

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWINSTRAND BIOSCIENCES, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

IPR2022-01400
Patent 11,149,306 B2

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

TwinStrand Biosciences, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–29 of U.S. Patent No. 11,149,306 B2 (Ex. 1001, “the ’306 patent”). Paper 2 (“Pet.”). Guardant Health, Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to Patent Owner’s Preliminary Response (Paper 7) and Patent Owner filed a Sur-reply to the Reply (Paper 8).

Considering the arguments and evidence of record, we determine that the Petition demonstrates “a reasonable likelihood that [P]etitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Accordingly, we institute an *inter partes* review.

A. *Related Proceedings*

The parties state that the ’306 patent has been asserted in *TwinsStrand Biosciences, Inc. et al. v. Guardant Health, Inc.*, 1-21-cv-01126 (D. Del.) and *Illumina, Inc. v. Guardant Health, Inc.*, 22-cv-00334 (D. Del.). Pet. 70; Paper 4, 1.

The parties identify the following IPRs involving patents related to the ’306 patent: IPR2022-00746, IPR2022-01115, IPR2022-00747, IPR22-01116, and IPR2022-01152. Pet. 70; Paper 4, 1. Patent Owner additionally identifies a number of IPRs that it has filed, i.e., IPR2022-00449, IPR2022-00450, IPR2022-00816, IPR2022-00817, IPR2022-00935, IPR2022-01158, IPR2022-01159, and IPR2022-01388, as related matters. Paper 4, 1.

B. *The ’306 Patent*

Genetic testing is useful for a number of diagnostic methods. Ex. 1001, 1:25–26. Disorders that are caused by rare genetic mutations (e.g., sequence variations) or changes in epigenetic markers, such as cancer and

partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information. *Id.* at 1:26–30.

Early detection and monitoring of genetic diseases is often useful and needed in the successful treatment or management of a disease. Ex. 1001, 1:31–33. According to the '306 patent, one approach may include monitoring a sample derived from cell-free nucleic acids, which are polynucleotides that can be found in different types of bodily fluids. *Id.* at 1:33–36. Cell-free DNA (“cfDNA”) may contain genetic aberrations, such as copy number variation or sequence variation, associated with a particular disease. *Id.* at 1:36–43.

The '306 patent explains that many methods have been developed to estimate copy number variation. Ex. 1001, 1:46–47. According to the Specification, most of those methods involve preparing a sample by converting the original nucleic acids into a sequenceable library, followed by massively parallel sequencing, and then conducting a bioinformatic analysis to estimate the copy number variation at one or more loci. *Id.* at 1:51–55.

The '306 patent states that although known methods for detecting cfDNA are able to reduce the errors introduced by the sample preparation and sequencing processes for the molecules that are converted and sequenced, these methods are not able to infer the counts of molecules that were converted, but not sequenced. Ex. 1001, 1:59–63. The '306 patent states this inability to count converted but unsequenced molecules “can dramatically and adversely affect the sensitivity that can be achieved.” *Id.* at 1:63–67. Accordingly, the '306 patent relates to a method of tagging and counting both halves of double-stranded DNA and estimating the number of unseen molecules based on the number of Pairs (i.e., molecules where both

strands were identified) and Singlets (i.e., molecules where only one strand was identified) detected in a particular region. *See id.* at 2:1–18.

C. Illustrative Claims

Petitioner challenges claims 1–29 of the '306 patent. Of these, claims 1 and 17 are independent. Claims 1 and 17 read as follows:

1. A method, comprising:
 - (a) providing a population of cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;
 - (b) tagging a plurality of the cfDNA molecules in the population with duplex tags comprising molecular barcodes to produce tagged parent polynucleotides, wherein the duplex tags are attached at both ends of a molecule of the plurality of the cfDNA molecules, wherein the plurality of the cfDNA molecules are tagged with n different combinations of molecular barcodes, wherein n is at least 2 and no more than $100,000 * z$, wherein z is a mean of an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence;
 - (c) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;
 - (d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and
 - (e) reducing or tracking redundancy of a plurality of sequence reads from the set of sequence reads using at least sequence information from the molecular barcodes of the duplex tags to determine distinct cfDNA molecules from among the tagged parent polynucleotides, wherein the distinct cfDNA molecules are determined based on (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from cfDNA molecules from among the tagged parent polynucleotides, or (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand

having no second tagged complementary strand derived from cfDNA molecules from among the tagged parent polynucleotides, wherein reducing or tracking the redundancy of the plurality of sequence reads comprises mapping at least a subset of the plurality of sequence reads to the reference sequence.

17. A method, comprising:

- (a) tagging a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules obtained or derived from a sample of a subject with a set of tags comprising molecular barcodes to produce tagged parent polynucleotides;
- (b) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;
- (c) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and
- (d) sorting a plurality of sequence reads from the set of sequence reads into (i) families comprising paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from double-stranded cfDNA molecules from among the tagged parent polynucleotides, and (ii) families comprising unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from double-stranded cfDNA molecules from among the tagged parent polynucleotides.

Ex. 1001, 61:6–43 (claim 1), 62:45–65 (claim 17).

D. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–29 would have been unpatentable on the following grounds:

Claims Challenged	35 U.S.C. § ¹	References/Basis
1–3, 5, 7, 9–14, 17–27, 29	103	Narayan ² and Schmitt ³
4, 6	103	Narayan, Schmitt, and Meyer ⁴
8,	103	Narayan, Schmitt, and Craig ⁵
15, 16, 28	103	Narayan, Schmitt, and Kivioja ⁶

Petitioner also relies upon the Declaration of Paul T. Spellman, Ph.D. (Ex. 1002) (“Spellman Declaration”).

Before turning to our analysis of these grounds, we address Patent Owner’s argument that, notwithstanding the merits of the Petition, we should exercise discretion to deny institution under 35 U.S.C. § 325(d).

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §103, effective March 16, 2013. The ’306 patent claims priority to a series of applications the earliest of which is a provisional application filed on December 28, 2013. Ex. 1001 code (60). Because the AIA became effective before the filing of the earliest of the application to which the ’306 patent claims priority, we apply the AIA version of the statute.

² Narayan et al., *Ultrasensitive Measurement of Hotspot Mutations in Tumor DNA in Blood Using Error-Suppressed Multiplexed Deep Sequencing*, 72(14) CANCER RES. 3492–98 (Ex. 1082) (“Narayan”).

³ Schmitt et al., WO 2013/142389 A1, published Sept. 26, 2013 (Ex. 1009) (“Schmitt”).

⁴ Meyer et al., *Parallel Tagged Sequencing on the 454 Platform*, 3(2) NATURE PROTOCOLS 267–78 (2008) (Ex. 1005) (“Meyer”).

⁵ Craig et al., *Identification of Genetic Variants Using Bar-coded Multiplexed Sequencing*, 5(10) NATURE METHODS 887–93 (2008) (Ex. 1007) (“Craig”).

⁶ Kivioja et al., *Counting Absolute Numbers of Molecules Using Unique Molecular Identifiers*, 9 NATURE METHODS 72–76 (2012) (Ex. 1006) (“Kivioja”).

II. DISCRETION UNDER 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise discretion to deny institution because “[t]he same art and arguments presented in this petition were considered and rejected by the Office multiple times” and Petitioner has “failed to . . . demonstrate material error.” Prelim. Resp. 1–2. Petitioner disagrees. *See* Pet. 21–24.

A. *Legal Standard*

Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. The statute states, in pertinent part, “[i]n determining whether to institute . . . the Director may take into account whether, and reject the petition . . . because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d).

The question of whether a petition presents art or arguments that are “the same or substantially the same” as art or arguments previously presented to the Office is a factual inquiry, which may be resolved by reference to the factors set forth in *Becton, Dickinson*.⁷ The precedential section of that decision sets forth the following non-exclusive factors for consideration:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;

⁷ *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”).

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;

(e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, 17–18.

*Advanced Bionics*⁸ sets out a two-part framework for analyzing these factors. In the first part, we consider factors (a), (b), and (d) to determine whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, 8–10. “If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office,” then we move on to the second part of the analysis to determine “whether the petitioner has demonstrated a material error by the Office” in view of factors (c), (e), and (f). *Id.*

B. Advanced Bionics Part One

Patent Owner argues that the disclosure in “Schmitt was considered by the Examiner and applied as the primary reference in prosecution.” Prelim. Resp. 10. We agree. Both parties acknowledge that Schmitt shares its specification with U.S. Patent No. 10,752,951 (“Salk”). Pet. 22; Prelim. Resp. 5. And it is undisputed that the Examiner asserted Salk in anticipation

⁸ *Advanced Bionics, LLC v. MED-EL Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

and obviousness rejections during prosecution. Pet. 17–18; Prelim. Resp. 6 (citing Ex. 1066, 539–41, 672–74). Thus, there is no dispute that the same disclosure the Petition relies upon in Schmitt was both before, and evaluated by,⁹ the Examiner during prosecution.

Narayan, Craig, and Kivioja were also before the Examiner during prosecution. Each of these references was listed in an IDS. Ex. 1066, 122–221; *see also* Pet. 21 (acknowledging this fact). Thus, all of the same references in three of the Petition’s four grounds and covering all but two of the challenged claims were previously presented to the Office. For these reasons, we determine that, on the whole, the Petition presents the same or substantially the same art as that previously presented to the Office and proceed to the second part of the *Advanced Bionics* framework.

C. *Advanced Bionics Part Two*

During prosecution, the Examiner rejected the then-pending claims as anticipated by and obvious over Salk, finding that Salk disclosed or rendered obvious each of the recited method steps. Ex. 1066, 539–40. Patent Owner’s initial response (*id.* at 554–65) did not succeed in overcoming those rejections. *Id.* at 671–75 (maintaining rejections).

Patent Owner next responded by amending claim element 1(b) to recite tagging with n different combinations of barcodes, “wherein n is at least 2 and no more than $100,000 * z$, wherein z is a mean of an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence.” *Id.* at 687. Patent Owner argued that this amendment distinguished Salk ’951. *Id.* at

⁹ We will address the extent of the Examiner’s evaluation of Schmitt’s disclosure (i.e., *Becton, Dickinson* Factor (c)) when we turn to the second part of the *Advanced Bionics* analysis.

694. Patent Owner also argued that Salk was not prior art because its priority applications did not provide written description support for “cfDNA” and “circulating DNA” as recited in Salk’s claims. Ex. 1066, 692–93. For support, Patent Owner pointed to the Board’s statement in the final written decision in IPR2019-00652 (the “’652 IPR”) that “‘Schmitt [’188]¹⁰ does not expressly teach that the target polynucleotide is cfDNA.’” *Id.* at 693 (quoting Ex. 1074, 31). The Examiner subsequently withdrew the rejections without expressly noting the reasons for allowance. *See id.* at 708 (notice of allowance).

Petitioner urges that the Examiner erred in a number of respects. *See* Pet. 21–24; Reply 4–5. Most of these alleged errors relate to arguments Patent Owner made in its first response to the Examiner’s rejections. As noted above, those initial arguments were not successful in overcoming the rejections, and the Examiner did not articulate any particular reasons for allowing the claims.

Nevertheless, based on its showing in Ground 1, we determine that Petitioner has sufficiently demonstrated a material error during the examination of claim 1. Claim 1 and its dependent claims were allowed shortly after Patent Owner’s amendment to recite a range of barcode combinations n between 2 and $100,000 * z$ in element 1(b). This suggests the Examiner determined that Salk and Schmitt ’188 did not disclose or suggest the recited range. As explained below, however, the record at this stage of the proceeding supports Petitioner’s argument that the number of barcode

¹⁰ The “Schmitt” referenced in the ’652 IPR decision is U.S. Patent No. 9,752,188 (“Schmitt ’188”). Ex. 1074, 3 n. 2. Schmitt ’188 claims priority to the international application publication (i.e., WO2013/142,389) referred to as “Schmitt” in this proceeding. Ex. 2008, code (87).

combinations for Schmitt's 3-mer hybrid tag embodiment falls within the recited range regardless of the value of z. *See infra* § III.E.1. To the extent the Examiner did not appreciate the relevance of the "hybrid method using a combination of sheared ends and shorter n-mer tags (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases)" taught in Salk and Schmitt '188 to claim element 1(b), this constitutes material error. Ex. 2012 9:20–24; Ex. 1083 ¶ 30. Moreover, the Petition presents additional evidence regarding element 1(b), e.g., Ex. 1002 ¶ 166, that warrants reconsideration of Schmitt in this proceeding.

We also note that Patent Owner's argument during prosecution that Salk was not prior art because it lacks written description support for cfDNA is a different issue than whether the challenged claims are obvious over Schmitt and Narayan and the other references cited in the Petition. The Examiner's rejection relied at least in part on the disclosure in Salk's claims. *See* Ex. 1066, 674. The Petition, however, relies on the disclosure in Schmitt's specification (and even more specifically on the disclosure in a priority application, provisional application 61/625,623 ("Schmitt-623" (Ex. 1083)). *See infra* § III.D.2. At this stage of the proceeding, Patent Owner does not dispute that the disclosure in Schmitt is prior art to the challenged claims. Moreover, as explained below, the Petition relies on Narayan's disclosure of cfDNA in combination with Schmitt.¹¹ Thus, to the extent the

¹¹ In this regard, Petitioner's obviousness theory is consistent with the ground on which claims were determined to be unpatentable in the '652 IPR. There, the panel determined that "although Schmitt ['188] does not expressly teach that the target polynucleotide is cfDNA, [other references cited in combination with Schmitt '188] teach the extraction and analysis of cfDNA." Ex. 1074, 29; *see also id.* at 51 (finding, based on the record in that proceeding, "that an ordinarily skilled artisan screening cfDNA for cancer

Examiner did not consider the disclosure in Salk’s specification to be prior art, or did not consider whether it would have been obvious to apply the methodology taught in Salk and Schmitt to cfDNA based on the teachings in other references such as Narayan, this was also a material error.

For these reasons, we find that Petitioner has demonstrated a material error, and therefore, will not exercise discretion to deny institution of *inter partes* review under 35 U.S.C. § 325(d).

III. ANALYSIS

A. *Legal Standard*

A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention, 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 the subject matter pertains. *See 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 skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention

mutations . . . would have looked to Schmitt’s DCS method” to reduce errors and improve detection).

does.” *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

B. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art (“POSA”) at the time of the invention would have had

(i) a Ph.D. in molecular biology, genetics, bioinformatics, or a related field, and have at least about two years of experience in the use and development of sequencing technologies; or (ii) a Master’s degree in one of the same fields with at least about five years of the same experience.

Pet. 18 (citing Ex. 1002 ¶¶ 27–30). Patent Owner does not offer a proposed definition of the level of ordinary skill in the art at this stage of the proceeding.

On this record, we adopt Petitioner’s uncontested definition of the level of ordinary skill in the art. We further note that the prior art itself is sufficient to demonstrate the level of skill in the art at the time of the invention. *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. Claim Construction

In an *inter partes* review, the Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of

the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Element 1(b) recites a range of “different combinations of molecular barcodes” between 2 and “no more than $100,000 \cdot z$, wherein z is a mean of an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence.” Ex. 1001, 61:15–21. Petitioner does not specify any formal claim construction, but contends a “POSA would understand that the population of cfDNA molecules that map to identical start and stop positions will vary, depending on the number of haploid gene equivalents (HGEs) in the sample.” Pet. 19 (citing Ex. 1002 ¶¶ 131–133). Moreover, Petitioner contends that Schmitt discloses tagging with barcodes having a number of combinations that falls within the recited range regardless of the value of z . *See id.* at 29 (arguing that Schmitt discloses the use of “3-mer barcodes” having “4,096 different combinations” that “would fall between 2 and $100,000 \cdot z$ ” regardless of “whether z is 1, 10, 100, 800, etc.”). Patent Owner disputes Petitioner’s showing for element 1(b), but does not seek any claim construction at this stage. Prelim. Resp. 19.

As explained below and based on the current record, Petitioner has shown sufficiently for institution that Schmitt discloses the use of barcodes having a number of different combinations that falls within the recited range regardless of the value of z . For this reason, it is unnecessary to expressly construe “ z ” or any other aspect of element 1(b) to decide the issues presented in the Petition. To the extent Patent Owner disagrees, it will have the opportunity to address this issue at trial.

Neither party refers to any other claim term in the claim construction sections of their papers. *See* Pet. 18–19; Prelim. Resp. 19. We agree that it is

unnecessary to expressly construe any claim term for purposes of rendering this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘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))).

D. Cited References

1. Narayan

Narayan is a journal article titled “Ultrasensitive Measurement of Hotspot Mutations in Tumor DNA in Blood Using Error-Suppressed Multiplexed Deep Sequencing,” and bearing a 2012 publication date. Ex. 1082, 3492.¹² Patent Owner does not dispute that Narayan is prior art in its Preliminary Response.

According to Narayan, “[d]etection of cell-free tumor DNA in the blood has offered promise as a cancer biomarker, but practical clinical implementations have been impeded by the lack of a sensitive and accurate method for quantification that is also simple, inexpensive, and readily scalable.” *Id.* Narayan describes “an approach that uses next-generation sequencing [“NGS”] to quantify the small fraction of DNA molecules that contain tumor-specific mutations within a background of normal DNA in plasma.” *Id.*

2. Schmitt

Schmitt is an international patent application entitled “Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing,” and published on September 26, 2013.

¹² Unless stated otherwise, citations to page numbers refer to the reference page numbers.

Ex. 1009, code (43). Petitioner contends that Schmitt is prior art under 35 U.S.C. § 102(a)(1) and (a)(2), relying on the fact that Schmitt claims priority to Schmitt-623. Pet. 20–21. Petitioner contends that Schmitt is prior art as of the filing date of Schmitt-623, i.e., April 17, 2012, because the disclosures Petitioner relies upon in Schmitt “were carried forward from Schmitt-623” and “Schmitt-623 provides §112 support for at least on[e] claim in Schmitt.” *Id.* (internal quotations omitted). Patent Owner does not dispute these contentions in its Preliminary Response.¹³

Schmitt describes a method called Duplex Consensus Sequencing (“DCS”) that, according to Schmitt, “greatly reduces sequencing errors by independently tagging and sequencing each of the two strands of a DNA duplex.” Ex. 1083, 47 (Abstract). Because the two strands of DNA are complementary, true mutations can be found at the same position on both strands. *Id.* As Schmitt explains:

Comparing the sequence obtained from each of the two strands comprising a single molecule of duplex DNA facilitates differentiation of sequencing errors from true mutations. When an apparent mutation is, due to a PCR or sequencing error, the substitution will only be seen on a single strand. In contrast, with a true DNA mutation, complementary substitutions will be present on both strands.

Id. ¶ 62. According to Schmitt, its DCS “method uniquely capitalizes on the redundant information stored in double-stranded DNA, thus overcoming

¹³ The Petition cites to the disclosure in Schmitt-623, rather than Schmitt itself, as support for the asserted grounds. *See, e.g.*, Pet. 27–61 (citing Ex. 1083 to support statements regarding the teachings in Schmitt). The Preliminary Response also cites Schmitt-623 to respond to Petitioner’s allegations. Prelim. Resp. 25 n.3. For ease of reference, we too cite to Schmitt-623. For purposes of our present analysis, we consider the disclosure in Schmitt-623 to be representative of the teachings in Schmitt.

technical limitations of prior methods of utilizing data from only one of the two strands.” *Id.* at 47 (Abstract).

In Schmitt’s DCS method, double-stranded DNA molecules are ligated to single molecule identifier (“SMI”) adapter molecules. Ex. 1083 ¶¶ 9–10. In one embodiment, “[s]heared double-stranded DNA that has been end-repaired and T-tailed is combined with A-tailed SMI adaptors and ligated.” *Id.* ¶ 11, Fig. 1. In this embodiment, “every adaptor contains a unique, double-stranded, complementary n-mer random tag on each end.” *Id.*; *see also* ¶ 16 (describing the embodiment in Example 1 in which “the SMI sequence is a random degenerate nucleotide n-mer sequence which is 12 nucleotides in length”). In another embodiment, Schmitt discloses a “hybrid method using a combination of sheared ends and shorter n-mer tags (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases)” to “serve as unique molecular identifiers.” *Id.* ¶ 30. The labeled DNA fragments are then amplified (e.g., by PCR) and sequenced. *Id.* ¶ 42

Schmitt teaches that sequence reads are “grouped into families of paired target nucleic acid strands based on a common set of SMI sequences” to produce “an error corrected double-stranded consensus sequence.” Ex. 1083 ¶¶ 43, 60. This data processing is described in Schmitt’s Example 1. *See id.* ¶¶ 60–69. There, “[r]eads having common (i.e., identical) SMI sequences were grouped together, and were collapsed to generate a consensus read.” *Id.* ¶ 60. “PCR consensus sequences arising from two complementary strands of duplex DNA” are then identified “by virtue of the complementary SMIs” that “identify the ‘partner SMI.’” *Id.* ¶ 63; *see also id.* ¶ 13, Fig. 3 (showing how sequence reads “sharing a unique set of SMI tags are grouped into paired families with members having strand identifiers in either the $\alpha\beta$ or $\beta\alpha$ orientation”). “Following partnering of two strands by

virtue of their complementary SMIs, the sequences of the strands are compared. Sequence reads at a given position are kept only if the read data from each of the two paired strands is in agreement.” *Id.*; *see also id.* ¶¶ 60, 68 (“Sequence reads were considered only when the read data from each of the two strands is in perfect agreement”).

3. *Meyer*

Meyer is a journal article titled “Parallel tagged sequencing on the 454 platform” and bearing a 2008 publication date. Ex. 1005, 267. Patent Owner does not dispute that *Meyer* is prior art in its Preliminary Response.

Meyer relates to a method called parallel tagged sequencing that allows for parallel sequencing of large numbers of double-stranded DNA samples on a next-generation sequencing system called the 454 Platform. *Id.*, Abstr. According to *Meyer*, the method involves blunt end repairing each DNA sample and then ligating sample-specific barcoding adapters to both ends of blunt-end repaired DNA molecules. *Id.* at 268, Fig. 1. The adapters “comprise single self-hybridized oligos containing a sequence tag and an *SrfI* restriction site.” *Id.* at 267. The barcoded samples are pooled in equimolar ratios, and untagged molecules are excluded from sequencing through dephosphorylation and restriction digestion. *Id.*, Fig. 1. The sample pool is then sequenced and the sequence reads are sorted according to their tag sequences and the source of each DNA can then be traced using the tag sequences. *Id.*

4. *Craig*

Craig is a journal article titled “Identification of genetic variants using bar-coded multiplexed sequencing,” and bearing an October 2008 publication date. Ex. 1007, 887. Patent Owner does not dispute that *Craig* is prior art in its Preliminary Response.

Craig relates to “a generalized framework for multiplexed resequencing of targeted human genome regions on the Illumina Genome Analyzer using degenerate indexed DNA bar codes ligated to fragmented DNA before sequencing” for simultaneously sequencing DNA from multiple individuals. Ex. 1007, 887. Craig refers to these bar codes as “indexes” and describes the use of “a six-base index with built-in redundancy for error correction.” *Id.* According to Craig, “only 48 of the 4,096 possible nucleotide combinations” were synthesized for use in their experiment. Craig explains that this design “allowed us to control, tolerate and measure error base calling of the index” because “one, and in some cases two, sequencing errors could be tolerated without an index being incorrectly identified as being a different valid index. *Id.* at 888; *see also id.* at 13¹⁴ (Supplementary Table 4 describing the design of the “DNA Indexes Appended to Each Adapter”).

5. *Kivioja*

Kivioja is a journal article titled “Counting absolute numbers of molecules using unique molecular identifiers,” and bearing a November 2011 publication date. Ex. 1006, 72. Patent Owner does not dispute that *Kivioja* is prior art in its Preliminary Response.

According to *Kivioja*, [d]etermining the relative abundance of two different molecular species or the absolute number of molecules [of DNA] in a single sample is challenging.” Ex. 1006, 72. *Kivioja* describes “an absolute counting method that can use amplification but does not require detecting each original molecule or keeping track of the number of copies made.” *Id.* In *Kivioja*’s method, “each molecule in a population is first made unique” by

¹⁴ This refers to the page number added to the exhibit.

labeling it with a unique molecular identifier (“UMI”). *Id.* “Upon deep sequencing, each UMI will be observed multiple times, and the number of original DNA molecules can be determined simply by counting each UMI only once. However, long before all UMIs are observed, increasingly precise estimates of the absolute molecule number can be made.” *Id.* (citing Online Methods).

In its Online Methods section, Kivioja teaches that “the original number of molecules in a sample can be estimated as the sum of observed and unobserved UMIs” and “[t]he number of unobserved UMIs can be estimated based on the distribution of the copy numbers of the observed UMIs.” *See* Ex. 1006, 4–5¹⁵ (explaining that “the number of molecules from each gene was estimated by fitting a zero-truncated Poisson distribution to the UMI copy number distribution using the generalized additive models for location, scale and shape (GAMLSS) R package and adding the predicted number of unobserved UMIs to the observed UMI count”).

E. Ground 1: Obviousness over Narayan and Schmitt

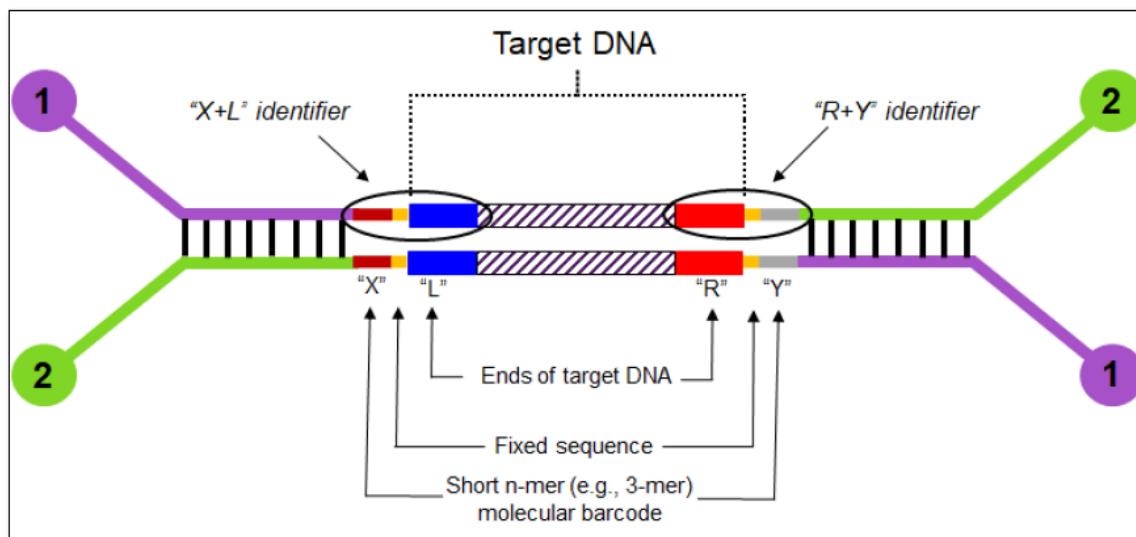
Petitioner asserts that claims 1–3, 5, 7, 9–14, 17–27 and 29 are unpatentable as obvious over Narayan and Schmitt. Pet. 25–58. Patent Owner opposes Petitioner’s assertions. Prelim. Resp. 20–45. On this record, we determine that Petitioner has established a reasonable likelihood that it will prevail in showing that claims 1–3, 5, 7, and 9–14 are unpatentable as obvious over the cited references, but has not met its burden for the other claims in this ground.

¹⁵ This refers to the page number added to the exhibit.

1. *Analysis of Claims 1–3, 5, 7, and 9–14*

We begin with claim 1. Petitioner contends claim 1 is rendered obvious by the application of Schmitt’s DCS method to screen cfDNA for cancer as taught in Narayan. *See* Pet. 34. Petitioner argues that “Schmitt alone” discloses all of the steps of the method recited in claim 1. *Id.*

Regarding element 1(b), Petitioner relies on Schmitt’s teaching of a “‘hybrid method’ of tagging, which uses a combination of the ends of the DNA fragments and ‘a shorter n-mer tag’” such as a “3-mer” barcode that “together with the sequence information within the target DNA, serve as ‘unique molecular identifiers.’” Pet. at 8–9 (quoting Ex. 1083 ¶¶ 30, 47, 75 (emphasis omitted)). Petitioner’s declarant, Dr. Spellman, provides a diagram depicting Schmitt’s hybrid tagging method that is reproduced below.



Id. at 9 (citing Ex. 1002 ¶ 89). In Dr. Spellman’s diagram above, “the ends of the DNA fragment are designated ‘L’ and ‘R,’ and the short 3-mer molecular barcodes are labeled ‘X’ and ‘Y.’” *Id.* According to Petitioner, the combination of X+L and R+Y “form unique molecular identifiers” even though the set of different 3-mer barcodes is “quite limited.” *Id.*; *see also*

Pet. 28 (explaining that a “3-mer barcode would yield a set of 4^3 (i.e., 64) different molecular barcodes” providing “4,096 (i.e., 64^2) total” combinations of barcodes “considering the tagging occurs on both ends of the target molecule”).

Petitioner offers evidence and argument for each of the other elements in claim 1 likewise premised on the use of 3-mer barcodes in Schmitt’s DCS method. *See* Pet. 26–34 (citing evidence for elements 1(a)-(e)). Moreover, Petitioner articulates reasoning why “[a] POSA would have been motivated to use Schmitt’s 3-mer hybrid tagging approach” as compared to other longer barcode embodiments taught in Schmitt. *Id.* at 35–36.

Petitioner further contends that a POSA would have had reason to combine Narayan’s teachings regarding cfDNA with Schmitt’s DCS method. *See* Pet 34–39. According to Petitioner,

Narayan discloses using NGS for analyzing cfDNA from cancer patients, and Schmitt discloses methods of error correction for NGS by generating duplex consensus sequences (i.e., reducing or tracking redundancy in sequence reads). A POSA would have known that error correction is important when using NGS for diagnostic or screening applications as taught in Narayan, and would have been motivated to use cfDNA as disclosed in Narayan and in Schmitt’s DCS methods. . . . A POSA would have understood that reducing or tracking sequence read redundancy using Schmitt’s DCS would improve the sensitivity of sequence detection and thus been motivated to use it in in [sic] clinical settings as suggested by Narayan.

Id. at 34–35 (citing Ex. 1002 ¶187–189). Petitioner further contends that “[a] POSA would have expected to successfully use cfDNA . . . in Schmitt’s DCS because the prior art expressly taught that DCS could ‘enhance accuracy’ when sequencing cfDNA from cancer patients” (*id.* at 37–38) and offers evidence supporting that a “POSA would have known that human

blood contains ample quantities of cfDNA for use in DCS.” *Id.* at 5–6, 13–14, 39 (citing, e.g., Ex. 1002 ¶¶ 209–215).

Based on the current record, Petitioner’s evidence and argument is sufficient to meet the burden for institution as to claim 1. Patent Owner raises several arguments to the contrary in its Preliminary Response, which are unavailing on the current record. We address those arguments below.

Patent Owner contends Petitioner has not shown that the cited art “discloses the tagging step of claim 1,” i.e., element 1(b). Prelim. Resp. 42–45. Patent Owner refers to the final written decision in the ’652 IPR, arguing that there “the Board considered Schmitt and found ‘the relationship between ‘z’ and the number of tags ‘n’ was unknown’” in the prior art. *Id.* at 43 (quoting Ex. 1074, 47). According to Patent Owner, “Petitioner’s challenge reflects the same deficiency the Office identified previously” because Petitioner does not “address the previously unknown relationship between n and z recited in the ’306 patent claims.” *Id.*

Based on the current record, we disagree. Contrary to Patent Owner’s argument, claim 1 does not require a particular “relationship” between the number of tags and the expected number of duplicate molecules (z), nor does it require “tailoring” the recited method based on z. *See* Prelim. Resp. 19, 43. Rather, element 1(b) recites a range for “n” the number of “different combinations of molecular bar codes, wherein n is at least 2 and no more than $100,000 * z$.” Ex. 1001, 61:16–17. Petitioner offers evidence, which is currently un rebutted, that n for Schmitt’s 3-mer barcode is 4,096. Ex. 1002 ¶ 164. Thus, the record at this stage of the proceeding supports Petitioner’s argument that Schmitt necessarily teaches a value for n that falls within the recited range “whether z is 1, 10, 100, 800, etc.” Pet. 29.

The circumstances of this case are materially different from those in the '652 IPR. The upper bound of the range at issue in the '652 IPR was "100*z," which is three orders of magnitude narrower than the upper boundary recited in claim 1 of the '306 patent. Ex. 1074, 47. As Petitioner points out, the broader upper boundary at issue here means that the n for Schmitt's 3-mer barcode falls within the recited range even where z is 1. Pet. 29. This would not be the case for 100*z upper boundary at issue in the '652 IPR. Accordingly, Patent Owner's attempt to analogize the facts of this proceeding to the Board's determination in the '652 IPR is unpersuasive.

Patent Owner also argues that the Petition "fails to establish that the cited prior art discloses step e of claim 1" because "Schmitt does not mention unpaired reads as claimed and certainly does not disclose a method for identifying or sorting unpaired reads." *See* Prelim. Resp. 35–38. According to Patent Owner, "the Examiner allowed claims of [related U.S. Patent No. 11,118,221 B2 (the "'221 patent'")] reciting substantially identical language finding that neither Schmitt nor any other prior art reference teaches or suggests the reducing or tracking step of claim 1" and "Petitioner gives no reason to second-guess the Examiner's findings." *Id.* at 36–37. Patent Owner also refers to our recent decision denying institution of *inter partes* review of the claims of the '221 patent. *See* Sur-reply 1–2.

As it relates to claim 1, Patent Owner's argument is unavailing. Element 1(e) of the '306 patent recites determining distinct cfDNA molecules "based on (i) paired reads . . . or (ii) unpaired reads" Ex. 1001, 61:29–36 (emphasis added).¹⁶ On the current record, Petitioner

¹⁶ By way of comparison, claim 29 depends from claim 1 and further limits element 1(e) by requiring the distinct cfDNA molecules be "determined

has sufficiently shown that the combination of Schmitt’s DCS method with Narayan’s cfDNA teaches or suggests the determination of cfDNA molecules based on paired reads. *See* Pet. 32–33 (“Schmitt discloses in a working example that ‘consensus sequences were then *paired with their strand-mate*’ and that the “complementary nature” of the double-stranded sequences “was used to *identify pairs of consensus groups* that arose from complementary DNA strands.”) (quoting Ex. 1083 ¶¶ 60, 68). This is sufficient to meet element 1(e) here regardless of whether Schmitt teaches or suggests the determination of cfDNA molecules based on unpaired reads.

Patent Owner’s attempt to analogize claim 1 of the ’306 patent to the ’221 patent claims ignores the fact that there is a significant difference in the pertinent claim language. *See* Sur-reply 2 (arguing that nothing “warrants a different conclusion regarding the parallel limitation[]” in element 1(e) of the ’306 patent). Unlike the presently challenged claim 1, which recites determining distinct cfDNA molecules from paired reads *or* unpaired reads, element 1(e) of the ’221 patent recites the generation of consensus sequences “from (i) paired reads . . . *and* (ii) unpaired reads” IPR2022-01152, paper 11, 13 (emphasis added).¹⁷ For this reason, we do not agree with Patent Owner that the Office’s previous consideration of the ’221 patent

based on (i) the paired reads *and* (ii) the unpaired reads.” Ex. 1001, 64:29–31 (emphasis added).

¹⁷ In IPR2022-01152, we determined “Petitioner ha[d] not sufficiently demonstrated that Schmitt’s DCS method generates consensus sequences ‘representative of the original cfDNA molecule . . . from . . . (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand’ as recited in element 1(e)” of the ’221 patent. IPR2022-01152, Paper 11, 16.

claims involved “substantially identical language” to that found in claim 1 here. *See* Prelim. Resp. 36.

Patent Owner also challenges Petitioner’s rationale for combining Schmitt and Narayan, urging these references “present fundamentally different and seemingly incompatible[] methods and Narayan expressly disparages consensus sequencing approaches like Schmitt as poorly suited for cfDNA.” *See* Prelim. Resp. 20–26. This argument too is unavailing on the current record. The Petition is premised on the application of Schmitt’s DCS method to cfDNA. The mere fact that, in addition to teaching that cfDNA can be screened for cancer, Narayan describes a different method for analyzing it, does not provide a teaching away from the combination of references articulated in the Petition. Moreover, Petitioner articulates reasoning, which is supported by the testimony of Dr. Spellman and other evidence, explaining why a POSA would have been motivated to apply Schmitt’s DCS method to cfDNA and would have had a reasonable expectation of successfully doing so. *See* Pet. 5–6, 13–14, 34–35, 37–39. Petitioner’s evidence is largely un rebutted at this stage of the proceeding and sufficiently supported to meet the burden for institution.

Patent Owner’s argument that “Narayan specifically disparages” consensus sequencing methods like DCS is not sufficiently developed and seems to overstate that reference’s teaching based on the current record. *See* Prelim. Resp. 24–26. Patent Owner points to the following statement in Narayan:

Kinde and colleagues recently described an elegant and powerful error reduction strategy that enables highly sensitive quantitation of DNA variants using massively parallel sequencing (21). However, this approach was not designed to

analyze multiple amplicons from samples containing limited DNA and was not tested on clinical specimens.

Id. at 24 (quoting Ex. 1082, 3497). According to Patent Owner, this statement also applies to Schmitt’s DCS method because it “bears the same fundamental design as Kinde.” *Id.* Even so, on the current record, we do not agree that Narayan disparages such an approach. To the contrary, Narayan praises Kinde’s methodology as “elegant,” “powerful,” and “highly sensitive,” even if it had not been designed specifically for cfDNA or tested on clinical specimens. *See* Ex. 1082, 3497. Moreover, Petitioner offers evidence, including Kukita,¹⁸ which it urges “expressly disclosed the potential benefit of using DCS for screening cfDNA from blood of cancer patients.” Pet. 14, 38 (citing Ex. 1008, 2, 7). Patent Owner disagrees with Petitioner’s evidence (*see* Prelim. Resp. 14–15), but we find on this record that Petitioner’s evidence is sufficient for institution. Patent Owner’s arguments to the contrary would benefit from further development at trial.¹⁹

Patent Owner’s arguments regarding what it calls Petitioner’s “routine blood draw theory” are also unavailing on the current record. *See* Prelim. Resp. 26–30. The Petition includes evidence and argument to show that a POSA would have understood that human blood contains sufficient amounts of cfDNA for use in DCS. *See* Pet. 5–6, 37, 39 (citing exhibits). As an

¹⁸ Kukita et al., *Quantitative Identification of Mutant Alleles Derived from Lung Cancer in Plasma Cell-Free DNA via Anomaly Detection Using Deep Sequencing Data*, 8 PLOS ONE METHODS 1–10 (2013) (Ex. 1008).

¹⁹ We also remind the parties of the panel’s observation in the ’652 IPR that “the test for obviousness does not require ‘actual success’ in the prior art.” Ex. 1074, 59 (quoting *Engo Pharm. Inc. v. Actavis LLC*, 992 F.3d 1365, 1379 (Fed. Cir. 2019)). The parties should consider this principle, and that panel’s related findings (*see id.* at 58–63), as they develop their arguments and evidence at trial in this proceeding.

example, Petitioner explains that 1 µg of cfDNA can be obtained from 7–12 ml of plasma. *Id.* at 6 (citing Ex. 1002 ¶¶ 68–71). Patent Owner argues that this “amount of DNA comes out of thin air” because “neither [Schmitt nor Narayan] discusses 1 µg of DNA and no explanation is provided.” Prelim. Resp. 28. We disagree. Dr. Spellman summarizes a number of references “teaching the use of [Next Generation Sequencing] on cfDNA extracted from [varying amounts of] plasma or blood” that are generally consistent with the exemplary sample amount of 1 µg of DNA in 7–12 ml of plasma referenced in the Petition. Ex. 1002 ¶ 72. This evidence, which is currently un rebutted, supports Petitioner’s assertion a POSA “would have known that sufficient amounts of cfDNA could be extracted from blood” using routine techniques and “that more cfDNA, if needed, could be obtained by simply increasing the amount of plasma sample used for cfDNA extraction.” Pet. 37 (citing Ex. 1002 ¶¶ 190–191; Ex. 1049: Ex. 1071, 718). To the extent Patent Owner disagrees, it will have the opportunity to respond more fully at trial.

Finally, Patent Owner criticizes Petitioner’s reliance on “a 3-mer hybrid tag” as opposed to the longer 12 nucleotide tag employed in Schmitt Example 1. *See* Prelim. Resp. 30–35. According to Patent Owner, Petitioner “never explains why one would specifically pair a hybrid 3-mer with the proposed cfDNA samples or why a POSA would reasonably expect success in such a scenario.” *Id.* at 32.

Patent Owner’s argument is unavailing on the current record. Petitioner asserts that a “POSA would have appreciated that Schmitt’s 3-mer hybrid tag embodiment offers advantages of simplified adapter synthesis, improved synthesis yield, and improved downstream PCR amplification compared to longer barcodes such as Schmitt’s 12-mer or 20-mer embodiments.” Pet. 35 (citing, e.g., Ex. 1002 ¶¶ 192–194). Petitioner

additionally asserts that a POSA “would have known that they could get more value per sequencing read when using Schmitt’s 3-mer hybrid tags.” *Id.* at 35–36 (citing, e.g., Ex. 1002 ¶¶ 194–196). These assertions are supported by Dr. Spellman’s testimony and sufficient to meet Petitioner’s burden at this stage of the proceeding. Patent Owner’s arguments to the contrary, e.g., that Petitioner’s publications “instruct avoiding tags less than 12 nucleotides” and “Schmitt teaches that tag diversity (e.g., tag size) should increase—rather than decrease—with increasing sample complexity,” are not well developed at this stage and would benefit from further development at trial. *See* Prelim. Resp. 31–32.

Petitioner’s showing for dependent claims 2, 3, 5, 7, and 9–14 is also sufficient to meet the burden for institution. The Petition presents evidence and argument to support Petitioner’s assertion that the cited references teach or suggest the additional limitations recited in each of these claims. Pet. 44–55 (addressing additional limitations in claims 2, 3, 5, 7, and 9–14).²⁰ At this stage, Patent Owner does not make any arguments against Petitioner’s showing for these dependent claims beyond its arguments for claim 1, which we have already explained are unavailing on the current record.

Accordingly, based on the record at this stage of the proceeding, Petitioner has established a reasonable likelihood it will prevail in

²⁰ For reasons explained in sections III.E.2 and III.H below, we are skeptical of the Petition’s showing for claim 14 to the extent Petitioner contends that Schmitt’s “pilot experiment” demonstrates “a quantitative measure of unpaired reads (more than 99%), as claimed.” Pet. 54. However, claim 14 recites determining quantitative measures of paired reads “or” unpaired reads. Ex. 1001, 62:32. Thus, on the current record, Petitioner’s showing relating to Schmitt’s quantification of paired reads is itself sufficient to teach this limitation.

demonstrating that claims 1–3, 5, 7, and 9–14 would have been obvious over Schmitt and Narayan.

2. *Analysis of Claims 17–27 and 29*

While on the current record Petitioner has met its burden with respect to claims 1–3, 5, 7, and 9–14, the same is not true for claims 17–27 and 29. Independent claim 17 differs from claim 1 in several respects, including its recitation of “sorting a plurality of sequence reads from the set of sequence reads into (i) families comprising paired reads . . . *and* (ii) families comprising unpaired reads” in element 17(d). Ex. 1001, 62:55–65 (emphasis added). Claim 29 depends from claim 1 and further limits element 1(e) by reciting that “the distinct cfDNA molecules in (e) are determined based on (i) the paired reads *and* (ii) the unpaired reads.” *Id.* at 65:29–31 (emphasis added). As discussed below, Petitioner has not sufficiently explained how the cited references teach or suggest the sorting of reads into families of unpaired reads as recited in element 17(d) or determining distinct cfDNA molecules based on unpaired reads as recited in claim 29.

For each of these elements, the Petition relies solely on the teachings in Schmitt. *See* Pet. 41–44 (claim 17); 58 (claim 29). Petitioner contends “a POSA would have known that Schmitt discloses ‘sorting’ the reads into paired and unpaired reads because Schmitt discloses generating duplex consensus sequence reads (paired reads), which requires ‘sorting’ the reads into paired reads and unpaired reads.” *Id.* at 42. For support, Petitioner points to Figures 1 and 3 and the related disclosure in Schmitt, urging that it teaches sorting reads into families based on their SMI tag that are then sorted into paired families. *Id.* at 44–45 (citing Ex. 1083 ¶¶ 43, 63, Figs 1, 3).

Petitioner also relies on its showing for element 1(e). Pet. 41, 58. There, the Petition points to the disclosure in Schmitt’s “working example

that ‘consensus sequences were then *paired with their strand-mate*’ and the ‘complementary nature’ of the double-stranded sequences ‘was used to *identify pairs of consensus groups* that arose from complementary DNA strands.” *Id.* at 32–33 (quoting Ex. 1083 ¶¶ 60, 68). Petitioner urges that “[b]y following this teaching in Schmitt, the POSA would have also determined distinct DNA molecules from sequence reads of a first tagged strand having no second complementary strand – i.e., unpaired reads.” *Id.* at 33. Petitioner also references “a separate working example” found in the “Schmitt PCT,” i.e., Ex. 1009.²¹ *Id.* According to Petitioner, the data in Table 1 of Ex. 1009 shows that in this example “more than half of the total SSCS reads remained unpaired, while the other reads were paired.” *Id.* at 33–34.

Patent Owner argues that Schmitt does not disclose the sorting of unpaired reads recited in element 17(d) or the use of unpaired reads recited in claim 29. *See* Prelim. Resp. 35–42. According to Patent Owner, “Schmitt does not identify unpaired reads, as that term is used in the challenged claims, at any step of its method.” *Id.* at 38. Patent Owner asserts that “Schmitt describes grouping as forming families of reads that share a common SMI tag” and this process is “agnostic to whether reads are paired or unpaired.”

Patent Owner further contends that the passages Petitioner cites from Schmitt’s working example “discuss only selecting consensus sequences based on a stringent filtering step,” i.e., where there is “‘perfect agreement’ between SMI sequences.” *Id.* at 38–40 (quoting Ex. 1083 ¶¶ 60, 68). Patent

²¹ Unlike its other arguments regarding Schmitt, for this argument Petitioner cites the text in Ex. 1009.

Owner argues that “sequences lack the requisite ‘perfect agreement’ where [a] sequence error occurs in the SMI or barcode.” *Id.* at 50. Patent Owner cites evidence, as well as Petitioner’s own argument, to show that “this problem was widely recognized in the scientific literature as specifically a problem in Schmitt’s DCS method and identified as a major cause of the data loss (e.g., >99% of tags) Schmitt describes.” *Id.* (citing Pet. 63 (relying on Ex. 1063, 2); Ex. 2013, 5–6).

Patent Owner also disputes Petitioner’s reliance on the data in Table 1 Ex. 1009, urging that it does not suggest the sorting of unpaired reads recited in element 17(d) or the use of unpaired recited in claim 29 because it “provides information on the basis of gross nucleotide count” as opposed to reads, i.e., “a series of nucleotides produced by sequencing a tagged strand derived from an original cfDNA molecule.” *Id.* at 41–42.

On the record at this stage of the proceeding, we determine that Patent Owner has the better argument. Beginning with element 17(d), the Petition points to two steps in Schmitt’s DCS method for element 17(d): (1) the grouping of reads into families “by virtue of having a common (i.e., the same) SMI tag sequence;” and (2) the subsequent grouping of those families “into *paired families*” based on the orientation of their tag. *See* Pet. 43 (quotations omitted). The first of these steps groups reads based on their SMI tag without regard to whether they have a complementary sequence. Thus, it does not disclose sorting “sequence reads into paired reads and unpaired reads” as recited in element 17(d). In the second of these steps, paired families comprising complementary sequences are formed. While this may result in the sorting of reads or SSCSs into families of paired reads, Petitioner has not shown that it teaches or suggests the sorting of reads into “families comprising unpaired reads” as recited in element 17(d).

Petitioner’s argument that the generation of duplex consensus sequences necessarily “requires” the sorting of unpaired reads is unavailing on the current record. *See* Pet. 42. Schmitt teaches that the complementary nature of its SMI tag sequences are “used to identify pairs of consensus groups that arose from complementary DNA strands.” Ex. 1083 ¶ 68. However, the Petition cites no corollary disclosure suggesting the sorting of reads into families that lack a complementary strand, nor do Petitioner or Dr. Spellman explain why the generation of duplex consensus sequences would require the sorting of sequence reads into families of unpaired reads. *See* Pet. 42; Ex. 1002 ¶ 233.

Instead, the figures and disclosures cited in the Petition and Dr. Spellman’s testimony show the grouping of families of reads with the same SMI into families of paired reads. *See* Pet. 42; Ex. 1002 ¶¶ 234–36. According to Schmitt, Figure 1 depicts that

two types of PCR products are produced from each capture event. Those derived from one strand will have the α SMI sequence adjacent to flow-cell sequence 1 and the β SMI sequence adjacent to flow cell sequence 2. PCR products originating from the complementary strand are labeled reciprocally.

Ex. 1083 ¶ 11. Thus, Figure 1 shows PCR products (i.e., reads) grouped into families based on their SMI sequence with an “ $\alpha\beta$ SMI family” and the *complementary* “ $\beta\alpha$ SMI family.” *Id.* at 56 (Fig. 1). Schmitt Figure 3 “(a-c) shows sequence reads . . . sharing a unique set of SMI tags . . . grouped into *paired* families” and an “error-corrected consensus sequence . . . for each *duplex*” in (d). Ex. 1083 ¶ 13 (emphases added). Petitioner has not explained how either figure depicts “families of unpaired reads corresponding to

sequence reads . . . having no second tagged complementary strand” as recited in element 17(d).

On the current record, Petitioner’s reliance on Schmitt Example 1 is also unavailing. Schmitt Example 1 describes the results of a “pilot experiment” in which “29,409 SMI partner pairs were found, indicative that fewer than 1% of tags had their corresponding partner pair tag present in the library.” Ex. 1083 ¶ 68. Petitioner argues this means the “measure of unpaired reads” in that experiment was “more than 99%” and thus a POSA following these teachings would have necessarily generated consensus sequences from unpaired reads.²² Pet. 54; *see also* Reply 3 (asserting that Schmitt paragraph 68 discloses “>99% unpaired sequence reads”). We are not convinced. As an initial matter, Schmitt Example 1 does not expressly describe the sorting of reads into families of unpaired reads as recited in element 17(d). Rather, Schmitt indicates that reads (i.e., “PCR duplicates”) were grouped into families based on their SMI tag, SSCSs were created from those families, and then the “complementary nature of the double-stranded SMI sequences was used to identify” and form double-stranded consensus sequences, but “only when the read data from each of the two strands [wa]s in perfect agreement.” *See* Ex. 1083 ¶¶ 67–68. Petitioner appears to assume that if a SMI partner pair was not found for a tag, the SSCS associated with that tag was necessarily generated from “unpaired reads . . . having no second tagged complementary strand” as recited in element 17(d). But neither the Petition, nor the testimony it cites from Dr. Spellman, provides

²² The Petition presents this argument for the “quantitative measures” limitations in dependent claims 14 and 27. Pet. 54. We address it here because Petitioner cites the same underlying disclosure to support its arguments for element 17(d). *See* Pet. 42 (citing Ex. 1083 ¶ 68).

sufficient explanation to support that assumption. *See* Pet. 54 (citing Ex. 1002 ¶ 309).

This is particularly so because Schmitt explains that for at least some tagged reads the reason a partner pair was not found was that the complementary strands were not in “perfect agreement.” *See* Ex. 1068 ¶ 68 (explaining that SMI partner pairs were found “after grouping of PCR duplicates” and “reads were considered only when the read data from each of the two strands is in perfect agreement”). In such instances, there would be a complementary strand, which seemingly undermines Petitioner’s theory that the tags that did not form SMI partner pairs in Schmitt’s working example were necessarily the result of unpaired reads.

In addition, Patent Owner cites evidence suggesting that the tags lacking a “corresponding partner tag” in Schmitt Example 1 may have resulted from sequencing errors in the SMI or barcode. *See* Prelim. Resp. 40–41 (Ex. 1063, 2; Ex. 2013, 5–6). Patent Owner relies on Stoler,²³ which explains that “sequencing errors within duplex tags” was known to be “one of the main causes of data loss” in DCS. Ex. 2013, 5–6. Indeed, both Petitioner and Dr. Spellman acknowledge that “sequencing errors in the barcode itself” were known to occur and ““can cause one tag to appear identical to another (crossover) or sufficiently alter a sequence tag such that it is unrecognizable (loss) and untraceable to the source material”” Pet. at 64; Ex. 1002 ¶ 355 (quoting Ex. 1063, 2). Based on the current record, it seems that in such instances the inability to form a SMI partner pair would result from the error in the SMI tag—not the lack of a complementary strand. The

²³ Stoler et al., *Streamlined Analysis of Duplex Sequencing Data with Du Novo*, 17:180 *Genome Biology* 1–10 (2016) (Ex. 2013).

fact that Petitioner does not account for the impact of such known sequencing errors in its analysis, further undermines its argument that Schmitt discloses “>99% unpaired sequence reads” as well as sorting between families of paired and unpaired reads. *See* Reply 2–3.²⁴

We are also skeptical of Petitioner’s arguments regarding the example reported in Table 1 of Exhibit 1009.²⁵ As Patent Owner points out, Table 1 appears to provide data based on “gross nucleotide count” for the overall experiment. *See* Prelim. Resp. 41–42. This supports Patent Owner’s argument that the data reported for “reads” in the fourth and fifth rows of Table 1 is calculated “as a measure of the total number of nucleotides (‘initial nucleotides’) divided by the total ‘SSCS [or DCS] nucleotides’” as opposed to “identifying paired and unpaired reads” (*id.* at 42), which in turn would seem to impact the “SSCS:DCS ratio” Petitioner relies upon for its arguments (*see* Pet. 33–34). Moreover, as explained above, Patent Owner

²⁴ In its Reply, Petitioner argues that “sequence reads with errors in the SMI or barcode are still *unpaired sequence reads* because they do not have a partner pair.” Reply. 4. But element 17(d) requires sorting into “families comprising unpaired reads corresponding to sequence reads generated from a first tagged strand *having no second tagged complementary strand* derived from double-stranded cfDNA molecules from among the tagged parent polynucleotides.” Ex. 1001, 62:60–65 (emphases added). We agree with Patent Owner that on the current record Petitioner has not sufficiently explained how these aspects of element 1(a) are met when a sequencing error in the SMI or barcode prevents the formation of a partner pair. *See* Sur-reply 2 (urging that “[e]rrors in the barcode may prevent SMI-based matching, but not describe an unpaired read *as claimed*”).

²⁵ It is unclear whether the fact that Table 1 and the related example Petitioner cites appear in Schmitt (i.e., Exhibit 1009) but apparently not in the priority application Schmitt-623 (Ex. 1083), affects the availability of this disclosure as prior art to the challenged claims. The parties are encouraged to address this issue in their subsequent papers.

cites evidence suggesting errors in the barcode and the lack of perfect agreement between complementary strands result in SSCSs not being paired to form DCS even where there is a “second tagged complementary strand” as recited in element 17(d). The analysis in the Petition and the corresponding testimony of Dr. Spellman do not account for these issues, undermining the persuasiveness of Petitioner’s argument. *See* Pet. 33–34, 44; Ex. 1002 ¶¶ 184–85, 237.

For these reasons, and based on the current record, Petitioner has not established a reasonable likelihood that it would ultimately prevail on its assertion that claim 17 would have been obvious over Narayan and Schmitt. Claims 18–27 depend from claim 17 and rely on the same showing for element 17(d). Thus, Petitioner has not met its burden for these claims for the same reasons noted for claim 17.

Petitioner’s showing for claim 29 is deficient for similar reasons. As explained above, the DCS method taught in Schmitt generates an “error corrected double-stranded consensus sequence.” Ex. 1083 ¶¶ 43, 60. Schmitt teaches that these consensus sequences are error corrected because “[s]equence reads at a given position are kept only if the read data from each of the two paired strands is in agreement.” *Id.* ¶¶ 60, 63, 68. Since only those reads having a complementary sequence in complete agreement are ultimately used to generate Schmitt’s duplex consensus sequences, the current record does not sufficiently show that Schmitt’s DCS method determines distinct cfDNA molecules “based on (i) the paired reads *and* (ii) *the unpaired reads*” as recited in claim 29.

F. Ground 2: Obviousness over Narayan, Schmitt, and Meyer

Petitioner asserts that claims 4 and 6 are unpatentable as obvious over Narayan and Schmitt. Claims 4 and 6 depend from claim 1 and additionally

recite a minimum percentage of cfDNA molecules from the population, i.e., “at least 20%” (claim 4) and “at least 40%” (claim 6), that must be tagged with duplex tags.²⁶ Ex. 1001, 61:53–55, 60–62. Petitioner asserts that each limitation of claims 4 and 6 is taught by the combination of Schmitt, Meyer, and Narayan, and that a POSA would have been motivated to combine Narayan’s cfDNA with Schmitt’s DCS method achieving the specified level of tagging efficiency in view of Meyer’s teaching of tagging 40–60% of DNA molecules. Pet. 58–61. Patent Owner disagrees, arguing that Petitioner fails to show that the cited references teach or suggest the tagging efficiency limitations of claims 4 and 6. Prelim. Resp. 45–47. Based on the current record, we agree with Patent Owner.

Petitioner relies solely on Meyers for the tagging efficiency limitations, asserting

A POSA would have understood that Meyer discloses that 40-60% of the DNA fragments are tagged because (i) Meyer’s Figure 1 depicts the DNA fragments tagged on both ends (Fig. 1), (ii) Meyer’s adapter ligation quantification “step 18” would only detect adapter-ligated DNA fragments, and (iii) Meyer expressly discloses successfully achieving at least 40-60% tagged DNA fragments.

Pet. 60 (citing Ex. 1002 ¶ 340; Ex. 1005, 274, Fig. 1). Petitioner further asserts that Meyer’s disclosure of an expected recovery “between 40 and 60” falls within the ranges recited in the tagging efficiency limitations. *Id.* at 59–60.

Petitioner asserts that a person of ordinary skill in the art would have been motivated to optimize adapter-DNA ligation for high efficiency using

²⁶ For ease of reference, we refer to these limitations collectively as the “tagging efficiency limitations.”

routine methods for doing so. Pet. 60–61. Petitioner argues “a POSA would have expected to successfully tag ‘at least 40%’ of the DNA molecules” because “Meyer expressly discloses successfully tagging 40–60% of DNA molecules.” *Id.* at 60 (citing Ex. 1002 ¶ 347; Ex. 1005, 274). And, according to Petitioner, Meyer’s disclosure of 40–60% tagging efficiency is consistent with other references. *Id.* For example, Petitioner cites the KAPA data sheet,²⁷ which teaches “15–40% of input DNA is typically recovered as adapter-ligated molecules.” *Id.* (quoting Ex. 1015, 4). Petitioner also cites Fisher²⁸ as disclosing “recovering 47% of the library as adapter-ligated DNA fragments.” *Id.* (citing Ex. 1031, Fig. 3). Finally, Petitioner asserts that a POSA “would have expected Schmitt’s sticky-end adapter-DNA ligation (using A- and T-overhangs) to be even more efficient than Meyer’s blunt-end adapter-DNA ligation, which nevertheless achieved 40–60% adapter-ligated DNA fragments.” *Id.* at 60–61 (citing Ex. 1002 ¶ 348; Ex. 1005, 273; Ex. 1083 ¶¶ 55–56). Even if the claimed amount is not expressly taught by the art, Petitioner asserts that tagging efficiency limitations would have been an obvious optimization of a result-effective variable. *See id.* at 62 (citing Ex. 1002 ¶ 348).

We are not persuaded by Petitioner’s arguments. As an initial matter, we note that Ground 2 in the instant Petition relies on nearly identical or similar arguments set forth by Petitioner in related proceedings, which we have previously rejected. *Compare, e.g.,* IPR2022-01115, Paper 2, 30–31,

²⁷ KAPA Technical Data Sheet for KAPA HTP Library Preparation Kit. Ex. 1015 (“KAPA data sheet”).

²⁸ Fisher et al., *A Scalable, Fully Automated Process for Construction of Sequence-Ready Human Exome Targeted Capture Libraries*, 12:R1 GENOME BIOLOGY 1–15 (2011). Ex. 1031 (“Fisher”).

35, 38, *with* Pet. 58–61. Thus, for the reasons stated in the decisions denying institution in those proceedings, we also find Petitioner’s showing for the tagging efficiency limitations in this proceeding to be deficient. *See, e.g.*, IPR2022-01115, Paper 14, 12–19.

That is, although Meyer teaches that its particular protocol results in 40–60% tagging efficiency, Petitioner has not sufficiently explained why a person of ordinary skill in the art would have expected Meyer’s tagging efficiency to apply to Schmitt’s DCS method when used with Narayan’s sequencing of cfDNA. For example, the Petition does not address the differences between Meyer’s adapters and Schmitt’s adapters and how those differences affect the tagging efficiency. Meyer’s barcodes comprise “single self-hybridized palindromic oligonucleotides, carrying an *Srf*I restriction site in the middle (GCCCGGGC), a sequence tag at the 3’ end and the reverse complementary tag sequence at the 5’ end.” Ex. 1005, Fig. 1. Schmitt, on the other hand, teaches a “hybrid method” of tagging that uses a combination of the sheared ends of the DNA fragments and a “shorter n-mer tag (such as 1 or 2 or 3 or 4 or more degenerate or semi degenerate bases) in the adaptor.” Ex. 1083 ¶ 30.

In addition, the KAPA data sheet states that tagging efficiency “can be significantly lower for DNA of lower quality.” Ex. 1015, 4. Fisher also explains that “the efficiency of adaptor ligation varies between samples, probably because of variation in input DNA quality.” Ex. 1031, 5–6. Petitioner does not address how the quality of the cfDNA of Narayan compares to the quality of the genomic DNA samples of Meyer and Schmitt or how that would affect the expected tagging efficiency. The KAPA data sheet discloses sticky-end adapter DNA ligation, but KAPA teaches that only 0.5 to 15% tagging efficiency is expected when the starting sample is

100 pg–100 ng of “high quality DNA.” Ex. 1015, 4. Thus, the KAPA data suggests that the use of sticky-end adapters, such as what Schmitt discloses, does not in and of itself teach or suggest the tagging efficiency limitations recited in claims 4 and 6 when using cfDNA.

We also determine that the current record does not sufficiently support Petitioner’s assertion “that adapter-DNA tagging efficiency is a *result-effective variable* that only requires routine skill to optimize.” Pet. 60 (citing Ex. 1002 ¶¶ 348). Dr. Spellman states “it was understood that increasing the concentration of adapters was a routine technique that could be used to maximize ligation efficiency such as by using a molar excess of adapters relative to DNA fragments in the ligation reaction.” Ex. 1002 ¶ 263. But the other evidence Petitioner relies upon suggests that achieving a particular level of tagging efficiency is not as simple as varying the concentration of adapters and is also affected by other factors, e.g., the amount of starting sample and the quality of the DNA. *See* Ex. 1015, 4; Ex. 1031, 6. Thus, we are not persuaded that Petitioner has shown sufficiently that adapter-DNA tagging efficiency, particularly for the cfDNA recited in the challenged claims, is a simple result-effective variable that can be determined by routine optimization.

For these reasons, and based on the current record, Petitioner has not established a reasonable likelihood that it will ultimately prevail on its assertion that claims 4 and 6 would have been obvious over Narayan, Schmitt, and Meyer.

G. Ground 3: Obviousness over Narayan, Schmitt, and Craig

Petitioner asserts that claim 8 would have been obvious over Narayan, Schmitt, and Craig. Pet. 61–63. Claim 8 depends from claim 1 and additionally recites that “the molecular barcodes have a length of 5 to 20

base pairs.” Ex. 1001, 61:64–65. Petitioner relies on Craig’s disclosure of a set of “48 6-mer barcodes” and articulates reasoning supported by the testimony of Dr. Spellman to explain why a POSA would have been motivated to use Craig’s “48 6-mer barcodes” in Schmitt’s DCS method with a reasonable expectation of success. Pet. 61–63 (citing Ex. 1002 ¶¶ 355–62).

At this stage of the proceeding, and based on the current record, we determine that Petitioner’s showing for claims 8 is sufficient to meet the burden for institution. Patent Owner does not presently dispute Petitioner’s showing beyond its arguments for claim 1, which we have addressed above. *See* Prelim. Resp. 47.

H. Ground 4: Obviousness over Narayan, Schmitt, and Kivioja

Petitioner asserts that claims 15, 16, and 28 would have been obvious over Narayan, Schmitt, and Kivioja. Pet. 63–69. Claim 15 depends from claim 14 (which in turn depends from claim 1) and recites “(g) estimating with a programmed computer processor a quantitative measure of tagged parent polynucleotides that map to the genomic locus based on the quantitative measure of the paired reads and the unpaired reads.” Ex. 1001, 62:34–39. Claim 16 depends from claim 15 and additionally recites “(h) detecting copy number variation in the population of cfDNA molecules by determining a normalized quantitative measure determined in (g) at each of one or more genomic loci.” *Id.* at 62:40–44. Claim 28 depends from a series of claims that depend from claim 17 and recites a limitation similar to that in claim 15. *See id.* at 64:22–28.

Petitioner relies on Kivioja’s methods for calculating the total number of molecules that map to a genetic locus and detecting copy number for the additional limitations recited in claims 15, 16, and 28. *See* Pet. 63–69.

Moreover, Petitioner articulates reasoning, supported by the testimony of Dr. Spellman, to explain why a POSA would have been motivated to use Kivioja's quantification methods in conjunction with the other cited references. *Id.* at 64, 66–67 (citing Ex. 1002 ¶¶ 367–76). At this stage, Patent Owner does not dispute Petitioner's showing for these claims beyond its arguments for independent claims 1 and 17. *See* Prelim. Resp. 47.

At this stage of the proceeding, and based on the current record, we determine that Petitioner's showing for claims 15 and 16 is sufficient to meet the burden for institution.²⁹ However, we express some skepticism to the extent the use of Kivioja's quantification methods may require quantitative measures of the number of unpaired reads that map to a genomic locus of the reference sequence. Petitioner's argument that Schmitt discloses a quantitative measure of unpaired reads is premised on its assumption that the tags that lacked partner pairs in Schmitt's "pilot experiment" corresponded to unpaired reads as recited in the challenged claims. *See* Pet. 54 (arguing that "Schmitt discloses . . . a quantitative measure of unpaired reads (more than 99%)"). As explained above, and based on the record at this stage of the proceeding, Petitioner has not sufficiently shown that this is the case. *See supra* § III.E.2. This in turn may impact Petitioner's arguments for combining Kivioja's methods with Schmitt and Narayan. In any event, these issues would benefit from further development, and we encourage the parties to address them in their subsequent papers at trial.

²⁹ Petitioner's showing for the additional limitation recited in claim 28 is also sufficient at this stage of the proceeding. However, as explained above, Petitioner has not met its burden for claim 17 from which claim 28 indirectly depends.

IV. CONCLUSION

Based on the current record, we determine Petitioner has shown a reasonable likelihood that it will prevail in establishing that at least one claim of the '306 patent is unpatentable. Accordingly, we institute review of all claims challenged on all of the grounds in the Petition. *See Patent Trial & Appeal Board Consolidated Trial Practice Guide November 2019 ("CTPG," available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>), 64.*

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing analysis could change upon completion of the record.

V. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–29 of the '306 patent based on the unpatentability challenges presented in the Petition;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

IPR2022-01400
Patent 11,149,306 B2

For PETITIONER:

Ralph Powers
David Holman
Kristina Kelly
Christopher Gallo
Tyler Liu
STERNE KESSLER GOLDSTEIN & FOX PLLC
tpowers-ptab@sternekessler.com
dholman-ptab@sternekessler.com
kckelly-ptab@sternekessler.com
cgallo-ptab@sternekessler.com
tliu@sternekessler.com

For PATENT OWNER:

Michael Rosato
Jad Mills
Sonja Gerrard
Patrick Medley
WILSON SONSINI GOODRICH & ROSATI
mrosato@wsgr.com
jmills@wsgr.com
sgerrard@wsgr.com
pmedley@wsgr.com