EXHIBIT A

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Paper No. 7
Date: June 5, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

Case IPR2019-00130
Patent 9,598,731 B2

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

MITCHELL, *Administrative Patent Judge.*

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

I. INTRODUCTION

Foundation Medicine, Inc. ("Petitioner")[1] filed a Petition (Paper 1, "Pet.") to institute an *inter partes* review of claims 1–17 of U.S. Patent No. 9,598,731 B2 (Ex. 1001, "the '731 patent"). Guardant Health, Inc. ("Patent Owner") timely filed a Preliminary Response (Paper 6, "Prelim. Resp.").

We have authority under 35 U.S.C. § 314(a) to determine whether to institute an *inter partes* review. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu,* 138 S. Ct. 1348, 1355–56 (2018). Also, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any challenged claim of the '731 patent. Therefore, we do not institute an *inter partes* review of claims 1–17 of the '731 patent.

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[1] Petitioner identifies Roche Holdings, Inc., Roche Finance Ltd, and Roche Holding Ltd as real parties-in-interest. Pet. 78.

A. Related Proceedings

Patent Owner has asserted the '731 patent against Petitioner in a litigation in the District of Delaware: *Guardant Health, Inc. v. Foundation Medicine, Inc.*, Case No. 17-cv-1616-LPS-CJB (D. Del.). Pet. 78; Paper 3, 2. Patent Owner has also asserted the '731 patent against Personal Genome Diagnostics, Inc. in a litigation in the District of Delaware: *Guardant Health, Inc. v. Personal Genome Diagnostics, Inc.*, Case No. 17-cv-1623-LPS-CJB (D. Del.). *Id.*

In addition, Petitioner has filed several petitions seeking *inter partes* review of patents related to the '731 patent, including: IPR2017-01170 (challenging U.S. Patent No. 9,340,830); IPR2017-01447 (challenging U.S. Patent No. 9,340,830); and IPR2017-01448 (challenging U.S. Patent No. 9,340,830). Paper 3, 2. Petitioner has also filed additional petitions challenging Patent Owner's patents as follows: IPR2019-00634 (challenging U.S. Patent No. 9,840,743); IPR2019-00636 (challenging U.S. Patent No. 9,902,992); IPR2019-00637 (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).

Personal Genome Diagnostics, Inc. has filed petitions seeking post-grant review of patents related to the '731 patent, including: PGR2018-00057 (challenging U.S. Patent No. 9,840,743) and PGR2018-00058 (challenging U.S. Patent No. 9,834,822). *Id.*

B. The '731 patent (Ex. 1001)

The '731 patent involves a system and method for detecting rare mutations and copy number variations in cell free polynucleotides. Ex. 1001, Abst. The '731 patent indicates 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 variations and/or single or multiple sequence variations associated with a particular disease that may be used to detect or monitor such disease. *Id*. at 1:29–45, 30:9–12.

The ’731 patent states that this system and method generally “comprise[s] 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 30:12–18. The ’731 patent further describes two tools for detecting genetic variation in a sample of cfDNA with high sensitivity. *Id*. at 32:37–39. These tools are described as follows:

> First, the efficient conversion of individual polynucleotides in a sample of initial genetic material into sequence-ready tagged parent polynucleotides [is done], so as to increase the probability that individual polynucleotides in a sample of initial genetic material will be represented in a sequence-ready sample. This can produce sequence information about more polynucleotides in the initial sample. Second, high yield generation of consensus sequences for tagged parent polynucleotides [is done] by high rate sampling of progeny polynucleotides amplified from the tagged parent polynucleotides, and collapsing of generated sequence reads into consensus sequences representing sequences of parent tagged polynucleotides. This can reduce noise introduced by amplification bias and/or sequencing errors, and can increase sensitivity of detection. Collapsing is performed on a plurality of sequence reads, generated either from reads of amplified molecules, or multiple reads of a single molecule.

Id. at 32:39–57.

Parent polynucleotides as described above are tagged with barcodes that may be unique or non-unique. *Id*. at 37:44–49.

> [T]he use of non[-]unique barcodes, in combination with sequence data at the beginning (start) and end (stop) portions of individual sequencing reads and sequencing read length may allow for the assignment of a unique identity to individual sequences. Similarly, 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.

Id. at 37:48–57.

C. Illustrative Claim

Claim 1 is the only independent claim. Claims 2 through 17 depend directly from claim 1. *See* Ex. 1001, 62:55–64:20. Thus, claim 1 is illustrative and reproduced below:

> 1. A method for quantifying single nucleotide variant tumor markers in cell-free DNA from a subject, comprising:
> (a) providing at least 10 ng of cell-free DNA obtained from a bodily sample of the subject;
> (b) attaching tags comprising barcodes having from 5 to 1000 distinct barcode sequences to said cell-free DNA obtained from said bodily sample of the subject, to generate non-uniquely tagged parent polynucleotides, wherein each barcode sequence is at least 5 nucleotides in length;
> (c) amplifying the non-uniquely tagged parent polynucleotides to produce amplified non-uniquely tagged progeny polynucleotides;
> (d) sequencing the amplified non-uniquely tagged progeny polynucleotides to produce a plurality of sequence reads from each parent polynucleotide, wherein each sequence read comprises a barcode sequence and a sequence derived from cell-free DNA;
> (e) grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families based on i) the barcode sequence and ii) at least one of: sequence information at a beginning of the sequence

derived from cell-free DNA, sequence information at an end of the sequence derived from cell-free DNA, and length of the sequence read, whereby each family comprises sequence reads of non-uniquely tagged progeny polynucleotides amplified from a unique polynucleotide among the non-uniquely tagged parent polynucleotides;

(f) comparing the sequence reads grouped within each family to each other to determine consensus sequences for each family, wherein each of the consensus sequences corresponds to a unique polynucleotide among the non-uniquely tagged parent polynucleotides;

(g) providing one or more reference sequences from a human genome, said one or more reference sequences comprising one or more loci of reported tumor markers, wherein each of the reported tumor markers is a single nucleotide variant;

(h) identifying consensus sequences that map to a given locus of said one or more loci of reported tumor markers; and

(i) calculating a number of consensus sequences that map to the given locus that include the single nucleotide variant thereby quantifying single nucleotide variant tumor markers in said cell-free DNA from said subject.

Ex. 1001, 62:8–54.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of the claims of the ’731 patent based on the following grounds:

References	Basis	Claims challenged
Kinde[2] and Schmitt[3] or Schmitt 2012[4]	§ 103	1–2 and 4–17
Schmitt or Schmitt 2012 and Taipale[5]	§ 103	1–2 and 4–17
Schmitt or Schmitt 2012 and Chiu[6]	§ 103	3

Petitioner further relies upon the declaration of Stacey Gabriel, Ph. D. to support its challenges. *See* Ex. 1002.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b) (2018);[7] *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131,

[2] Isaac Kinde et al., *Detection and Quantification of Rare Mutations with Massively Parallel Sequencing*, 108 PROC. NATL. ACAD. SCI. 9530 (2011) (Ex. 1009).
[3] U.S. Patent No. 9,752,188 B2 (Ex. 1005).
[4] Michael W. Schmitt et al., *Detection of Ultra-rare Mutations by Next-generation Sequencing*, 109 PROC. NATL. ACAD. SCI. 14508 (2012) (Ex. 1007).
[5] PCT App. No. WO 2012/042,374 A2 (Ex. 1010).
[6] Rossa W. K. Chiu et al., *Noninvasive Prenatal Diagnosis of Fetal Chromosomal Aneuploidy by Massively Parallel Genomic Sequencing of DNA in Maternal Plasma*, 105 PROC. NATL. ACAD. SCI. 20458 (2008) (Ex. 1049).
[7] The Final Rule changing the claim construction standard to the federal court claim construction standard that is used to construe a claim in a civil action under 35 U.S.C. § 282(b) does not apply here, as the Petition was filed before the effective date of the Final Rule, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial

2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Only terms in controversy must be construed and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

1. "barcode"

Claim 1 requires the step of "attaching tags comprising barcodes having from 5 to 1000 distinct barcode sequences to said cell-free DNA obtained from said bodily sample of the subject, to generate non-uniquely tagged parent polynucleotides, wherein each barcode sequence is at least 5 nucleotides in length." Ex. 1001, 62:12–17. Petitioner contends that the '731 patent "explains that barcodes can be attached to polynucleotides" and "may include a single nucleotide or a sequence of nucleotides." Pet. 18 (citing Ex. 1001, 15:36–47, 38:8–13, 39:11–15, 62:8–17). Given these disclosures, Petitioner concludes that a POSITA "would have understood a 'barcode' to mean 'a nucleotide or a sequence of nucleotides used as a tag or identifier.'" *Id.* (citing Ex. 1002 ¶ 57). Patent Owner states that "Petitioner's constructions should be rejected," but does not propose a

Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,344 (Oct. 11, 2018).

definition for barcode or otherwise dispute Petitioner's construction. Prelim. Resp. 7–11.

Although the majority of references to the term "barcode" in the '731 patent describes a polynucleotide, *see* Ex. 1001, 15:36–47, other references describe different identifiers. For instance, the '731 patent states that the unique identifier or barcode may be a dye or a metal isotope. *See id*. at 38:12–25; *see also* Ex. 2001, 3–4 (Patent Owner's District Court position on the meaning of "barcode"). Therefore, we do not agree with Petitioner that the broadest reasonable interpretation of the term "barcode" is only a nucleotide or a sequence of nucleotides.

Although we disagree with Petitioner's too narrow definition of "barcode," we find that we need not construe expressly the claim term "barcode" to resolve whether we should institute an *inter partes* review. *See Vivid Techs*, 200 F.3d at 803 (stating need to construe claim terms only as necessary to resolve the controversy).

2. "non-uniquely tagged" and "parent polynucleotides"

Claim 1 requires the generation of "non-uniquely tagged parent polynucleotides." Petitioner contends that "parent polynucleotides are 'non-uniquely tagged' whenever the number of different identifiers attached to the polynucleotides is fewer than the number of polynucleotides." Pet. 19 (citing Ex. 1001, 41:47–52).

In response to Petitioner's proposed construction of non-uniquely tagged parent polynucleotides, Patent Owner refers us to its Opening Claim Construction Brief (Ex. 2001) from its infringement suit against Petitioner in the District of Delaware. Prelim. Resp. 8. Patent Owner argues that the term "non-uniquely tagged parent polynucleotides" should be construed in

accordance with its proposed definition in the Opening Claim Construction Brief and contends that the term means "the number of different identifiers is at least 2 and fewer than the number of polynucleotides, such that neither every polynucleotide nor nearly every polynucleotide receives a unique identifier." *Id.* (citing Ex. 2001, 7).

Patent Owner further argues that "non-uniquely tagged" need not be expressly construed, only "parent polynucleotide" needs construction. Patent Owner also asserts that Petitioner's construction of non-uniquely tagged parent polynucleotides is "incomplete," "attempts to read the term 'parent polynucleotide' out of the '731 patent claims," and is inconsistent with or contradicts several of Petitioner's arguments. *Id.* at 9–11. Patent Owner explains that the construction of the term can be gleaned from the language of claim 1 in which "[t]he non-uniquely tagged parent polynucleotides are generated by attaching barcodes to the cell-free DNA obtained from the bodily sample of a subject." *Id.*

As Patent Owner notes, Petitioner's proposed construction of "non-uniquely tagged parent polynucleotides" only addresses what "non-uniquely tagged" means. *See* Pet. 19; PO Resp. 9. We agree with Patent Owner that for purposes of this Decision on this record, we need not construe expressly the claim term "non-uniquely tagged" to resolve the issues in controversy. We do find, however, that we need to determine the meaning of "parent polynucleotides." Although not set forth in Petitioner's claim construction section of its brief, Petitioner provides three different express definitions of the term "parent polynucleotides" in other sections of its brief.

First, in Petitioner's "Technology Background" description discussing next generation sequencing, Petitioner recognizes that "the '731 patent refers

to the original DNA fragments as 'parent polynucleotides' and to the amplified copies as 'progeny polynucleotides.'" Pet. 5 (citing Ex. 1001, Fig. 9). Second, in analyzing its first challenge to the claims of the '731 patent, Petitioner defines "'parent polynucleotide,' as used in the '731 patent, [as] simply the DNA fragment that is analyzed for the presence of mutations." Pet. 35. Third, in analyzing its second challenge to the claims, however, Petitioner defines "parent polynucleotide" as "simply the DNA fragment from the initial genetic material that is examined for the presence of mutations." Pet. 63. Thus, we agree with Patent Owner that Petitioner's constructions of "parent polynucleotides" as used in the '731 patent are not the same and are not necessarily consistent. *See NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005) (finding same claim terms in related patents should be interpreted consistently).

In reviewing the claim language itself of claim 1, the broadest reasonable interpretation of "parent polynucleotides" as used in the '731 patent is Petitioner's first construction, referring to the original DNA fragments from the cf-DNA as parent polynucleotides. *See* Pet. 5. For instance, in step (b) of claim 1, barcodes are attached "to said cell-free DNA obtained from said bodily sample of the subject, *to generate non-uniquely tagged parent polynucleotides*." Ex. 1001, 62:12–17 (emphasis added).

This interpretation is also consistent with how the term "parent polynucleotides" is used in the Specification of the '731 patent. *See* Ex. 1001, Figs. 8–11 (stating "[c]onvert polynucleotides from initial starting genetic material into tagged parent polynucleotides"); 6:22–23 (stating that initial starting genetic material may be cell-free nucleic acid); 6:6–8 (referencing "converting initial starting genetic material into the tagged

parent polynucleotides"). The '731 patent distinguishes between "parent polynucleotides" that are tagged with barcodes and the amplified "progeny polynucleotides" that are produced from amplification. *See, e.g.*, *id*. at 5:54–58.

Therefore, we agree with Patent Owner that the term "parent polynucleotides" refers to the cell-free DNA obtained from the bodily sample of a subject.

We determine that no other claim terms need to be construed for purposes of our analysis in this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("we need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Level of Ordinary Skill in the Art

Relying on Dr. Gabriel's declaration, Petitioner contends that a person of ordinary skill in the art ("POSITA") for the '731 patent "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. 17 (citing Ex. 1002 ¶ 55). Petitioner further contends that a POSITA would "have had knowledge of DNA sequencing, including next generation (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 does not propose a definition for the level of skill in the art in its Preliminary Response or otherwise dispute Petitioner's definition. Petitioner's definition appears consistent with the level of ordinary skill in the art reflected in the prior art, and we will apply it for purposes of this Decision. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

C. Patentability Analysis

1. *Principles of Law*

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for

a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see In re Translogic Technology, Inc*., 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles. In making such an analysis, we find that Petitioner has failed to show a reasonable likelihood of prevailing for any claim on any ground asserted in the Petition because for each challenge, Petitioner has failed to show that all the limitations of any challenged claim are taught by the asserted art.

2. Obviousness Over Kinde and Schmitt or Schmitt 2012

Petitioner asserts that claims 1, 2, and 4–17 of the '731 patent are unpatentable as obvious over Kinde and Schmitt or Schmitt 2012. Pet. 28–

47. Patent Owner asserts that the asserted combination does not teach all the limitations of each challenged claim and the Petition fails to establish a clear reason as to how or why the teachings of the asserted references would be combined to arrive at the claimed invention with a reasonable expectation of success. *See* PO Resp. 15–34.

We find for the following reasons that Petitioner has failed to show a reasonable likelihood of success in establishing that any of the challenged claims 1, 2, or 4–17 would have been obvious over Kinde and Schmitt or Schmitt 2012. Specifically, we find that Kinde does not teach step (b) of claim 1 as Petitioner contends. Therefore, we begin our analysis of Petitioner's first challenge with a description of the pertinent teachings of Kinde upon which Petitioner relies for step (b) of claim 1.

a. Kinde (Ex. 1009)

Kinde describes a method for increasing the sensitivity of massively parallel sequencing instruments to identify rare mutations in DNA. Ex. 1009, Abst. According to Kinde, massively parallel sequencing can be used to analyze multiple bases "sequentially and easily" in an automated fashion but "cannot generally be used to detect rare variants because of the high error rate associated with the sequencing process." *Id.* at Abst., 9530.

Kinde refers to its improved method as the "Safe-Sequencing System" or "Safe-SeqS." *Id.*, Abst. Kinde describes "how templates can be prepared and the sequencing data obtained from them [can be] more reliably interpreted, so that relatively rare mutations can be identified with commercially available instruments." *Id.* at 9530. Kinde also states that the Safe-SeqS involves the following two basic steps: (1) assignment of a unique identifier (UID) to each DNA template molecule to be analyzed; and

(2) amplification of each uniquely tagged template, so that many daughter molecules with the identical sequence are generated (defined as a UID family). *Id.* "A UID family in which at least 95% of family members have the identical mutation is called a 'supermutant'. Mutations not occurring in the original templates, such as those occurring during the amplification steps or through errors in base calling, should not give rise to supermutants." *Id*.

In explaining how UIDs (also called barcodes and indexes) are assigned to nucleic acid fragments, Kinde describes using endogenous and exogenous UIDs. *Id*. at 9531–32; SI1. Petitioner particularly relies on the materials and methods for endogenous UIDs using inverse PCR to show that step (b) of claim 1 is taught by Kinde, namely, the generation of non-uniquely tagged parent polynucleotides wherein each barcode sequence is at least 5 nucleotides in length. *See* Pet. 35–39. Kinde describes the inverse PCR experiment upon which Petitioner relies as follows, referencing Figure S1 set forth below.

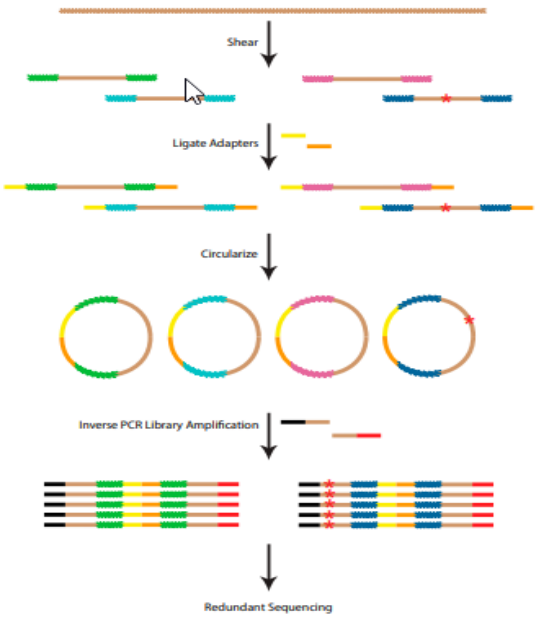


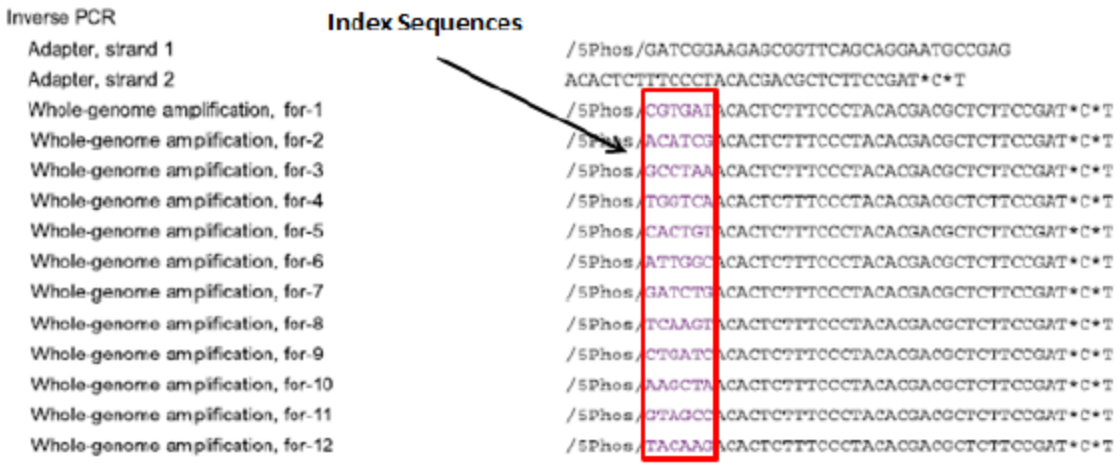
Fig. S1. Safe-SeqS with endogenous UIDs plus inverse PCR. The sequences of the ends of fragments produced by random shearing serve as unique identifiers (UIDs) (variously colored bars). These fragments are ligated to adapters (yellow and orange bars) as in a standard Illumina library preparation. One uniquely tagged fragment is produced from each strand of the double-stranded template; only one strand is shown. Following circularization with a ligase, inverse PCR is performed with gene-specific primers that also contain 5′ "grafting" sequences (black and red bars). This PCR produces UID families that are directly sequenced. Supermutants are defined as in Fig. 1.

> For the inverse PCR experiments (Fig. S1), we ligated custom adapters (IDT) (Table S4) instead of standard Y-shaped Illumina adapters to sheared cellular DNA. These adapters retained the region complementary to the universal sequencing primer but lacked the grafting sequences required for hybridization to the Illumina GA IIx flow cell. The ligated DNA was diluted into 96 wells and the DNA in each column of 8 wells was amplified with a unique forward primer containing one of 12 index sequences at its 5' end plus a standard reverse primer (Table S4). . . . The resulting DNA fragments contained UIDs composed of three sequences: 2 endogenous ones, represented by the two ends of the original sheared fragments, plus the exogenous sequence introduced during the indexing amplification. As 12 exogenous sequences were used, this increased the number of distinct UIDs by 12-fold over that obtained without exogenous UIDs.

Ex. 1009, SI1.

b. Analysis

Petitioner refers to Table S4, set forth below with Petitioner's annotations, when asserting that the "index sequences attached to the DNA fragments are 'sequences of nucleotides used as an identifier' and therefore are barcodes as described in the '731 patent." Pet. 36–37.



Pet. 37 (citing Ex. 1009, Table S4, SI 10) (annotated).

Petitioner asserts that, because the number of barcodes, twelve, is less than the 1057 different polynucleotides analyzed in the inverse PCR experiment, "the DNA fragments are 'non-uniquely tagged' within the meaning of the '731 patent." Pet. 37, 38. Also, because each of the twelve barcodes as shown in Table S4 above are six nucleotides in length, Petitioner asserts that "Kinde teaches attaching tags comprising barcodes having from 5 to 1000 distinct barcode sequences to polynucleotides, to generate non-uniquely tagged parent polynucleotides, wherein each barcode sequence is at least 5 nucleotides in length." Pet. 37–38 (citing Ex. 1002 ¶¶ 93–104).

For the limitation set forth in step (b) of claim 1, Petitioner asserts that "[a] 'parent polynucleotide,' as the term is used in the '731 patent, is simply the DNA fragment that is analyzed for the presence of mutations." Pet. 35 (citing Ex. 1001, Fig. 9). Because Kinde teaches attaching barcodes to DNA fragments, Petitioner reasons, Kinde teaches "parent polynucleotides." *Id*.

Patent Owner responds that Kinde does not teach tagging parent polynucleotides as required by claim 1, but instead "incorporates indexed primers through PCR amplification. In other words, Kinde tags ***amplification progeny***—not any ***parent polynucleotides*** in the manner recited in claim 1." PO Resp. 16. In examining the inverse PCR experiment upon which Petitioner relies, Patent Owner asserts that "Kinde describes first ligating adapters (not index sequences) to sheared genomic DNA, then subsequently amplifying the sheared genomic DNA fragments with indexed primers so as to generate index-tagged PCR amplicons . . . . [T]he index sequences are found in the PCR primers (not the sheared DNA or adapters) such that they are incorporated downstream in the amplified polynucleotides." PO Resp. 16–17. Patent Owner points to Petitioner's

annotated Table S4 set forth above as showing the index sequences are in the PCR primers. *Id*. at 17.

We agree with Patent Owner's assessment of the teachings of Kinde upon which Petitioner relies to teach step (b) of claim 1. Although we agree with Petitioner that the index sequences are indeed non-unique barcodes, they are not attached to parent polynucleotides as required by the challenged claims of the '731 patent. As we discussed in construing the term "parent polynucleotides," the '731 patent distinguishes between parent polynucleotides and the progeny polynucleotides that are generated in the amplification process. *See supra* Section II.A.2. Also, as we found, the claim term "parent polynucleotides" refers to the cfDNA obtained from the bodily sample of a subject. *Id*.

In the description of the inverse PCR experiment upon which Petitioner relies, Kinde states that the original DNA or parent polynucleotide "was amplified with a unique forward primer containing one of 12 index sequences at its 5' end plus a standard reverse primer (Table S4)." Ex. 1009, SI1. We agree with Patent Owner that this disclosure unequivocally states that the tag or indexed sequence upon which Petitioner relies is attached to the amplified product or progeny polynucleotide and not to the parent polynucleotide as required by claim 1 before amplification. Therefore, we find that Kinde does not teach non-uniquely tagged parent polynucleotides as required by claim 1.

For the reasons set forth above, we find that Petitioner has failed to establish a reasonable likelihood of success in showing any

of challenged claims 1, 2, and 4–17[8] would have been obvious over Schmitt or Schmitt 2012 and Kinde.

3. Obviousness Based on Schmitt or Schmitt 2012 and Taipale

Petitioner asserts that claims 1, 2, and 4–17 of the '731 patent are unpatentable as obvious over Schmitt or Schmitt 2012 and Taipale. Pet. 59–75. Patent Owner asserts that the asserted combination does not teach all the limitations of each challenged claim, and the Petition fails to establish how to combine the teachings of the asserted references to arrive at the claimed invention with a reasonable expectation of success. *See* PO Resp. 34–46.

We find for the following reasons that Petitioner has failed to show a reasonable likelihood of success in establishing that any of the challenged claims 1, 2, or 4–17 would have been obvious over Schmitt or Schmitt 2012 and Taipale. Specifically, we find that Taipale does not teach non-unique tagging. Therefore, we begin our analysis of Petitioner's second challenge with a description of the pertinent teachings of Taipale.

a. Taipale (Ex. 1010)

Taipale describes "methods for determining the number or concentration of entities in a sample. In particular, the present invention relates to methods for determining the number or concentration of molecules, e.g. biomolecules such as nucleic acid, in a sample." Ex. 1010, 1:5–7. Taipale explains this method more specifically as follows.

> The present invention relates to counting, measuring or determining the absolute number of entities of a species of interest in a sample by ensuring that the entities of that species

[8] Because all claims of the '731 patent depend from claim 1, each claim requires non-uniquely tagged parent polynucleotides that are not taught by Kinde. *See* Ex. 1001, 62:55–64:20.

> of interest differ from each other, and determining the absolute number of the different entities. By ensuring that the entities of the species of interest are detectably different, this allows the absolute number of entities of the species of interest to be determined based on the number of different entities of that species.

Id. at 2:24–29; 9:28–30 (defining "species of interest" as "the defined physical entity to be counted, e.g. a specific or defined molecular structure" such as a DNA sequence).

To render the species of interest detectably different from each other, Taipale describes either applying unique labeling, a "bottlenecking" procedure where a small enough sample of the entities of interest is taken to ensure that the species of interest differ from one another, or both unique labeling and bottlenecking procedures. *Id*. at 2:31–39. Taipale describes these procedures more in detail as follows.

> Entities of a species of interest can be modified to render them different, e.g. by labelling or other modification . . . . This facilitates determination of the absolute number of those entities of the species of interest, since one can determine how many differently modified entities of the species are present, and from this information the number of original entities of the species of interest in the sample can be derived.
>
> Alternatively, where a population of entities of a species of interest comprises some entities of the species of interest which are the same and some which differ from one another (for example, where the species of interest is nucleic acid, and a population comprises examples of the same and different nucleotide sequences), it is possible to ensure that the species of interest differ from one another by taking a sample from that population, where the sample size is sufficiently small that the entities of the species of interest in the sample differ from one another (e.g. where each nucleic acid molecule in the sample has a different nucleotide sequence). The absolute number of entities of the species of interest in the sample can then be determined by

> determining the number of different entities of the species of interest in the sample. The step of sampling to ensure that the entities of the species of interest differ from one another represents a "bottlenecking" approach, to restrict the number of entities of the species of interest which are subsequently amplified and is subsequently performed.

Id. at 2:31–3:10; 5:25–30 (suggesting applying both unique labeling and bottlenecking); *see also* 9:7–13 (describing a method of tracking where the entities of interest such as nucleic acids are different from each other and thus, the "nucleic acids are effectively labels, even though no step of attaching a label is performed"); 31:24–32:4 (same).

The disclosure of Taipale is replete with discussion of embodiments that use unique labeling and bottlenecking to achieve determining the number or concentration of entities in a sample. *See, e.g., id*. at 6:8–19 (describing unique or "variant" labeling where the "label is selected from a group of different labels"), 6:24–32 (describing "label" as unique, i.e. "a marker, tag, adapter, part, sequence or structure that serves to distinguish a molecule of the species of interest from another molecule of the species of interest"), 12:7–11, 31–34, 13:27–33 (describing preferred method "comprise[s] amplifying the different, or *differently-modified*, molecules to provide a library of amplicons," normalizing such a population of differently-modified molecules that have been amplified, and allowing "accurate counting of the original number of molecules of a species of interest . . . for example to improve detection of rare species of interest") (emphasis added), 37:1–19 (quantifying absolute number of DNA-species in a sample using unique labels "because making the DNA molecules different from each other during the step of labelling the DNA molecules stores the information about the original number of DNA molecules").

Taipale touts that one benefit of the described method is preservation of information about the original number of molecules of a species of interest in a sample. *See id*. at 13:35–23. Taipale states that, in contrast to the previous methods that don't preserve such information,

> [t]he method of the invention stores information about the original number of molecules of a species of interest in the sample by ensuring that the molecules differ from one another, e.g. modifying those molecules to produce a plurality of *differently-modified* molecules. The original number of molecules of the species of interest in the sample can be determined based on the number of different *differently-modified* molecules, or the number of different molecules. The population of *differently-modified* molecules can be amplified and/or normalised such that differences between them are preserved, and therefore information about the original number of molecules in the sample is preserved during subsequent rounds of processing of the sample, such that it is possible to accurately determine the number of molecules of interest in a sample, even when the population of molecules from the sample has been amplified and/or normalised.

Id. at 14:13–23 (emphases added).

Although Taipale states that the described method can accommodate non-unique labeling because the chance of such labeling is small when the group of modifications used is sufficiently large, *see id*. at 15:1–24, Taipale emphasizes the importance of unique labeling to achieve maximum accuracy.

> For maximum accuracy, and to avoid the problem of under counting which may occur if two or more molecules of the same species of interest in a sample are identical, e.g. if they are by chance labelled in the same way (i.e. labelled with identical labels) to provide two or more identical conjugates, it is preferable to optimise the probability that every entity of the species of interest in the sample to be counted is rendered unique, i.e. that it is distinguishable from every other entity of the species

> of interest in the sample. This is particularly relevant when amplification and/or normalisation steps are to be performed on the sample. If two or more identical entities of the species of interest were amplified, the resulting identical amplicons would be counted as representative of only one entity.

Id. at 15:26–34. The methods listed to maximize the proportion of entities that are unique are (1) assigning unique labels, *see id*. at 16:6–17:2; (2) bottlenecking after non-unique labeling, *see id*. at 8:27–9:5, 17:5–19:25; or bottlenecking alone, *see id*. at 20:14–22:31 (referencing Example 4).

b. Analysis

Petitioner asserts that Taipale describes non-unique tagging as a "significant advantage." Pet. 60. With reference to the teaching of non-unique tagging, Petitioner and its declarant Dr. Gabriel point to the following single sentence in Taipale for such teaching: "It is a significant advantage of the present invention that the same labels can be used to label molecules of different species of interest." Pet. 60, 66 (citing Ex. 1010, 26:22–23); *see also* Ex. 1002 ¶ 203.

Patent Owner responds that "a review of the full scope and content of Taipale reveals that it teaches unique tagging. In fact, Taipale emphasizes the benefits of ***uniquely tagging*** molecules." PO Resp. 35. Patent Owner points to much of the disclosure of Taipale that we discussed above to establish that Taipale teaches unique tagging and bottlenecking to achieve unique labeling. *See id*. at 35–38.

As we point out above in our analysis of the teachings of Taipale, we agree with Patent Owner's assessment that Taipale's focus on uniquely labeling sample molecules can be seen throughout its different embodiments. *See supra* Section II.C.3.a. Taipale emphasizes repeatedly

that unique tagging or labeling, whether by attaching unique labels or by attaching nearly unique labels followed by a bottlenecking step to achieve unique tagging, is preferred to achieve maximum accuracy in determining the number of concentration of molecules in a sample. *See, e.g.*, Ex. 1001, 15:26–34 (stating maximum accuracy is achieved by unique labeling); 2:31–3:10 (describing unique labeling and bottlenecking); 5:25–30 (same).

Taipale's reference to alleged non-unique labeling, when read in context and with the emphasis on unique labeling for maximum accuracy, appears to refer to the problem when two molecules of a sample are labeled with an identical label by happenstance. *See id*. at 7:27–33. In previous teachings of Taipale, such a problem is minimized by providing a sufficient number of unique labels. *See id*. at 15:1–24. For instance, Taipale states:

> The method of the present invention depends on the distribution of different modifications within the molecules of the species of interest . . . so even if each molecule is expected to be differently modified (for example, when each molecule is labelled with a label selected from a group of different labels), it is possible that some molecules of the species of interest may be modified in the same way just by chance (e.g. two or more molecules of the species of interest are labelled with identical labels selected from the group of different labels). However, provided that the fraction of molecules modified in the same way is small in relation to the total number of molecules of the species of interest, the method of the invention will provide an accurate determination of the number of molecules of the species of interest. The probability that two or more molecules of the same species of interest will be modified in the same way is lower for species of interest that are present in the sample in low number, and lower for larger groups of modification (e.g. groups of different labels having a larger number of different labels). Therefore, if the method of the present invention is used to determine the number or concentration of molecules of a species of interest that is rare in the sample and the group of

> modifications used to modify the molecules is sufficiently large, then the chances of more than one molecule of the species [of] interest being modified in the same way are non-significant or negligible. In other words, the methods of the present invention do not require that each molecule of the species of interest is modified such that it differs from every other molecule of that species of interest.

Id. at 15:5–24.

This discussion in Taipale is not a teaching of the use of non-unique tagging, but an explanation of how Taipale's method is robust enough to maintain accuracy with the happenstance same labeling of a species of interest. By the same token, Petitioner's cited Taipale statement—that it is a significant advantage of the invention that the same labels can be used to label molecules of different species of interest—appears merely to repeat the observation by Taipale that the method is robust enough to handle some duplication of labeling. Taipale states that the key to the method "is that each molecule in the sample becomes different – even if two species of interest are labelled with the same sequence, it is possible to tell which is which as long as the species of interest themselves have different sequence." *Id*. at 26:28–31.

Taipale provides the following example where a duplicate label happens to be attached to two difference species of interest or DNA nucleotide sequences.

For example, as set out below for a DNA-counting application:

LABEL--species of interest
AATA--TAGGAATAGAA
AATC--TAGGAATAGAA
AATA--CAGACAGATAA
TTCC--CAGACAGATAA

Even if both the TAGGAATAGAA and CAGACAGATAA are labelled by "AATA", one can tell them apart.

Id. at 27:1–10. Because the same label is attached to two different nucleotide sequences of interest, they can still be distinguished from each other by their sequence despite having the same label. We agree with Patent Owner that Taipale does not teach non-unique labeling or tagging.

Even if the teaching cited by Petitioner could be read to teach non-unique labeling, we find that such picking and choosing among the myriad references in Taipale to non-unique tagging is improper hindsight analysis in the obviousness framework. The United States Court of Appeals for the Federal Circuit ("Federal Circuit") has stated that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)).

Here, as in *Bausch & Lomb*, Petitioner took a single sentence out of the context of the full disclosure of Taipale, which teaches the use of unique labeling as one of the best ways to carry out the disclosed method. Here, as in *Bausch & Lomb*, Petitioner viewed an isolated line in Taipale in light of the teaching of the '731 patent to establish obviousness, ignoring those

portions of Taipale that counsel against an obviousness determination. *See id*. at 448–49. This type of analysis is an exercise of improper hindsight.

For the reasons set forth above, we find that Petitioner has failed to establish a reasonable likelihood of success in showing any of challenged claims 1, 2, and 4–17[9] would have been obvious over Schmitt or Schmitt 2012 and Taipale.

4. *Obviousness Based on Schmitt or Schmitt 2012 and Chiu*

Petitioner asserts that claim 3, which depends from claim 1, of the '731 patent is unpatentable as obvious over Schmitt or Schmitt 2012 and Chiu. Pet. 72–74. Petitioner fails to include either Kinde or Taipale as part of the challenge, although it relies upon these two reference for each of the first two challenges to claim 1. *See* Pet. 28–71. Because claim 3 depends from claim 1, each of the limitations of claim 1 must also be met for claim 3. Petitioner has failed to provide how these limitations are met for this third challenge. *See* PO Resp. 46 (stating that the Schmitt references are not offered to teach all of the elements of claim 1 anywhere in the Petition). Petitioner does not point to teachings in Chiu that meet each limitation of claim 1. *See* Pet. 72–74. Therefore, we find that Petitioner has not shown a reasonable likelihood of succeeding in showing that claim 3 would have been obvious over Schmitt or Schmitt 2012 and Chiu.

III. CONCLUSION

For the foregoing reasons, we determine that the Petition and evidence in this record do not establish that there is a reasonable likelihood that

[9] Because all claims of the '731 patent depend from claim 1, each claim requires non-uniquely tagged parent polynucleotides that are not taught by Taipale. *See* Ex. 1001, 62:55–64:20.

Petitioner would prevail in challenging claims 1–17 of the '731 patent based on the grounds discussed above.

IV. ORDER

Accordingly, it is:

ORDERED that under 35 U.S.C. § 314(a), the petition is *denied* and no *inter partes* review is instituted.

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