion; determining whether the dose indicates that the defined portion is “affected[.]”

Ex. 1055, col. 39, ll. 23–33; Ex. 1002 ¶ 23.

2. *Analysis of Proposed Substitute Claim 27*

Proposed substitute claim 27 is similar to claim 1 discussed above with the added limitations that the copy number variation is sub-chromosomal and that the predefined region contains up to 100 kb. MTA 4–5.

a) *A method for detecting sub-chromosomal copy number variation comprising*

Petitioner contends that Rava discloses this limitation. MTA Opp. 7. Specifically, Petitioner contends that Example 20 of Rava discloses a

method for noninvasively detecting fetal sub-chromosomal abnormalities including sub-chromosomal copy number variations. *Id.*

Patent Owner contends that Rava is directed to the detection of aneuploidy and that aneuploidy is outside the scope of the proposed substitute claims. MTA Reply 5.

We have considered the arguments presented by the parties and the evidence of record and conclude that Rava discloses a method for detecting sub-chromosomal copy number variation. Example 20 of Rava specifically discloses a method for detecting “mosaic sub-chromosomal copy number change . . . and [] sub-chromosomal duplication.” Ex. 1055, col. 218, ll. 50–61; Ex. 1060 ¶ 32.

Patent Owner argues that Petitioner relies on examples in Rava that are directed to aneuploidy, which is not sub-chromosomal copy number variation. MTA Reply 5. While Patent Owner may be correct with respect to some examples, Petitioner specifically references Example 20 of Rava with respect to the limitation calling for detection of sub-chromosomal copy number variation. MTA Opp. 7. , Example 20 of Rava clearly relates to sub-chromosomal copy number variations. Ex. 1055, col. 218, ll. 50–61; Ex. 1060 ¶ 32.

Patent Owner also argues that a related Rava reference⁹ (“Rava 2”) was cited in prosecution as an anticipatory reference and that the rejection based on Rava 2 was overcome based on the lack of the filtering step. MTA Reply 6. We are not persuaded by this argument.

⁹ Rava et al, US 2013/0029852 A1, published January 31, 2013 (Ex. 3002) (“Rava 2”). While both parties reference Rava 2 in their arguments, neither party made the reference part of the record.

We begin by noting that that 35 U.S.C. § 325(d) does not apply to motions to amend: “*In determining whether to institute or order a proceeding* under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” *Id.* (emphasis added). In particular, § 325(d) does not apply to motions to amend because the Office has not previously passed on a proposed substitute claim before it was proposed.

Moreover, even if we were to consider whether the same or substantially the same prior art or arguments were previously presented to the Office, we find that there are significant differences between the two Rava references. The Rava reference cited by Petitioner is a continuation-in-part of U.S. Appl. No. 13/555,037. Ex. 1001, code (63). Rava 2 is the publication that corresponds to that application. Ex. 3002 (21). As Petitioner points out, Rava 2 does not contain Example 20, which serves as the basis for most, if not all of Petitioner’s arguments opposing Patent Owner’s motion to amend. MTA Sur-Reply 6; *compare* Ex. 1055, col. 218, l. 43 – col. 226, l. 50 *with* Ex. 3002 ¶¶ 916–922 (Example 19 is the last example in Ex. 3002). As discussed above, Example 20 relates specifically to detecting sub-chromosomal aberrations including sub-chromosomal copy number variations. Thus, for purpose of this decision, we find that Rava 2 is not substantially the same as Rava, and irrelevant to Petitioner’s arguments in its opposition to Patent Owner’s motion to amend.

- b) Sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads*

Petitioner contends that Rava discloses this limitation. MTA Opp. 7–8. Petitioner contends that Rava discloses “sequencing cell free DNA from the maternal test sample to provide the sequence reads.” *Id.* (quoting Ex. 1055, col. 12, ll. 5–34). Petitioner also contends that Example 20 of Rava discloses obtaining polynucleotides from maternal plasma samples, which are then sequenced to produce sequence reads. *Id.* (citing Ex. 1055, col. 219, ll. 32–40).

Patent Owner does not present a specific argument with respect to this limitation. *See* MTA Reply 5–9.

We find that Rava discloses the recited limitation. Rava discloses using sequences that originated from maternal blood samples. Ex. 1055, col. 219, ll. 10–31. The samples were then sequenced to produce a set of sequence reads. *Id.* at col. 219, ll. 31–44.

- c) Filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold*

Petitioner contends that Rava discloses this limitation. MTA Opp. 8–9. Petitioner contends that, in Example 20, Rava only uses reads that can be unambiguously mapped to a single genomic location and that up to two mismatches during alignment were allowed to be used in the analysis. *Id.* (citing Ex. 1055, col. 220, ll. 31–38).

Patent Owner contends that Rava does not disclose a filtering step. MTA Reply 6–7. Rather Rava discloses a threshold of unique tags in a sample, which is not the same as a mapping score or mapping threshold. *Id.* Patent Owner also contends that Rava allows a certain amount of mismatches in its analysis. *Id.*

We have considered the arguments presented by the parties and the evidence of record and conclude that Rava discloses the recited filtering step. Example 20 of Rava discloses

Sequence reads were aligned to the human genome assembly hg19 obtained from the UCSC database (hgdownload.cse.csc.edu/goldenPath/hgl 9/bigZips/). Alignments were carried out utilizing the Bowtie short read aligner (version 0.12.5), allowing for up to two base mismatches during alignment. *Only reads that unambiguously mapped to a single genomic location were included.*

Ex. 1055, col. 220, ll. 31–38 (emphasis added). We agree with Dr. Gabriel that this discloses the recited filtering step of substitute claim 27. Ex. 1060 ¶¶ 40–42.

d) Mapping the plurality of sequence reads to a reference sequence

Petitioner contends that Rava discloses this limitation. MTA Opp. 9–10. Petitioner contends that Rava discloses “aligning the sequence reads to one or more chromosome reference sequences using a computing apparatus and thereby providing sequence tags corresponding to the sequence reads.” *Id.* (quoting Ex. 1055, col. 10, ll. 49–52). Petitioner also contends that Example 20 of Rava discloses “[s]equence reads were aligned to the human genome assembly hg19 obtained from the UCSC database.” *Id.* at 10 (quoting Ex. 1055, col. 220, ll. 31–43).

Patent Owner does not provide a specific argument regarding this limitation. *See* MTA Reply 5–9.

We find that Rava discloses the mapping step recited in substitute claim 27. Rava discloses aligning the sequences to the human genome assembly hg19. Ex. 1055, col. 220, ll. 31–42. Dr. Gabriel testifies, and we

agree, that this disclosure in Rava meets the requirement that the sequences are mapped against a reference sequence. Ex. 1060 ¶¶ 44–45.

e) Quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence

Petitioner contends that Rava discloses this limitation. Petitioner contends that Rava discloses “determin[ing] the amount of DNA (e.g., the number of reads) that map to defined portions the reference sequence (e.g., to defined chromosomes or chromosome segments).” MTA Opp. 10 (quoting Ex. 1055, col. 39, ll. 17–36). Petitioner also contends that this step is exemplified in Example 20 of Rava where it states “reads that unambiguously mapped to a single genomic location were included,” and “[g]enomic sites at which [those] reads mapped were counted as tags.” *Id.* at 11 (quoting Ex. 1055, col. 220, ll. 36–38).

Patent Owner contends that Rava does not disclose the quantification step as the portions of Rava relied upon by Petitioner are directed to detection of aneuploidy and not sub-chromosomal copy number variation. MTA Reply 5. Patent Owner also contends that Rava does not disclose predefined regions as the term is used in substitute claim 27. *Id.* at 7. Patent Owner contends that the term predefined means that the regions are defined in advance and that Rava does not define the regions until after the mapping and quantification steps are performed. *Id.*

We have considered the arguments presented by the parties and the evidence of record and find that Rava discloses the quantification step of substitute claim 27.

Rava discloses the step of “determin[ing] the amount of DNA (e.g., the number of reads) that map to defined portions the reference sequence (e.g., to defined chromosomes or chromosome segments).” Ex. 1055, col.

39, ll. 17–36. In Example 20, Rava discloses that “reads that unambiguously mapped to a single genomic location were included,” and “[g]enomic sites at which [those] reads mapped were counted as tags.” *Id.*, col. 220, ll. 36–38. Thus, we agree with Dr. Gabriel that Rava discloses the quantification step of substitute claim 27. Ex. 1060 ¶ 49.

We are not persuaded by Patent Owner’s argument regarding Rava being limited to detecting aneuploidy. As discussed above, Example 20 of Rava specifically discloses detecting sub-chromosomal copy number variation. Ex. 1055, col. 218, ll. 50–61; Ex. 1060 ¶ 32.

We are also not persuaded by Patent Owner’s argument that Rava does not disclose predefined regions. While Rava discloses that the sequences can be sorted into bins after the tags are counted, the bins themselves are defined before the tags are sorted. For example, in Example 20, the bins are defined by size. Ex. 1055, col. 220, ll. 44–47. Moreover, Rava discloses that the bin boundaries can be defined prior to alignment. *Id.* at col. 143, ll. 10–11; *see also id.* at col. 142, ll. 4–17; col. 143, ll. 10–27 and col. 145, ll. 46–59.

f) Determining sub-chromosomal copy number variation in one or more of the plurality of predefined regions by i) normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or ii) processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample,

Petitioner contends that Rava discloses these limitations. MTA Opp. 11. Petitioner contends that Rava discloses “[d]etection of a sub-chromosomal abnormality was a multi-step process for classifying specific regions as having a copy number variant.” *Id.* (quoting Ex. 1055, col. 221, ll.

41–54). Petitioner contends that Rava discloses both the normalization step and the processing step of substitute claim 27. *Id.* at 11–14.

Patent Owner presents the same arguments regarding this claim element as it did with respect to the quantification step discussed above. *See* MTA Reply 5–7.

We have considered the arguments presented by the parties and the evidence of record and find that Rava discloses determining sub-chromosomal copy number variation using normalization and processing steps. In Example 20, Rava discloses “[d]etection of a sub-chromosomal abnormality was a multi-step process for classifying specific regions as having a copy number variant.” Ex. 1055, col. 221, ll. 41–43. Rava teaches that the data for each bin is first normalized. *Id.* at col. 220, ll. 44–57. Rava then discloses that the results of the normalization step were then examined for deviations from the median values measures across multiple samples to detect sub-chromosomal differences including copy number variations. *Id.* at col. 220, l. 63 – col. 221, l. 12.

As discussed above, we are not persuaded by Patent Owner’s arguments that Rava is limited to detecting aneuploidy or that Rava does not disclose predefined regions.

g) Wherein each of the predefined regions is up to 100kb.

Petitioner contends that Rava discloses this limitation in that Rava teaches that the bins can be up to 100 kb in size. MTA Opp. 14.

Patent Owner does not present a separate argument with respect to this limitation. *See* MTA Reply 5–9.

We find that Rava discloses this limitation. In Example 20, Rava discloses dividing the sequences into 1Mb and 100 kb bins. Ex. 1055, col. 220, ll. 44–45. Dr. Gabriel has testified that the bins of Rava are the

equivalent of the predefined regions recited in proposed substitute claim 27 and that Rava discloses bins of up to 100 kb. Ex. 1060 ¶¶ 52, 61–62.

h) Conclusion

Based on the foregoing we conclude that Petitioner has demonstrated by a preponderance of the evidence that proposed substitute claim 27 is unpatentable as anticipated by Rava.

3. Proposed substitute claims 37–41

Proposed substitute claims 37–41 depend from proposed substitute claim 27. Proposed substitute claim 37 recites that the method comprises both steps e)i) and e)ii). Proposed substitute claims 38 and 39 recite that step e) comprises i) normalizing the number of reads or unique sequence reads, respectively, in the plurality of predefined regions to each other; and proposed substitute claims 40 and 41 recite that step e) comprises ii) processing the number of reads or unique sequence reads, respectively, in the plurality of predefined regions with numbers obtained from the control sample. MTA 25.

Petitioner contends that proposed substitute claims 37–41 are anticipated by Rava because Rava discloses the elements recited in the claims. MTA Opp. 12. Specifically, Petitioner contends that Rava discloses using both a normalization and a processing step and that Rava discloses the use of unique reads which also satisfies the read limitation. *Id.*

Patent Owner contends that the proposed substitute claims are not anticipated for the reasons proposed substitute claim 27 is not anticipated. MTA Reply 8. Patent Owner also argues that Petitioner has not established that Rava discloses “unique sequence reads.” *Id.* Patent Owner supports this argument by pointing out that Dr. Gabriel has been inconsistent in the use of the term when analyzing Rava. *Id.*

We have considered the arguments presented by the parties and the evidence of records and find that proposed substitute claims 37–41 are anticipated by Rava.

Proposed substitute claim 37 calls for the use of both the normalization step and the processing step of claim 27. MTA 25. As discussed above, in Example 20, Rava discloses the use of both a normalization step and a processing step.

Proposed substitute claim 38 calls for performing the normalization step of proposed substitute claim 27 using reads. MTA 25. As discussed above, Rava discloses normalizing sequences, which “are unambiguously mapped to a single genomic location.” Ex. 1055, col. 220, ll. 32–43. Dr. Gabriel testifies, and we agree, that the sequences constitute reads as the term is used in the substitute claims. *See* Ex. 1060 ¶¶ 46, 48–49.

Proposed substitute claim 39 calls for performing the normalization step of proposed substitute claim 27 using unique sequence reads. MTA 25. As discussed above, Rava discloses normalizing sequences, which “are unambiguously mapped to a single genomic location.” Ex. 1055, col. 220, ll. 32–43. Dr. Gabriel testifies, and we agree, that sequences that can be mapped to only one location are unique sequence reads. Ex. 1060 ¶¶ 48–49. This conclusion is consistent with our construction of unique sequence reads. Section II.C.3 *supra*.

Proposed substitute claim 40 calls for performing the processing step of proposed substitute claim 27 using reads. MTA 25. As discussed above, Rava discloses processing sequences, which “are unambiguously mapped to a single genomic location.” Ex. 1055, col. 220, l. 63–col. 221, l. 12. Dr. Gabriel testifies, and we agree, that the sequences constitute reads as the term is used in the substitute claims. *See* Ex. 1060 ¶¶ 46, 48–49.

Proposed substitute claim 41 calls for performing the processing step of proposed substitute claim 27 using unique sequence reads. MTA 25. As discussed above, Rava discloses normalizing sequences, which are “unambiguously mapped to a single genomic location.” Ex. 1055, col. 220, l. 63–col. 221, l. 12. Dr. Gabriel testifies, and we agree, that sequences that can be mapped to only one location are unique sequence reads. Ex. 1060 ¶¶ 48–49. This conclusion is consistent with our construction of unique sequence reads. Section II.C.3 *supra*.

We are unpersuaded by Patent Owner’s arguments. As discussed above, we find that proposed substitute claim 27 is anticipated by Rava. Section III.E.2 *supra*.

With respect to the term unique sequence reads, while Dr. Gabriel may have used two different definitions for the term, as discussed above, Rava’s disclosure of using sequences that are “unambiguously mapped to a single genomic location” meets the definition of the term as we have construed it. Moreover, in the method disclosed in Example 20, Rava does not resort to the use of bar codes or other tags to sort or identify the sequences. *See* Ex. 1055 col. 220, ll. 32–43.

Based on the foregoing we conclude that Petitioner has demonstrated by a preponderance of the evidence that proposed substitute claims 37–41 are unpatentable as anticipated by Rava.

F. Obviousness based on Rava

Petitioner contends that the subject matter of proposed substitute claims 28–36 would have been obvious to one skilled in the art at the time the invention was made over Rava. MTA Opp. 15.

1. Proposed Substitute Claim 28

Proposed substitute claim 28 depends from proposed substitute claim 27 and adds the step of “isolating extracellular polynucleotides from the bodily sample.” MTA 23. Petitioner contends that Rava teaches this step. MTA Opp. 15.

Patent Owner argues that proposed substitute claim 28 is not rendered obvious by Rava, because Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the step of isolating extracellular polynucleotides from a bodily sample. Rava teaches that “[t]o separate cell-free DNA from cells in a sample, various methods including, but not limited to fractionation, centrifugation (e.g., density gradient centrifugation), DNA-specific precipitation, or high-throughput cell sorting and/or other separation methods can be used.” Ex. 1055, col. 54, ll. 2–7. Dr. Gabriel testifies, and we agree, that a person of ordinary skill in the art would have understood that, applying Rava’s teachings “[t]o separate cell-free DNA from cells in a sample” to maternal plasma samples, which include cells and cell-free DNA, would isolate cell-free DNA from a bodily sample. Ex. 1060 ¶ 67.

Patent Owner’s argument to the contrary is unpersuasive. As discussed above, we find that Rava discloses all of the elements of proposed substitute claim 27.

2. Proposed Substitute Claim 29

Proposed substitute claim 29 depends from proposed substitute claim 27 and adds the step of generating copies of the extracellular polynucleotides prior to sequencing. MTA 23. Petitioner contends that Rava teaches this step. MTA Opp. 16.

Patent Owner argues that proposed substitute claim 29 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the step of generating copies of the extracellular polynucleotides prior to sequencing. Rava teaches that “[i]n various embodiments the cfDNA present in the sample can be enriched specifically or non-specifically prior to use (e.g., prior to preparing a sequencing library).” Ex. 1055, 54:15–17. Rava explains that nonspecific enrichment of sample DNA can refer, e.g., “to the whole genome amplification of the genomic DNA fragments of the sample that can be used to increase the level of the sample DNA prior to preparing a cfDNA sequencing library.” *Id.* at 54:17–42. Dr. Gabriel testifies, and we agree, that one skilled in the art would understand that Rava teaches generating copies of the extracellular polynucleotides prior to sequencing. Ex. 1060 ¶¶ 69–71.

Again we are unpersuaded by Patent Owner’s argument to the contrary for the reasons set forth above.

3. Proposed Substitute Claim 30

Proposed substitute claim 30 depends from proposed substitute claim 27 and adds the step of “determining a percent of sequences having copy number variation or rare mutation or variant in the bodily sample.” MTA 23. Petitioner contends that Rava teaches this step. MTA Opp. 16–17.

Patent Owner argues that proposed substitute claim 30 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the step of determining a percent of sequences having copy number variation or rare mutation or variant in the bodily sample. Rava teaches

The fraction of the minor allele for any given informative marker is calculated by dividing the peak height of the minor component by the sum of the peak height for the major component, and the fraction is expressed as a percent for each informative locus as

$$(\% \text{ fetal fraction}) = \left[\frac{\text{peak height of minor allele(s)}}{\sum (\text{peak height of major allele(s)})} \right] \times 100 \quad \text{Equation 3}$$

Ex. 1055, col. 134, ll. 40–50. Dr. Gabriel testifies, and we agree, that this method teaches one skilled in the art how to calculate the percentage of sequences having copy number variation or rare mutation or variant in the bodily sample. Ex. 1060 ¶¶ 72–74.

Again we are unpersuaded by Patent Owner’s argument to the contrary for the reasons set forth above.

4. Proposed Substitute Claim 31

Proposed substitute claim 31 recites that the method of proposed substitute claim 27 further comprises “attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to sequencing.” MTA 23.

Petitioner contends that Rava teaches each of the limitations recited in substitute claim 31. MTA Opp. 17–18.

Patent Owner argues that proposed substitute claim 31 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the limitation of proposed substitute claim 31.

Rava teaches “Parallelizing sequencing for multiple samples i.e. multiplex sequencing, requires the incorporation of sample-specific index sequences, also known as barcodes, during the preparation of sequencing

libraries.” Ex. 1055, col. 77, ll. 14–17. Rava teaches that one application of the index sequences is to verify the integrity of the multiple samples, which is “accomplished by first grouping sequence tags associated with identical index sequences to associate the genomic and marker sequences and distinguish sequences belonging to each of the libraries made from genomic molecules of a plurality of samples.” *Id.* at col. 78, ll. 9–14. Dr. Gabriel testifies, and we agree, that because Rava discloses adding “sample-specific” barcodes prior to sequencing in order to later distinguish sequences from each sample, a person of ordinary skill in the art would have understood that extracellular polynucleotides in a sample would have a common (i.e., non-unique) index (i.e., barcode). Ex. 1060 ¶¶ 76-77.

In addition, Rava describes that the sample-specific barcodes can be incorporated into PCR primers used for amplification. Ex. 1055, col. 77, ll. 14–25. Dr. Gabriel testified that a person of ordinary skill in the art would have understood that a “sample specific” barcode sequence would be known or “fixed” prior to adding the barcode to polynucleotides. Ex. 1060 ¶ 78. Dr. Gabriel also testifies, and we agree, that because unique molecules in a multiplex sample can be identified by (1) mapping sequence reads to determine their start/end coordinates (*see, e.g.*, Ex. 1055 166:58–167:5), and (2) attributing different reads with the same start/end coordinates to particular samples using sample-specific barcodes (*id.*, 77:14–17), a person of ordinary skill in the art would have understood that Rava’s fixed sample-specific barcodes in combination with the sequenced molecules enable identification of unique molecules. Ex. 1060 ¶¶ 78–79; *see also* Ex. 1001, col. 37, ll. 50–59.

Again we are unpersuaded by Patent Owner’s argument for the reasons set forth above.

5. *Proposed Substitute Claim 32*

Proposed substitute claim 32 adds the limitation to proposed substitute claim 31 that the barcode attached to the polynucleotides or fragments thereof are not unique. MTA, 24.

Petitioner contends that proposed substitute claim 32 is unpatentable as obvious over Rava. MTA Opp. 17–18. Petitioner contends that Rava teaches that the index sequences, i.e. barcodes, are sample specific and that one skilled in the art would understand this to mean that the barcodes are not unique. *Id.* (citing Ex. 1055, col. 77, ll. 14–17; col. 78, ll. 9–14; Ex. 1060 ¶¶ 76–77).

Patent Owner argues that proposed substitute claim 32 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the limitation of proposed substitute claim 32.

Rava teaches

Parallelizing sequencing for multiple samples i.e. multiplex sequencing, requires the incorporation of sample-specific index sequences, also known as barcodes, during the preparation of sequencing libraries. Sequencing indexes are distinct base sequences of about 5, about 10, about 15, about 20 about 25, or more bases that are added at the 3' end of the genomic and marker nucleic acid.

Ex. 1055, col. 77, ll. 14–20. Rava also teaches

Verification of the integrity of 10 each of the plurality of source samples is accomplished by first grouping sequence tags associated with identical index sequences to associate the genomic and marker sequences and distinguish sequences belonging to each of the libraries made from genomic molecules of a plurality of samples.

Id. at col. 78, ll. 9–14. We agree with Dr. Gabriel that one skilled in the art would understand that Rava teaches that use of barcodes that are not unique. Ex. 1060 ¶¶ 76–77.

Again we are unpersuaded by Patent Owner’s argument for the reasons set forth above.

6. Proposed Substitute Claim 33

Proposed substitute claim 33 adds the limitation that each barcode comprises a fixed on semi-random oligonucleotide sequence that in combination with a diversity of molecules sequenced from a selected region enables identification of unique molecules.

Petitioner contends that Rava teaches this limitation. MTA Opp. 18. Petitioner contends that Rava teaches that the barcodes sequences are known or fixed prior to adding them to the polynucleotide sequence and that the fixed sequences in combination with the sequences molecules enables identification of unique molecules. *Id.* (citing Ex. 1055, col. 77, ll. 14–25; col. 166, l. 58–col. 167, l. 5; Ex. 1060 ¶¶ 78–79).

Patent Owner argues that proposed substitute claim 33 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the limitation of proposed substitute claim 33.

As discussed above, Rava teaches the incorporation of sample specific barcodes into PCR primers used for amplification. Ex. 1055, col. 77, ll. 14–25. Rava also teaches “Sequencing indexes are distinct base sequences of about 5, about 10, about 15, about 20 about 25, or more bases.” *Id.* at col. 77, ll. 17–19. Rava goes on to teach that the combination of the fixed or known barcodes in combination with the sequenced molecule allows for the

identification of unique molecules. *Id.* at col. 77, ll. 5–43; col. 166, l. 58–co. 167, l. 5. We agree with Dr. Gabriel that claim 33 would have been obvious over the teachings of Rava. Ex. 1060 ¶ 79.

Again we are unpersuaded by Patent Owner’s argument for the reasons set forth above.

7. *Proposed Substitute Claim 34*

Proposed substitute claim 34 depends from proposed substitute claim 27 and adds the step of “selectively enriching regions from a genome or transcriptome of the subject prior to sequencing.” MTA 24. Petitioner contends that Rava teaches this step. MTA Opp. 18–19.

Patent Owner argues that proposed substitute claim 34 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the step recited in proposed substitute claim 34. Rava discloses that “[i]n various embodiments the cfDNA present in the sample can be enriched specifically or non-specifically prior to use (e.g., prior to preparing a sequencing library).” Ex. 1055, col. 54, ll. 15–17. For example, Rava describes a method comprising “enriching the mixture of nucleic acids for polymorphic target nucleic acids in operation” and “sequencing the enriched mixture of nucleic acids in operation.” *Id.* at col. 128, ll. 35–42; *see also, e.g., id.* at col. 131, ll. 7–12 (“[i]n other embodiments, the cfDNA in the sample is enriched specifically. Specific enrichment refers to the enrichment of a genomic sample for specific sequences, e.g. polymorphic target sequence”); col. 54, ll. 21–27; col. 128, ll. 57–67; col. 29, ll. 1–25; col. 129, ll. 32–37. We agree with Dr.

Gabriel that Rava teaches the selective enrichment step of substitute claim 34. Ex. 1060 ¶¶ 80–82.

Again we are unpersuaded by Patent Owner’s argument for the reasons set forth above.

8. Proposed Substitute Claim 35

Proposed substitute claim 35 depends from proposed substitute claim 27 and adds the limitation of “attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to an amplification or enrichment step.” MTA 24. Petitioner contends that Rava teaches this limitation. MTA Opp. 19. Petitioner contends that Rava teaches that “the index sequence is incorporated into the adaptor which is ligated to the cfDNA prior to PCR amplification.” *Id.* (quoting Ex. 1055, col. 77, ll. 25–28.)

Patent Owner argues that proposed substitute claim 35 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the step recited in proposed substitute claim 35. Rava teaches “the index sequence can be incorporated into the adaptor, which is ligated to the cfDNA prior to the PCR amplification.” Ex. 1055, col. 77, ll. 25–28. As discussed above, the index sequence of Rava is the same as a barcode. Ex. 1055, col. 77, ll. 15–16. Dr. Gabriel also testifies, and we agree that this passage of Rava teaches attaching one or more barcodes to the extracellular polynucleotide prior to amplification. Ex. 1060 ¶ 84.

Again we are unpersuaded by Patent Owner’s argument for the reasons set forth above.

9. Proposed Substitute Claim 36

Proposed substitute claim 36 depends from proposed substitute claim 27 and adds the limitation that “each of the plurality of predefined regions is a single base.” MTA 24. Petitioner contends that Rava teaches this limitation. MTA Opp. 19–21.

Patent Owner argues that proposed substitute claim 36 is not rendered obvious by Rava, as Rava does not teach all the limitations of proposed substitute claim 27. MTA Reply 9.

We find that Rava teaches the limitation calling for the predefined region to be a single base. Rava teaches identifying single nucleotide polymorphisms (SNPs) in fetal and maternal DNA. *See, e.g.*, Ex. 1055, col. 22, ll. 54–59, Fig. 12. Rava also teaches that “the smaller the bin length, the greater the resolution that is obtained to localize the CNV of the segment in the chromosome of interest.” *Id.* at col. 49, ll. 65–67. Dr. Gabriel testifies, and we agree, that a person of ordinary skill in the art “reading Rava would have thus understood that a smaller predefined region should be used in order to resolve or detect a small mutation, and that predefined regions of a single base should be used in order to resolve or detect a single base mutation, such as a SNP.” Ex. 1060 ¶ 86.

Again, we are unpersuaded by Patent Owner’s argument for the reasons set forth above.

10. Conclusion

Based on the foregoing we conclude that Petitioner has demonstrated by a preponderance of the evidence that proposed substitute claims 28–36 are unpatentable as obvious over Rava.

G. Obviousness based on Hyland

Petitioner contends that the subject matter of proposed substitute claims 27 and 38–41 would have been obvious to a person of ordinary skill in the art at the time the invention was made over Hyland. MTA Opp. 21–25.

Patent Owner contends that Hyland does not render proposed substitute claim 27 obvious in that Hyland fails to teach certain steps of the substitute claim including the filtering step. MTA Reply 9–12.

As discussed more fully below, after considering the arguments presented by the parties and the evidence of record, we conclude that Hyland does not render proposed substitute claims 27 and 38–41 unpatentable for obviousness.

1. Hyland

Hyland describes, *inter alia*, methods “for copy number variation determination from analyzing biomolecule-related sequence reads.” Ex. 1061 ¶ 7. Hyland states

According to the present teachings, nucleic acid sequencing technologies can be utilized for genome-wide interrogation of CNV s. In contrast to conventional approaches (e.g., array-based methods, etc.), with sequencing, genomic coverage data is available at single base resolution which allows for high levels of fidelity when researchers and clinicians search for genomic variants such as CNVs in a genome.

Id. ¶ 27.

a) Analysis of Proposed Substitute Claim 27

Like claim 1 discussed above, proposed substitute claim 27 includes the limitation “filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold.” MTA 22–23. Petitioner contends that

Hyland teaches this step of substitute claim 27. MTA Opp. 22. Petitioner contends that Hyland teaches filtering out reads that do not meet predetermined length requirements or mappability thresholds. *Id.*

Patent Owner contends that Hyland does not teach filtering out reads but teaches thresholds for merging window regions, which refer to the reference sequence and not the sequence reads. MTA Reply 11–12.

We have considered the arguments presented by the parties and the evidence of record and conclude that Petitioner has not demonstrated that Hyland teaches the filtering step of proposed substitute claim 27. While Hyland teaches filtering windows, the filtering is done as part of the data analysis to determine if copy number variation exists and not as part of eliminating sequence reads. Hyland teaches the filtering step as one embodiment of step 514, which relates to using the copy number states of each window to identify copy number variation. Ex. 1061 ¶ 99. As shown in Figure 5 of Hyland, step 514 is the final step of the method coming after the normalization step.

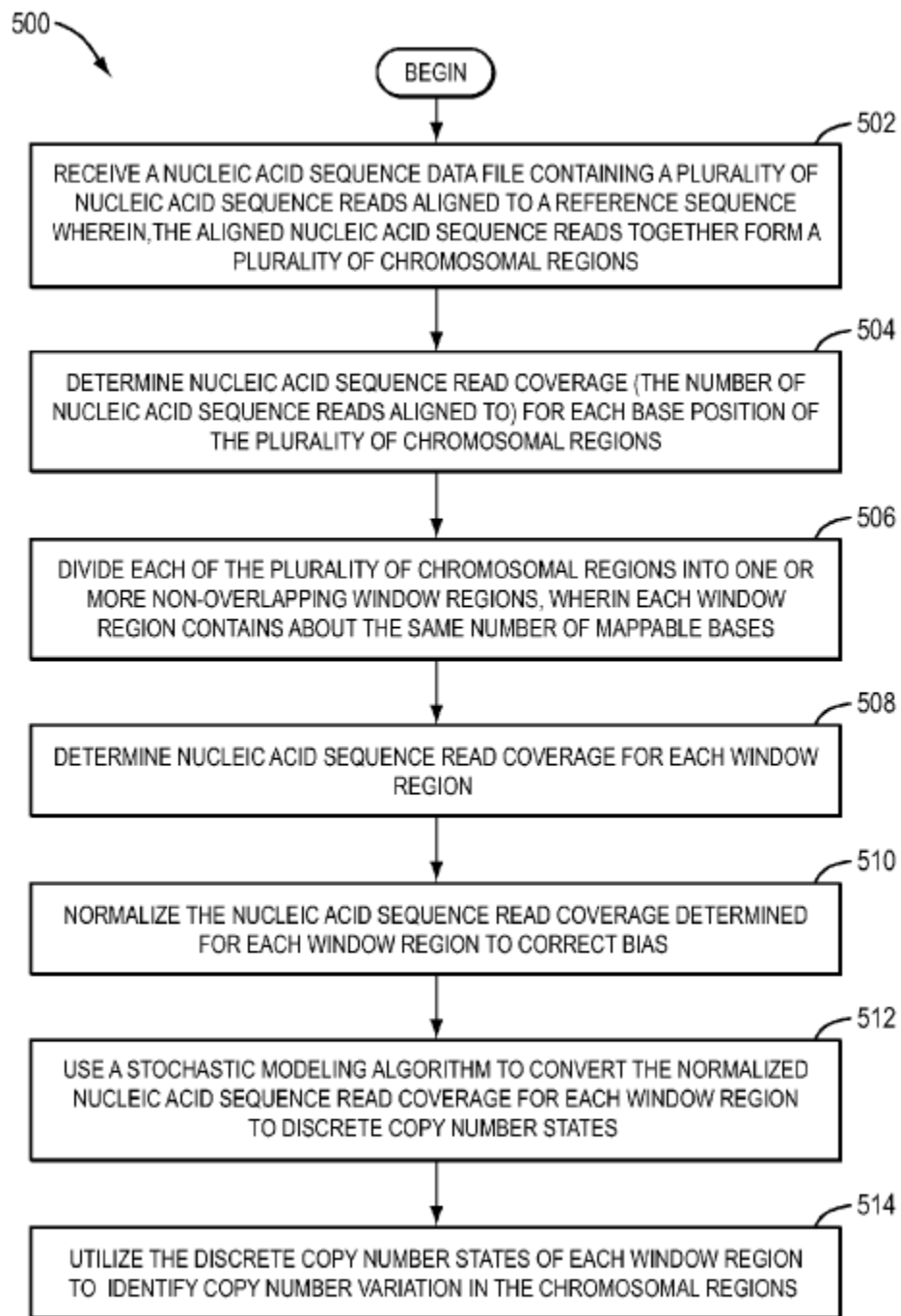


FIG. 5

Figure 5 of Hyland showing a flow chart of a method for determining copy number variation.

As Patent Owner points out, the filtering operation is done to determine if the windows can be merged. MTA Reply 11; Ex. 1061 ¶ 99. We discern nothing in the cited paragraph nor has Petitioner pointed to any teaching in Hyland that teaches filtering out reads.

Petitioner contends that the disclosure in Hyland is strikingly similar to the disclosure in the present Specification and that this supports the contention that Hyland teaches filtering out reads. MTA Sur-Reply 11. We are not persuaded. Both the passage in Hyland and the passage in the present Specification relate to merging window regions as part of the reporting process. *Compare* Ex. 1001, col. 46, ll. 40–47, *with* Ex. 1061 ¶ 99.¹⁰

b) Proposed Substitute Claims 38–41

Proposed substitute claims 38–41 depend from proposed substitute claim 27 and include all the limitations of proposed substitute claim 27. 35 U.S.C. § 112(d). As discussed above, Hyland does not render proposed substitute claim 27 obvious as Hyland does not teach or suggest the filtering step of proposed substitute claim 27. For the same reasons, Hyland does not render proposed substitute claims 38–41 obvious.

c) Conclusion

We conclude that Petitioner has failed to demonstrate by a preponderance of the evidence that proposed substitute claims 27 and 38–41 are unpatentable as obvious over Hyland.

¹⁰ Petitioner presents a comparison of Ex. 1061 paragraph 99 with paragraph 64 of Ex. 2043. MTA Sur-Reply 11. Ex. 2034 is a copy of the Provisional Application, which led to the '743 Patent. *Id.* The paragraph is identical to the cited paragraph in the present Specification.

H. Patent Owner's Motion to Exclude

Patent Owner has moved to exclude exhibits 1002, 1004, 1007, 1008, 1013, 1015, 1017, 1019, 1025, 1032, 1043, 1048, 1052–1054, 1057–160, and 1063. Paper 42 (“PO Mot. Excl.”). Petitioner filed an Opposition Paper 45 (“Pet Opp. PO Mot Excl.”) and Patent Owner filed a reply. Paper 46 (“Reply PO Mot. Excl.”).

With respect to Exhibits 1004, 1007, 1008, 1013, 1015, 1017, 1019, 1025, 1032, 1043, 1052–105, 1057–59, and 1063, we dismiss Patent Owner’s Motion as moot. The panel did not rely on those exhibits in reaching its decision in this proceeding.

We also dismiss as moot the motion with respect to Exhibit 1058. Exhibit 1058 was cited only to define the acronym COSMIC used in the present Specification.

Patent Owner seeks to exclude Exhibits 1002 and 1060, which are the declarations of Dr. Gabriel. PO Mot. Excl. 1–4, 6–8. Patent Owner contends that they are irrelevant and misleading. *Id.* Petitioner contends that the declarations of Dr. Gabriel are highly relevant and are not misleading. Opp. PO Mot. Excl. 2–7, 9–11.

We have considered the arguments presented by the parties and we are not persuaded that Exhibits 1002 and 1060 should be excluded. Petitioner has shown and Patent Owner does not dispute, that Dr. Gabriel is an expert in the relevant art. Opp. PO Mot. Excl. 2–3. As an expert in the relevant art, Dr. Gabriel’s testimony is highly relevant regarding how one skilled in the art would interpret the references as well as to the general knowledge in the field at the time the invention was made.

Patent Owner contends that Ex. 1002 should be excluded because Dr. Gabriel applied an inappropriate definition of a person of ordinary skill in

the art. PO Mot. Excl. 1–3. We are not persuaded that this constitutes sufficient grounds to strike Exhibit 1002. As Petitioner points out, Dr. Gabriel applied the same definition of a person of ordinary skill in the art as the one we adopted in our Decision to Institute. Opp. PO Mot Excl. 4.

With respect to Exhibit 1060, Patent Owner contends that Dr. Gabriel failed to apply the plain and ordinary meaning to certain terms in her analysis of the art asserted against the substitute claims. PO Mot. Excl. 6–9. Even if we were to accept Patent Owner’s contentions as true, we find that any such errors go to the weight given Dr. Gabriel’s testimony and not its admissibility.

For the reasons set forth above, Patent Owner’s Motion to Exclude is denied.

I. Petitioner’s Motion to Exclude

Petitioner seeks to exclude Exhibits 2017, 2023, 2024, 2026, 2037, 2035, 2037, and 2038 in whole or in part. Paper 43 (“Pet. Mot Excl.”) 1. Patent Owner filed an Opposition, Paper 46 (“Opp. Pet. Mot. Excl.”) and Petitioner filed a Reply. Paper 47 (“Reply Pet. Mot. Excl.”).

With respect to Exhibits 2017, 2035 and 2038, we deny Petitioner’s motion as moot. These exhibits do not form any basis in reaching our decision in this proceeding.

The remaining exhibits are the declarations of Patent Owner’s experts, Drs. Bustamante and Quackenbush. Petitioner contends that portions of these declarations should be excluded as the testimony “fails to rely on sufficient facts and is not the product of reliable principles and methods.” Pet. Mot. Excl. 2.

As with the Declarations of Dr. Gabriel discussed above, we find that these alleged deficiencies go to the weight that should be afforded the

experts' testimony and does not support a motion to exclude. The testimony of Drs. Bustamante and Quackenbush is highly relevant to the issues before us and the risk of any possible prejudice is very low. "Where, as here, the decision is by an administrative agency, rather than a jury, there is a diminished concern that [] exhibits would be prejudicial." *Eli Lilly and Co., v. Teva Pharms. Int'l GMBH*, IPR2018-01710, Paper 68 at 161 (PTAB Mar. 31, 2020) (citing *Corning Inc. v. DSM IP Assets B.V.*, IPR2013-00053, Paper 66 at 19 (PTAB May 1, 2014)).

For the reasons set forth above, Petitioner's Motion to Exclude is denied.

IV. CONCLUSION¹¹

We conclude that Petitioner has satisfied its burden of demonstrating by a preponderance of the evidence that original claims 1–9, 20, and 22–26 are unpatentable.

We conclude that Petitioner has not satisfied its burden of demonstrating by a preponderance of the evidence that claims 10–19 and 21 are unpatentable.

We conclude that Petitioner has shown by a preponderance of the evidence that proposed substitute claims 27–41 are unpatentable.

¹¹ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–9, 20, and 22–26 of U.S. Patent 9,840,743 B2 have been shown to be unpatentable;

FURTHER ORDERED that claims 10–19 and 21 have not been shown to be unpatentable;

FURTHER ORDERED that Patent Owner’s Contingent Motion to Amend is denied;

FURTHER ORDERED that Patent Owner’s Motion to Exclude is denied;

FURTHER ORDERED that Petitioner’s Motion to Exclude is denied; 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.

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–3, 22–26	102(a)	Chiu	1–3, 22–26	
1–9, 20, 22–26	103	Kinde 2011, Kinde 2012	1–9, 20, 22, 23, 25	24, 26
10–13, 15–19, 21	103	Kinde 2011, Forshew		10–13, 15–19, 21
14	103	Kinde 201, Kinde 2012, Forshew		14
Overall Outcome			1–9, 20, 22–26	10–19, 21

Motion to Amend Outcome	Claims(s)
Substitute Claims Proposed in the Amendment	26–41
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	26–41
Substitute Claims: Not Reached	

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