

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*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Denying Patent Owner's Motion to Strike
Denying Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

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.”). We instituted trial on all of the grounds in the Petition. Paper 9, 44 (“Dec.”).

Guardant Health, Inc. (“Patent Owner”) subsequently filed its Response to the Petition (Paper 18, “Resp.”), Petitioner filed its Reply (Paper 25, “Reply”) and Patent Owner filed its Sur-reply (Paper 30, “Sur-reply.”). In addition, with our authorization, Patent Owner filed a motion to strike certain exhibits submitted with the Reply (Paper 29, “MTS”), which Petitioner has opposed (Paper 31, “MTS Opp.”). Patent Owner also filed a motion to exclude (Paper 32 (“MTE”)), which Petitioner has opposed (Paper 34 (“MTE Opp.”)). We held a hearing on November 17, 2023, and a transcript is of record. Paper 40 (“Tr.”).

After considering the parties’ arguments and evidence, we find that Petitioner has not shown by a preponderance of the evidence that the challenged claims of the ’306 patent are unpatentable. *See* 35 U.S.C. § 316(e). Moreover, we deny Patent Owner’s motions to strike and exclude.

II. BACKGROUND

A. *Real Parties in Interest*

Petitioner identifies itself as a real party in interest and the University of Washington as a potential real party in interest. Pet. 69. Patent Owner identifies itself as a real party in interest. Paper 19, 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 are 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

In support of these grounds, Petitioner relies upon the Declaration of Paul T. Spellman, Ph.D. (Ex. 1002), submitted with the Petition, and the Declarations of Rahul Satija, D.Phil. (Ex. 1098) and Aleksandar Rajkovic, M.D., Ph.D. (Ex. 1099), submitted with the Reply. Patent Owner relies on the Declarations of Dr. John Quackenbush (Ex. 20115) and Dr. Ian Hageman (Ex. 2016).

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”).

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 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*

Relying on Dr. Spellman’s testimony, 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 agrees that a POSA would have had the knowledge suggested by Dr. Spellman, and its declarants apply “Dr. Spellman’s definition of a POSA in their analyses.” Resp. 6–7.

We adopt Petitioner’s uncontested definition of the level of ordinary skill in the art. This definition is supported by the record (Ex. 1002 ¶¶ 27–30) and consistent with the disclosure in the ’306 patent and references cited in the Petition.

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).

In our Institution Decision, we noted Petitioner’s assertions regarding a POSA’s understanding of “z” in element 1(b) and its contention that Schmitt discloses a number of different combinations of molecular barcodes that was within the range recited in element 1(b) regardless of the z value. Dec. 14 (citing Pet. 19). Based on the record at that time, we explained that “[f]or this reason, it is unnecessary to expressly construe ‘z’ or any other aspect of element 1(b) to decide the issues present in the Petition.” *Id.* We also noted that, at least at the institution stage, neither side had proposed any express claim construction. *Id.*

In its Response, Patent Owner asserts that “[n]o specific construction is believed necessary here to determine that the recited terms are disclosed in the cited prior art.” Resp. 7. Nevertheless, Patent Owner offers a “discussion” to “provide[] context” regarding its interpretation of certain terms relating to tagging of cfDNA molecules in element 1(b). *Id.* at 7–8. According to Patent Owner, “claim construction must begin with the words of the claims themselves,” and here the “language of claim 1 distinguishes the duplex tags” comprising molecular barcodes in element 1(b) “from the cfDNA molecules” to which they are attached. *Id.* at 8 (quoting *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1301 (Fed. Cir. 2006)). In particular, Patent Owner points to the fact that claim 1 “expressly recites ‘wherein the duplex tags are attached to both ends of a molecule of the plurality of the cfDNA molecules.’” *Id.* (quoting Ex. 1001, 61:13–14).

Petitioner does not directly reply to Patent Owner’s argument that the claim language distinguishes between the duplex tags and cfDNA molecules. *See generally* Reply. Instead, Petitioner contends that Patent Owner “ignores the [’]306 patent’s definition of *duplex tags*.” Reply 8. Moreover, Petitioner contends that the ’306 patent “admits” that its methods encompass the tagging methodology, i.e., “Schmitt’s hybrid tagging embodiment,” it relies upon in the Petition. *Id.* at 9.

Thus, while neither party proposes any formal claim construction, some of their arguments regarding the application of Schmitt’s teachings to element 1(b) present issues relating to the proper interpretation of element 1(b). We address those issues below in context of the parties’ other arguments relating to element 1(b). No other claim construction is necessary for this decision.

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, 3492.⁷ Patent Owner does not dispute, and we agree, that Narayan is prior art to the challenged claims here.

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 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. 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

⁷ Unless stated otherwise, citations to page numbers refer to the reference page numbers.

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 and we agree that Schmitt is prior art to the challenged claims here.⁸

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

In Schmitt’s DCS method, double-stranded DNA molecules are ligated to single molecule identifier (“SMI”) adapter molecules. Ex. 1083

⁸ 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.

¶¶ 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^[9] 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

⁹ An n-mer is a sequence where n is the number of nucleotides. A 3-mer, for example, is a sequence of three nucleotides.

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, and we agree, that *Meyer* is prior art to the challenged claims here.

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, and we agree, that *Craig* is prior art to the challenged claims here.

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 13¹⁰ (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, and we agree, that Kivioja is prior art to the challenged claims here.

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

¹⁰ 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, 4–5¹¹ (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. Resp. 10–60.

For the reasons explained below, we find that Petitioner has not shown by a preponderance of the evidence that any of these claims would have been obvious over the asserted combination of Narayan and Schmitt. More specifically, for independent claim 1, and those claims that depend from claim 1, Petitioner has not sufficiently shown that any of these references teach or suggest “tagging a plurality of the cfDNA molecules . . .

¹¹ This refers to the page number added to the exhibit.

with duplex tags comprising molecular barcodes . . . wherein the duplex tags are attached to both ends of a molecule of the plurality of the cfDNA molecules,” as recited in element 1(b). Ex. 1001, 61:10–14. For independent claim 17 and those claims that depend from claim 17, Petitioner has not sufficiently shown that any of these references teach or suggest “sorting a plurality of sequence reads from the set of sequence reads into (i) families comprising paired reads . . . *and* (ii) families comprising unpaired reads” as recited in element 17(d). Ex. 1001, 62:55–65 (emphasis added). Because these issues are dispositive for all of the challenged claims, our analysis below focuses on the parties’ arguments and evidence pertaining to these claim elements.

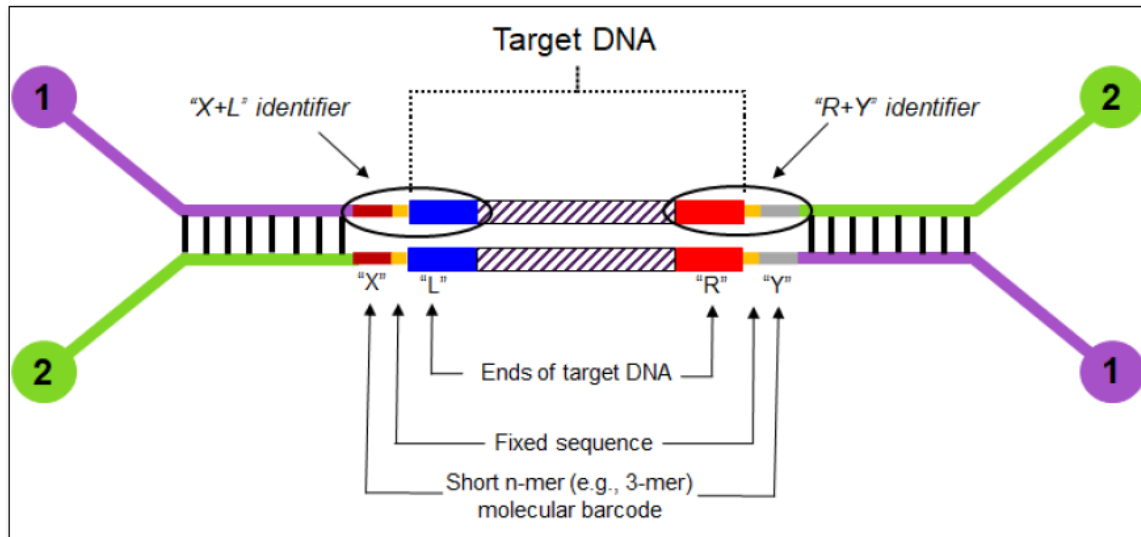
1. Analysis of Claims 1–3, 5, 7, 9–14, and 29

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. 25, 34. That is, Petitioner asserts that “Narayan discloses isolating cfDNA . . . from the blood of cancer patient, sequencing it, and analyzing the sequence reads.” *Id.* at 26. In the asserted combination, Petitioner contends a POSA would have substituted Schmitt’s DCS method for the sequencing method used in Narayan. *Id.* at 34. According to Petitioner, “Schmitt alone” discloses all of the steps, i.e., “tagging, amplifying, sequencing, and reducing or tracking redundancy of sequencing reads,” of the method 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)). We refer to this as “Schmitt’s hybrid method” or “Schmitt’s hybrid embodiment” herein.

Petitioner’s declarant, Dr. Spellman, provides the following diagram depicting Schmitt’s hybrid embodiment.



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 3-mer molecular barcodes are labeled ‘X’ and ‘Y.’” *Id.*

Petitioner asserts that Schmitt’s hybrid embodiment discloses ““duplex tags comprising molecular barcodes’ that are ‘attached to both ends’ of a cfDNA molecule” as those terms are recited in element 1(b). Pet. 27. Petitioner contends that “duplex tags” are “tags that differently label the complementary strands . . . of a double-stranded molecule.” *Id.* (quoting Ex. 1001, 17:9–13). According to Petitioner,

Schmitt’s hybrid tag embodiment differently labels the complementary strands by tagging both ends of the molecule and relying on the asymmetrical nature of the duplex tags. And Schmitt’s hybrid tag embodiment comprises molecular barcodes because the duplex tags comprise both the fragment DNA end sequences [i.e., L and R in the diagram above] and “a

shorter n-mer tag” [i.e., X and Y in the diagram] to serve as “unique molecular identifiers.”

Id. (citing Ex. 1002 ¶ 162; Ex. 1083 ¶¶ 11, 30).

For the “n different combinations of molecular barcodes” requirement of element 1(b), Petitioner points to Schmitt’s disclosure of “3-mer barcodes.” Pet. 28–29. Petitioner contends that this 3-mer barcode provides a total of 4,096 “different combinations of molecular barcodes, considering the tagging occurs on both ends of the target molecule.” *Id.* at 28 (citing Ex. 1002 ¶ 164) (internal quotations omitted). Based on this calculation, Petitioner urges that Schmitt discloses an “n” with the recited range of “at least 2 and no more than $100,000 \times z$ ” regardless of the z value for a given sample. *Id.* at 29 (citing Ex. 1002 ¶¶ 166–167).

In response, Patent Owner urges that “[t]he petition materials fail to establish the cited prior art discloses or teaches the tagging step of claim 1,” i.e., element 1(b). Resp. 10. Patent Owner contends “[t]he petition materials acknowledge SMIs as the ‘molecular barcodes’ in Schmitt, and they acknowledge hybrid SMIs as the combination of shear sequence and exogenous n-mer sequence, but they improperly and inconsistently map only the exogenous 3-mer portion of the hybrid SMI in the discussion of the challenged claims.” *Id.* (citing Pet. 28–29).

More specifically, Patent Owner argues that claim 1 does not encompass Schmitt’s hybrid embodiment because “even if the hybrid SMI sequences are viewed as molecular barcodes in Schmitt’s DCS process, those are not contained in adapter molecules or duplex tags that are attached to the DNA molecules.” *Id.* at 18 (citing Ex. 2015 ¶ 59). According to Patent Owner, “the language of claim 1 specifies that the duplex tags are attached to the cfDNA molecules and distinguishes the ‘cfDNA molecules’ from the

‘duplex tags’ with the molecular barcodes.” *Id.* (citing Ex. 2015 ¶ 60); *see also id.* at 8 (discussed *supra* § III(C)). But in Schmitt’s hybrid embodiment, the SMI includes both the n-mer and a portion of the endogenous end sequence of the DNA molecule. *Id.*; *see also id.* at 16–17 (citing testimony from Dr. Spellman that Patent Owner contends “acknowledges the combination of the endogenous shear sequence and exogenous 3-mer sequence together provide the SMI used for grouping and matching in Schmitt’s DCS process”). Thus, urges Patent Owner, Petitioner’s attempt to map this “amalgamation of sequences that together function as the SMI” to the duplex tag in element 1(b) “improperly conflates the DNA molecule with the attached duplex tags.” *Id.* at 19 (citing Ex. 1002 ¶ 162.).

Patent Owner also asserts that Petitioner has not shown that the number of different combinations of the SMI in Schmitt’s hybrid embodiment is within the recited range for “n” because Dr. Spellman’s calculations only consider the nucleotides in the 3-mer tag and not those in the “shear sequences of the DNA molecule . . . included in the hybrid SMIs.” *Id.* at 20–21.

In reply, Petitioner asserts that Patent Owner’s arguments ignore the ’306 “patent’s definition of *duplex tags*” as “tags that differently label the complementary strands of a double-stranded molecule.” Reply 8 (quoting Ex. 1001, 17:9–13). According to Petitioner, the “salient point” is that Schmitt teaches “tagging the double-stranded DNA molecules such that the tags *differently label the complementary strand* (i.e., ‘duplex tags,’ under the [’]306 patent’s definition.”). *Id.* (citing Ex. 1002 ¶ 162; Ex. 1098 ¶¶ 38–40; Ex. 1097, 98:16–99:1). Moreover, Petitioner contends that the ’306 “patent admits that tagging can be achieved using the *combination of a DNA barcode and one or more endogenous sequences* of the polynucleotide.”

Reply 9 (citing Ex. 1001, 21:23–25, 21:39–42, 22:44–51, 34:55–58)
(internal quotations omitted).

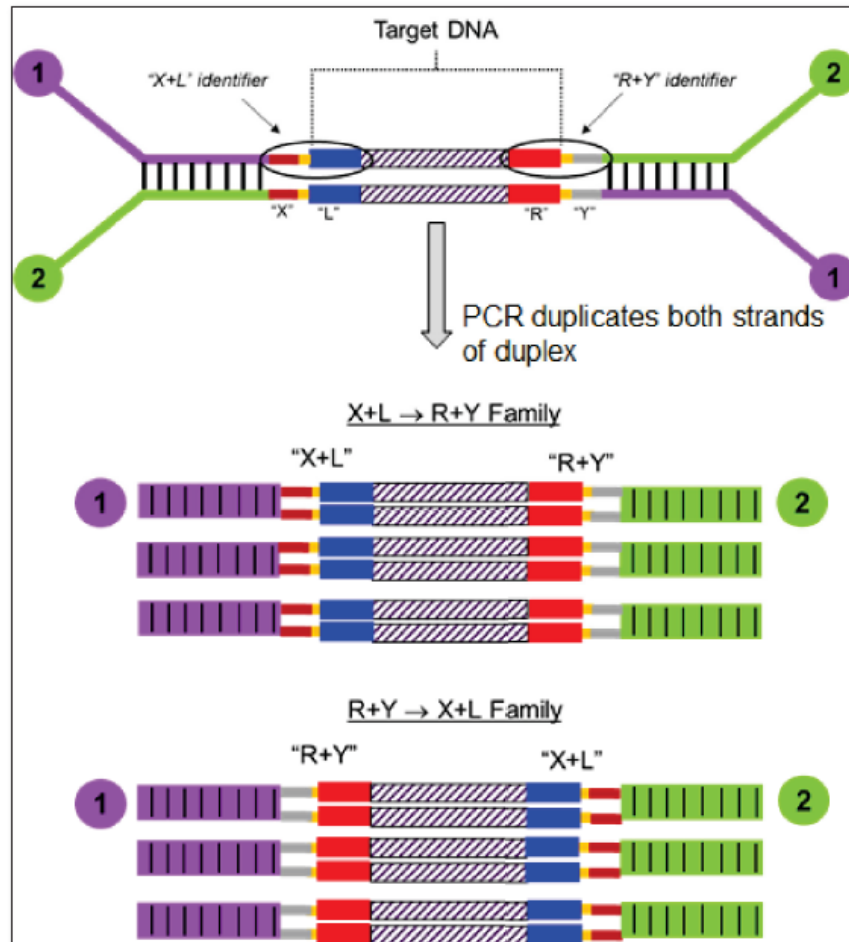
In sur-reply, Patent Owner urges that the Reply “never addresses the plain language” of claim 1 stating “that 1) the duplex tags include the molecular barcodes and 2) those duplex tags are attached to and distinguished from the ‘cfDNA molecules.’” Sur-reply 3. Patent Owner argues that the functional description of duplex tags “in the specification as labeling complementary strands of cfDNA . . . in no way negates claim language placing structural limitations on duplex tags such as those recited in claim 1.” *Id.* at 5.

Patent Owner further contends that Petitioner’s argument that the ’306 patent “admits that ‘tagging’ can be achieved by the combination of a DNA barcode and one or more endogenous sequences of the polynucleotide” (*see* Reply 9), “misquotes and mischaracterizes the ’306 specification.” Sur-reply 6. According to Patent Owner, none of the provisions Petitioner cites refer to tagging, but rather “describe molecular barcodes as exogenous sequences just like the claims.” *Id.*

Having considered these arguments on the full trial record, we find Patent Owner has the better position because Petitioner’s showing that element 1(b) is taught by Schmitt is unpersuasive. We begin with Patent Owner’s argument concerning the distinction between the cfDNA molecules and the duplex tag comprising the molecular barcode found in the text of claim 1. Element 1(a) recites “a population of cell-free deoxyribonucleic acid (cfDNA) molecules.” Ex. 1001, 61:7–9. Element 1(b) recites “tagging a plurality of the cfDNA molecules in the population” of element 1(a) “with duplex tags comprising molecular barcodes to produce tagged parent polynucleotides . . . wherein *the duplex tags are attached to both ends of a*

molecule of the plurality of the cfDNA molecules.” Id. at 61:10–14 (emphasis added). We agree with Patent Owner and credit the testimony of its declarant that this claim language distinguishes the duplex tags from the ends of the cfDNA molecule to which they are attached. Resp. 8; Ex. 2015 ¶¶ 38–39, 60, 61. That is, the duplex tag is not part of the cfDNA molecule itself, but rather is “attached to both the ends” of that molecule by “tagging” it as recited in element 1(b).

We also agree with Patent Owner that given this distinction, claim 1 does not encompass Schmitt’s hybrid embodiment. Resp. 18–20. As Petitioner notes, “[i]n Schmitt’s hybrid-tag embodiment, the strands are grouped based on *the combination* of the short n-mer barcode and the end of the target DNA.” Pet. 11; *see* Resp. 17 (“[T]he combination of the endogenous shear sequence and exogenous 3-mer sequence together provide the SMI used for grouping and matching in Schmitt’s DCS process.”). Petitioner and its declarant illustrate the grouping in Schmitt’s hybrid embodiment with the following diagram. Pet. 12; Ex. 1002 ¶¶ 96–98.



Petitioner's diagram shows the PCR products produced from sequencing a "Target DNA" molecule that has been tagged with 3-mers X and Y according to Schmitt's hybrid embodiment. *See* Ex. 1002 ¶ 98 (describing diagram). A portion of the endogenous sequence of the DNA molecule labeled L and R is used in combination with the 3-mer sequence to group the resulting strands into two families labeled the "X+L→R+Y Family" and the "R+Y→X+L Family." Ex. 1002 ¶ 98; Ex. 2015 ¶ 62 (explaining that Petitioner's diagram shows that "the relied upon hybrid SMI sequences of Schmitt include sequence from the sample DNA molecule not contained in the adapter or the duplex tags").

Petitioner contends that Schmitt's X+L and R+Y identifiers, i.e., the SMIs, differently label the strands and therefore are the recited "duplex tags." *See* Pet. 27–28 ("duplex tags comprise *both* the fragment DNA end sequences and a shorter n-mer tag") (emphasis added) (internal quotations omitted). However, we credit Dr. Quackenbush's testimony that end sequences L and R are not "attached to both ends" of the cfDNA molecule by "tagging" it as recited in element 1(b). *See* Ex. 2015 ¶ 59–62 (explaining that Schmitt's hybrid SMI sequences include a portion of the sample DNA molecule, which is "not contained in adapter molecules or duplex tags that are attached to the DNA molecules"). Rather, end sequences L and R *are* the pre-existing, endogenous ends of that molecule. *Id.* Thus, Petitioner's theory of unpatentability does not account for the distinction the claim language draws between the cfDNA molecule and the duplex tags.

Petitioner's argument that the '306 patent defines "duplex tag" as a "tag that differently label the complimentary strands . . . of a double-stranded molecule" does not overcome this short-coming. Pet. 27; Reply 8 (citing Ex. 1001, 17:11–12). First, the same passage Petitioner cites for this definition further indicates those tags as molecules "attached to a polynucleotide" using various methods of "[t]agging" such as hybridization or ligation to attach the duplex tag to the polynucleotide. *See* Ex. 1001, 17:16–40. Thus, the Specification is consistent with the claim language in drawing a distinction between the tag and the polynucleotide to which it is attached. Second, even if we accept Petitioner's definition and agree that the combination of the end sequence and 3-mer in Schmitt's hybrid tag embodiment could be a "duplex tag," Petitioner's argument does not account for element 1(b)'s additional requirement that the duplex tag be "attached to both ends" of the cfDNA molecule.

Petitioner's argument that the '306 patent "admits that 'tagging' can be achieved using 'the *combination of a DNA barcode and one or more endogenous sequences* of the polynucleotide" is unpersuasive because it conflates "identif[ying]" the cfDNA molecule with "tagging" it as recited in element 1(b). *See* Reply 9 (citing Ex. 1001, 21:23–25, 21:39–42, 22:44–51, 34:55–58). The Specification explains that a polynucleotide can be "uniquely *identified* in various ways," including by "a unique DNA barcode" or alternatively "by the combination of a DNA barcode and one or more endogenous sequences." Ex. 1001, 21:19–44 (emphasis added). However, none of the passages Petitioner cites describes the use of part of the polynucleotide's own sequence for purposes of identification as "tagging." To the contrary, these passages distinguish between a "tag" or "barcode," which is attached to the polynucleotide, and the endogenous sequence of polynucleotide itself. *See* Ex. 1001, 21:23–25 ("[A] polynucleotide can be uniquely identified by the combination of a DNA barcode and one or more endogenous sequences of the polynucleotide."); 21:39–42 ("Each polynucleotide in the sample can be identified by the combination of the DNA barcodes and about 10 base pair endogenous sequence on an end of the polynucleotide."); 22:44–51 ("[B]arcodes may be attached (e.g., by ligation) to individual molecules such that the combination of the barcode and the sequence it may be ligated to creates a specific sequence that may be individually tracked."); 34:55–58 (describing reads being grouped based on "various types of sequences, e.g., sequences of an oligonucleotide tag (e.g., a barcode), sequence of a polynucleotide fragments [sic], or any combinations").

Accordingly, while the Specification describes alternative embodiments that use a portion of the endogenous sequence to identify the

cfDNA molecule, Petitioner has not shown that claim 1 encompasses those embodiments given the distinction drawn in the claim language between the “duplex tags comprising molecular barcode” and the cfDNA “molecule” to which those tags are attached. Ex. 1001, 61:10–14. Indeed, it is well-settled that “claims need not be construed to encompass all disclosed embodiments when the claim language is clearly limited to one or more embodiments,” as is the case here. *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008); *see also Baran v. Med. Device Techs., Inc.*, 616 F.3d 1309, 1316 (Fed. Cir. 2010) (“It is not necessary that each claim read on every embodiment.”).

Finally, we address a new theory Petitioner presented at the oral hearing. There, Petitioner changed its mapping of Schmitt’s hybrid method to element 1(b), asserting that the alleged duplex tag did not include the ends of the cfDNA molecule in the SMI. Tr. 10:12–11:5. That is, Petitioner asserted that the duplex tag was *only* the “Y shaped adaptor,” i.e., the “green and purple arms” in Petitioner’s diagrams above, the “fixed sequence yellow portion,” and the n-mer tag (X and Y), and did not include the ends of the target cfDNA molecule (L and R). *Id.*

We are not persuaded. First, this is an inappropriate new argument. The Petition presents a different mapping, alleging that the “duplex tag” comprises *both* the endogenous end sequence of the cfDNA molecule and the 3-mer barcode of Schmitt’s hybrid tag embodiment. Pet. 27 (“the duplex tags comprise both the fragment DNA end sequences and ‘a shorter n-mer tag’ to serve as ‘unique molecular identifiers’”) (quoting Ex. 1083 ¶ 30, Ex. 1002 ¶¶ 162–163); *see also* Tr. 62:13–63:19 (Petitioner’s counsel noting he was unaware of any explicit statement in the Petition that Schmitt’s duplex tag comprised just the 3-mer without the end sequence). Nor did Petitioner

present this argument in its Reply in response to Patent Owner's arguments regarding element 1(b). *See* Reply 8–10. Rather, consistent with the mapping in the Petition, the Reply identifies “Schmitt’s hybrid tags,” i.e., the combination of the endogenous end sequence and the n-mer, as the duplex tags in element 1(b). *See* Reply 8 (urging that “duplex tags” are “tags that differently label the complementary strands,” which “is precisely what Schmitt’s hybrid tags do”). Because this argument was not previously presented, Patent Owner has not been afforded a sufficient opportunity to address it. Thus, Petitioner’s new argument excluding the end sequences in Schmitt’s hybrid tag embodiment from the alleged “duplex tags comprising molecular barcodes” has been waived.

Second, even if we were to consider it on the merits, Petitioner’s new mapping for element 1(b) is inconsistent with Petitioner’s allegations for element 1(e). Element 1(e) recites “reducing or tracking redundancy” in sequence reads “using at least sequencing information from the molecular barcodes of the duplex tags to determine distinct cfDNA molecules.” Ex. 1001, 61:26–30. For these limitations, the Petition points to Schmitt’s grouping of reads into families based on their SMI and asserts that Schmitt determines distinct cfDNA molecules based on “the complementary nature of the SMI on the two strands of the duplex.” *See* Pet. 30–32 (internal quotations omitted). Thus, like Petition’s mapping for element 1(b), Petitioner’s allegations for element 1(e) rely on a duplex tag that includes both the 3-mer and the end sequence of the cfDNA molecule. Petitioner has not sufficiently explained, much less shown by a preponderance of the evidence, that Schmitt teaches or suggests the limitations in element 1(e) based on its new mapping of the 3-mer alone as duplex tags.

For these reasons, Petitioner has not shown by a preponderance of the evidence that the asserted combination of Narayan and Schmitt teaches or suggests element 1(b). Thus, Petitioner has not met its burden for claim 1. Petitioner has not met its burden for dependent claims 2, 3, 5, 7, 9–14, and 29 for the same reasons.

2. *Analysis of Claims 17–27 and additional analysis of claim 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 explained below, Petitioner has not met its burden to show that the asserted combination of references teaches or suggests 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. As 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. *Id.* (citing Ex. 1009 ¶¶ 120–137; Ex. 1002 ¶¶ 184–185). According to Petitioner, the data in Table 1 of Ex. 1009 shows that in this example “more than half of the total SSCS [i.e., single-strand consensus sequence] reads remained unpaired, while the other reads were paired.” Pet. 33–34.

At the institution stage, we found Petitioner’s showing unpersuasive in view of certain arguments in Patent Owner’s Preliminary Response. *See* Dec. 30–37. Patent Owner reasserts those arguments in the Response. Resp. 55–60. In particular, 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 Id.* 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 57. Instead, Patent Owner contends “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.” *Id.* at 57–58.

Moreover, Patent Owner points to reasons why Schmitt's identification of paired reads (i.e., reads with a common SMI tag) does not inherently results in the grouping of unpaired reads. According to Patent Owner, Schmitt describes "selecting consensus sequences based on a stringent filtering step," i.e., where there is "'perfect agreement' between SMI sequences." Resp. at 58–59 (quoting Ex. 1083 ¶¶ 60, 68). Patent Owner argues that "[s]equences lack the requisite 'perfect agreement' where a sequence error occurs in the SMI or barcode." *Id.* at 59. 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) that Schmitt describes." *Id.* (citing Pet. 62 (relying on Ex. 1063, 2); Ex. 2013, 5–6).

Patent Owner also disputes Petitioner's reliance on the data in Table 1 of Ex. 1009, urging that it does not suggest the sorting of unpaired reads recited in element 17(d) or the use of unpaired reads 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." Resp. 59–60.

In reply, Petitioner urges that a skilled artisan "reading Schmitt would understand from simple logic and knowledge in the art that there can only be three possible outcomes when amplifying a DNA template to generate sequence reads: (1) raw reads generated from both strands; (2) raw reads generated from the first or second strand only; or (3) no reads generated from either strand." Reply 11 (citing Ex. 1098 ¶¶ 48–50). According to Petitioner, "where Schmitt sorts sequence reads into families—either raw or consensus sequence reads—there will necessarily be groups comprising

either paired or unpaired sequence reads. Said another way, Schmitt necessarily sorts reads into paired *and unpaired reads*, because after sorting the paired reads all that remains is *unpaired reads*.” *Id.* (citing Ex. 1083 ¶¶ 13, 60, 68, 71–72, Fig. 3; Ex. 1009 ¶ 128; Ex. 1002 ¶¶ 180–185, 231–237; Ex. 1098 ¶¶ 48–50).

In sur-reply, Patent Owner again points out that Petitioner’s analysis does “not account for the impact of sequencing errors” and urges that the Reply does not address this deficiency. Sur-reply 25.

Having considered these arguments on the full trial record, we find Patent Owner has the better position and that Petitioner’s arguments for element 17(d), and the similar element recited in claim 29, are unpersuasive. 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 unpersuasive. *See* Pet. 42; Reply 11. Schmitt teaches that the complementary nature of its

SMI tag sequences is “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 its declarants 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; Ex. 1098 ¶¶ 46-53.

Instead, the disclosures and testimony Petitioner cites 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).

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.¹² Pet. 54. 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 an 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). *See* Reply 11 (“[W]here Schmitt sorts sequences reads into families—either raw or consensus sequence reads—there will necessarily be groups comprising either paired or unpaired sequence reads.”). But neither Petitioner’s briefing, nor the testimony Petitioner cites from its declarants, provides sufficient explanation to support that assumption. *See* Pet. 54 (citing Ex. 1002 ¶ 309); Reply 10–12 (citing Ex. 1098 ¶¶ 46–53).

¹² 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).

This is 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 albeit one with imperfect agreement to the corresponding strand, which 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.

Moreover, Patent Owner shows that a POSA would have understood that sequencing errors in the SMI result in reads that cannot be matched with their partner pair, not because of the lack of a complementary strand, but because of the error in the SMI. *See* Resp. 59–60 (Ex. 1063, 2; Ex. 2013, 5–6). Stoler¹³ explains that “sequencing errors within duplex tags” were known to be “one of the main causes of data loss” in DCS. Ex. 2013, 5–6. Moreover, 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). In such instances, the inability to form a SMI partner pair results from the error in the SMI tag—not the lack of a complementary strand. That is, these reads are not

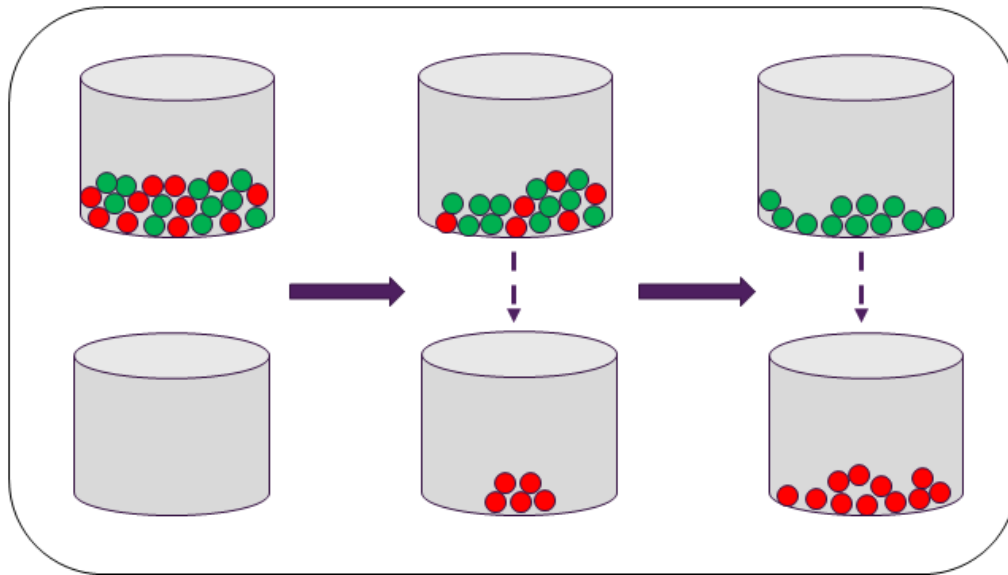
¹³ Stoler et al., *Streamlined Analysis of Duplex Sequencing Data with Du Novo*, 17:180 GENOME BIOLOGY 1–10 (2016) (Ex. 2013).

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

Petitioner’s arguments regarding the additional example in Exhibit 1009 and the data in Table 1 are likewise unpersuasive. As Patent Owner points out, Table 1 appears to provide data based on “gross nucleotide count” for the overall experiment. Resp. 60; *see* Ex. 1009 ¶¶ 126–128. 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 number of total ‘SSCS [or DCS] nucleotides’” as opposed to “identifying paired and unpaired reads” (*id.*), which in turn would impact the “SSCS:DCS ratio” Petitioner relies upon for its arguments (*see* Pet. 33–34). Moreover, as explained above, Patent Owner cites evidence suggesting sequencing errors in the barcode and the lack of perfect agreement between complementary strands results in SSCSs not being paired to form DCS even where there is a “second tagged complementary strand” as recited in element 17(d). Ex. 1063, 2; Ex. 2013, 5–6; *see also* Ex. 1002 ¶ 355 (acknowledging that such errors “result in a sequencing read being erroneously assigned to the wrong barcode family”). Petitioner’s argument and the corresponding testimony of Petitioner’s declarants does not account for these issues. *See* Pet. 33–34, 44; Ex. 1002 ¶¶ 184–85, 237; Ex. 1098 ¶¶ 46–53.

The fact that Petitioner does not account for these issues undermines its argument that Schmitt necessarily teaches element 17(d) because “after sorting the paired reads, all that remains is *unpaired reads*.” Reply. 11. The institution decision identified sequencing errors in the SMI as one shortcoming in Petitioner’s showing for claim 17. Dec. 35–36. Petitioner’s Reply does not dispute this point. *See* Reply 10–12. Instead, Petitioner and

its declarant, Dr. Satija, offer the following diagram analogizing Schmitt's sorting of reads to identify partner pairs to the sorting of red and green marbles representing paired and unpaired reads. *Id.* at 11–12 (citing Ex. 1098 ¶ 50).



According to Petitioner, the diagram above shows that “if one were to take a jar of red and green marbles [as shown on the far left] and only remove the red marbles [representing paired reads] to another jar, one would have sorted the marbles into a jar (family) of red marbles and a jar (family) of green marbles [representing unpaired reads]” as shown by the set of jars on the far right. *Id.* at 11.

The problem with Petitioner’s marble analogy, and the related testimony of Dr. Satija, is that it ignores those instances where reads having a complementary strand (i.e., paired reads as recited in element 17(d) and claim 29) cannot be matched with their partner because of, e.g., a sequencing error in the SMI. Because of these and other instances where there is not perfect agreement between the strands in Schmitt’s DCS method, it seems that at least some red marbles (paired reads) will remain mixed

together with the green marbles (unpaired reads).¹⁴ For this reason, Dr. Satija’s testimony on this point is unpersuasive. *See* Ex. 1098 ¶¶ 46–53. Thus, Petitioner has not shown that it is *necessarily* the case that Schmitt’s DCS method will result in families of unpaired reads as recited in element 17(d) and claim 29. *See Par Pharma., Inc. v. TWI Pharms, Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (stating in an obviousness analysis, “the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art”).

Finally, Petitioner asserts that “Figure 5 of the Schmitt PCT [Exhibit 1009] demonstrates that raw sequence reads passing a quality threshold are available to be aligned to a reference genome” and therefore “a POSA would have known that the unpaired reads in Schmitt’s methods *are not lost* in the process of pairing sequence reads.” Reply 12 (citing Ex. 1009, Figs. 5A-B; Ex. 1098 ¶¶ 51–53). This is an inappropriate new argument. The Petition does not refer to Figure 5 of Exhibit 1009, nor is it clear how Petitioner’s reliance on such is responsive to any argument in the Response. Thus, this argument has been waived. However, even if we were to consider it on its merits, Petitioner’s new argument is unpersuasive because the mere fact that unpaired reads “are available to be aligned” and “are not lost” does not show sorting of such reads into families as recited in element 17(d).

For these reasons, Petitioner has not shown by a preponderance of the evidence that the asserted combination of Narayan and Schmitt teaches or suggests element 17(d). Thus, Petitioner has not met its burden for claim 17.

¹⁴ In this sense, the more apt comparison is the set of jars in the middle of Petitioner’s diagram—where the jar on the top continues to be a mixture of red and green marbles even though some red marbles have been moved to the bottom jar.

For the same reasons, Petitioner has not met its burden for claims 18–27, which depend directly or indirectly from claim 17.

Petitioner’s showing for claim 29 is similarly deficient. 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 that can be identified (e.g., because there is no sequencing error in the SMI) and are in complete agreement are ultimately used to generate Schmitt’s duplex consensus sequences, Petitioner has not shown by a preponderance of the evidence 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. Thus, Petitioner has not met its burden for claim 29 both for this reason and the deficiency explained above for element 1(b).

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.¹⁵ 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

¹⁵ For ease of reference, we refer to these limitations collectively as the “tagging efficiency limitations.”

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.

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 POSA would have been motivated to optimize adapter-DNA ligation for high efficiency using 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,¹⁶ which teaches "15–40% of input DNA is typically recovered as adapter-ligated

¹⁶ KAPA Technical Data Sheet for KAPA HTP Library Preparation Kit. Ex. 1015 ("KAPA data sheet").

molecules.” *Id.* (quoting Ex. 1015, 4). Petitioner also cites Fisher¹⁷ 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).

At the institution stage, we found Petitioner’s showing unpersuasive. *See* Dec. 39–41. We noted that Petitioner had not sufficiently explained why a POSA would have expected Meyer’s tagging efficiency to apply to Schmitt’s DCS method, particularly in light of evidence suggesting that tagging efficiency depends on the quality of the input DNA. *Id.* at 40–41. We also noted that Petitioner had not sufficiently shown that tagging efficiency was understood to be a result effective variable. *Id.* at 41.

Patent Owner refers to these preliminary findings in its Response, urging that Petitioner has not met its burden for claims 4 and 6 for these reasons in addition to its arguments for claim 1. *See* Resp. 61.

In reply, Petitioner urges the evidence showing lower tagging efficiency for lower quality DNA relates to “chemically damaged DNA[]—far different from cfDNA isolated from fresh blood cells.” Reply 25–26

¹⁷ 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”).

(citing Ex. 1015, 2, 4; Ex. 1098 ¶¶ 96–98). Petitioner further asserts that it was “well-known . . . that significant quantities of cfDNA could be isolated from blood samples.” *Id.* at 26 (citing Ex. 1002 ¶¶ 64–80).

Having considered these arguments on the full trial record, we find Petitioner’s showing for the tagging efficiency limitations unpersuasive. 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, 35, 38, *with* Pet. 58–61. Thus, for the reasons stated in the decisions denying institution in those proceedings, we similarly 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.

Petitioner's argument that a "POSA would have expected Schmitt's sticky-end adapter-DNA ligation to be even more efficient than Meyer's blunt-end adapter-DNA ligation" is also unpersuasive. *See* Pet. 60–61. 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.

Moreover, the record shows that tagging efficiency depends on a variety of other factors, including the quality of the input DNA. 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's argument that the DNA the KAPA data sheet refers to as "lower quality" is "from *formalin-fixed, paraffin-embedded* ('FFPE') samples (well known for having chemically damaged DNA)" is unavailing. *See* Reply 25–26 (citing Ex. 1098 ¶¶ 96–98). First, neither Petitioner, nor its declarant, address the similar teaching in Fisher. Second, even if the specific type of lower quality DNA in the KAPA data sheet is different, the salient point, i.e., that tagging efficiency depends on DNA quality, remains unrebutted. This is significant because Petitioner does not sufficiently 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. Petitioner's assertion that "significant quantities of cfDNA could be isolated from blood samples" (*see* Reply 26),

does not overcome this shortcoming. Even if we credit that assertion, the fact that a significant quantity of cfDNA could be obtained does not show that the quality of that DNA is similar such that a POSA using such would have expected to achieve a tagging efficiency similar to that in Meyer.

Finally, Petitioner has not shown “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, as we preliminarily found at the institution stage, 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. Dec. 41 (citing Ex. 1015, 4; Ex. 1031, 6). As explained above, Petitioner’s Reply does not sufficiently address these issues, much less demonstrate that a POSA would have understood that the tagging efficiency recited in claims 4 and 6 could be achieved by increasing the adapter concentration through routine optimization.

For these reasons, Petitioner has not shown by a preponderance of the evidence that the tagging efficiency limitations would have been obvious over the asserted combination of Narayan, Schmitt, and Myer. In addition, claims 4 and 6 depend from claim 1 and Petitioner’s Ground 2 relies on the same showing for element 1(b) in Ground 1. *See* Pet. 60 (incorporating “[t]he rationales for obviousness of claims 1 and 5”). As explained above,

that showing is deficient. Thus, Petitioner has not met its burden to show that claims 4 and 6 are unpatentable.

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 Petitioner’s Ground 3 relies on the same showing for element 1(b) in Ground 1. *See* Pet. 62 (incorporating “[t]he rationales for obviousness of claim 1). That is, Petitioner’s contentions regarding element 1(b) do not rely on any teaching in Craig.

As explained above, Petitioner’s showing for element 1(b) based on Narayan and Schmitt is deficient. Thus, Petitioner has not shown by a preponderance of the evidence that claims 8 is unpatentable.

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. Claims 15 and 16 depend from claim 1 and Petitioner’s Ground 4 relies on the same showing for element 1(b) in Ground 1. *See generally* Pet. 63–69. Claim 28 depends from claim 17 and Petitioner’s Ground 4 relies on the same showing for element 17(d) as in Ground 1. *Id.* That is, Petitioner does not rely on any teaching in Kivioja for its contentions regarding elements 1(b) and 17(d). *Id.*

As explained above, Petitioner’s showing for elements 1(b) and 17(d) based on Narayan and Schmitt is deficient. Thus, Petitioner has not shown by a preponderance of the evidence that claims 15, 16, and 28 are unpatentable.

IV. PATENT OWNER’S MOTION TO STRIKE

Patent Owner moves to strike the declarations of Dr. Satija (Ex. 1098) and Dr. Rajkovic (Ex. 1099). MTS 9. According to Patent Owner, Petitioner

“improperly attempt[s] to replace its original expert, Dr. Spellman” with testimony from these “replacement witnesses to backfill identified deficiencies” in the Petition and offer “perfunctory testimony . . . often conflicting with earlier deposition testimony” from Dr. Spellman. *Id.* at 1–3. Patent Owner further contends that Petitioner relies on their testimony to introduce new theories in the Reply, including a “new ‘developmental research testing’ motivation” for combining Narayan and Schmitt and new claim constructions. *See id.* at 4–8.

Patent Owner also moves to strike Exhibits 1093–1095 and 1102–1105, which it characterizes as “newly introduced exhibits that are primarily attempts to backfill content missing from the petition case, irrelevant . . . and/or not properly responsive to argument made in the” Response. *Id.* at 8–9. For these reasons, Patent Owner contends all of these exhibits “should be stricken or given no weight.” *Id.* at 9.

Petitioner opposes Patent Owner’s motion, urging that “neither the Reply nor Reply evidence raise[s] new theories for proving Petitioner’s prima facie case,” but rather are “directly responsive to arguments in the” Response. MTS Opp. 1. Petitioner explains it “encountered scheduling hurdles with Dr. Spellman during Petitioner’s reply period.” *Id.* According to Petitioner, “neither Dr. Satija nor Dr. Rajkovic ‘replaced’ Dr. Spellman,” but rather “provide rebuttal opinions directly responding to arguments raised in the Quackenbush and Hagemann declarations.” *Id.* at 2. Petitioner further contends that its Reply materials do not raise new theories, but are properly responsive to issues raised in the Reply and institution decision. *See* 3–10. Finally, Petitioner argues that Patent Owner is not prejudiced because it has been able to cross-examine Drs. Satija and Rajkovic and brief these issues in the Sur-Reply. *Id.* at 10.

Having considered the parties' arguments, Patent Owner's motion to strike is denied. We accept Petitioner's explanation that there were scheduling difficulties arising from Dr. Spellman's acceptance of a new position at an out-of-state academic institution that prevented his submission of declaration with the Reply. *See* MTS Opp. 1. Patent Owner's arguments that testimony offered by Drs. Satija and Rajkovic is "perfunctory" or conflicts with admissions in Dr. Spellman's earlier deposition testimony, at most, relate to the weight that testimony should be afforded, not its admissibility. Therefore, those arguments are not a sufficient basis for striking these declarations from the record.

Patent Owner's assertion that the Satija and Rajkovic Declarations, and other Reply materials, improperly introduce new theories requiring that those declarations and materials be stricken from the record is unpersuasive. *See* MTS 4–9. "In most cases, the Board is capable of identifying new issue or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belated presented evidence that exceeds the proper scope of reply." Consolidated Trial Practice Guide, Nov. 2019, 80 ("TPG").¹⁸ Accordingly, "striking the entirety or a portion of a party's brief," or in this case the entirety of both of Petitioner's Reply declarations and a number of related exhibits, is an "exceptional remedy." *Id.* Patent Owner has not shown that such a remedy is warranted on the circumstances of this case. We have identified those issues pertaining to our analysis that exceed the proper scope of reply and addressed them accordingly in our analysis of the merits above. We have also considered the

¹⁸ available at <https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf>

credibility of Drs. Satija and Rajkovic's testimony within the context of the record as a whole and afforded it appropriate weight in our analysis.

Accordingly, Patent Owner's motion to strike is denied.

V. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude four categories of exhibits, which it characterizes as follows: (1) "exhibits related to other proceedings" (Exhibits 1069, 1074, 1078, 1079, and 1085–1088); (2) "uncited exhibits" (Exhibits 1010, 1013, 1016, 1017, 1029, 1030, 1035–1037, 1042–1045, 1058, 1061, 1062, 1065, 1068, 1070, 1072, 1075–1077, 1080, 1081, and 1104); (3) "exhibits in support of untimely reply arguments" (Exhibits 1093–1095, 1102, 1103, and 1105); and (4) "replacement expert declarations" (Exhibits 1098 and 1099). *See* MTE 1–4. Petitioner opposes Patent Owner's motion. *See* MTE Opp. 1–15. We address each category below.

A. *Exhibits 1069, 1074, 1078, 1079, and 1085–1088*

Patent Owner objects to these exhibits under Federal Rules of Evidence (FRE) 106, 401, 402, and 403, asserting they should be excluded because they are "briefing and evidence filed in other cases and court statistics" and "cannot be used to prove any fact relevant to resolution of this case." MTE 1.

Petitioner explains that these exhibits pertain to particular issues in the Petition, i.e., "discuss[ion] of discretionary denial under 35 U.S.C. § 314(a)" and "Patent Owner's previous arguments regarding objective indicia," and therefore meet the threshold for relevancy. MTE Opp. 1–4.

We do not rely on any of these exhibits in rendering our decision on Petitioner's grounds. Therefore, we dismiss as moot Petitioner's motion to exclude Exhibits 1069, 1074, 1078, 1079, and 1085–1088.

B. Exhibits 1010, 1013, 1016, 1017, 1029, 1030, 1035–1037, 1042–1045, 1058, 1061, 1062, 1065, 1068, 1070, 1072, 1075–1077, 1080, 1081, and 1104

Patent Owner objects to these exhibits under FRE 401, 402, and 403, asserting they should be excluded because they “were not cited in the petition or in any other briefing.” MTE 2.

Petitioner explains that these exhibits were cited by Dr. Spellman and Dr. Satija in their declarations and properly identified in the exhibit lists included with Petitioner’s briefing. *See* MTE Opp. 5–6. According to Petitioner, while Petitioner “does not rely on these exhibits to meet claim elements or to prove its *prima facie* case,” they are relevant to “the background knowledge of a POSA” and “general knowledge in the art.” *Id.* at 5–6.

Patent Owner’s argument that these exhibits should be excluded is unpersuasive. Here, Dr. Spellman and Dr. Satija rely on the identified exhibits in their declarations. As such, they are relevant to understanding the weight to be given the declarants’ testimony. Accordingly, we deny Petitioner’s motion to exclude Exhibits 1010, 1013, 1016, 1017, 1029, 1030, 1035–1037, 1042–1045, 1058, 1061, 1062, 1065, 1068, 1070, 1072, 1075–1077, 1080, 1081, and 1104.

C. Exhibits 1093–1095, 1102, 1103, and 1105

Patent Owner objects to these exhibits under FRE 401, 402, and 403, asserting they should be excluded because they are cited in support of untimely arguments in the Reply. MTE 3. More particularly, Patent Owner argues these exhibits could have been presented with the Petition and that Petitioner improperly relies on them to try to “fill[] a gap in the *prima facie* case that Patent Owner identified in its response to the petition.” *Id.* at 3–4.

Petitioner asserts that “Patent Owner’s argument regarding the scope of reply evidence is improper in a motion to exclude.” MTE Opp. 8. In addition, Petitioner’s motion fails on its merits because these exhibits properly respond to arguments raised by Patent Owner and its declarants in the Response. *See id.* at 9–10.

We agree with Petitioner. As explained above, we deny Patent Owner’s motion to strike these exhibits and the related testimony of Drs. Satija and Rajkovic. The motion to exclude reraises the same arguments we have already found unpersuasive for the motion to strike. Accordingly, Patent Owner’s motion to exclude exhibits 1093–1095, 1102, 1103, and 1105 is denied.

D. Exhibits 1098 and 1099

Patent Owner objects to these exhibits under FRE 401, 402, 403, 701, 702, and 703, asserting that the declarations of Drs. Satija and Rajkovic “should be excluded as based on legally erroneous claim constructions, representing the testimony of improper replacement witnesses, and as non-responsive under [37 C.F.R. §] 42.23.” MTE 4–8. Patent Owner also asserts that Dr. Satija’s declaration is “not ‘the product of reliable principles’ and methods ‘reliably applied’ to the facts of this case” because it “is predicated on erroneous legal standards for claim construction.” *Id.* at 5.

Petitioner argues that “the majority of Patent Owner’s Motion to Exclude is a re-briefing of its Motion to Strike” and should be rejected for the same reasons. MTE Opp. 13. Petitioner further asserts that Dr. Satija did not rely on an erroneous legal standard, but rather “[i]n responding to Dr. Quackenbush’s opinions, Dr. Satija interpreted the claim terms based on their plain and ordinary meaning *in light of the specification* just as *Phillips*

[*v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc)] instructs.” *Id.* at 12 (citing Ex. 1098 ¶¶ 24–37).

We agree with Petitioner that Patent Owner has not presented a sufficient basis for excluding the declarations of Drs. Satija and Rajkovic. As an initial matter, we agree that Patent Owner’s motion to exclude largely reraises the same arguments in the motion to strike. Those arguments are unpersuasive for the reasons explained above.

Patent Owner’s argument that Dr. Satija’s testimony should be excluded under FRE 702 because he applied legally erroneous claim constructions is also unpersuasive. Dr. Satija offers testimony regarding his understanding of how the cited prior art relates to the challenged claims. *See, e.g.*, Ex. 1098 ¶¶ 24–45. While some of that testimony is unpersuasive, particularly as it relates to Petitioner’s arguments that we have addressed and rejected in our analysis above, Patent Owner’s arguments for exclusion go to the weight that should be accorded that testimony, not its admissibility. *See* PTAB Consolidated Trial Practice Guide (Nov. 2019) 79 (“A motion to exclude must explain why the evidence is not admissible (e.g., relevance or hearsay) but may not be used to challenge the sufficiency of the evidence to prove a particular fact.”). As it relates to our findings and analysis above, we have afforded appropriate weight to the testimony of Drs. Satija and Rajkovic in view of the record as a whole.

Accordingly, Patent Owner’s motion to exclude Exhibits 1098 and 1099 is denied.

VI. CONCLUSION

Petitioner has not shown by a preponderance of the evidence that any of claims 1–29 of the ’306 patent are unpatentable. Moreover, Patent Owner’s motions to strike and exclude are denied.

Claims	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–3, 5, 7, 9–14, 17– 27, 29	103	Narayan, Schmitt		1–3, 5, 7, 9– 14, 17–27, 29
4, 6	103	Narayan, Schmitt, Meyer		4, 6
8	103	Narayan, Schmitt, Craig		8
15, 16, 28	103	Narayan, Schmitt, Kivioja		15, 16, 28
Overall Outcome				1–29

VII. ORDER

Accordingly, it is:

ORDERED that Petitioner has not shown that claims 1–29 of U.S. Patent 11,149,306 B2 are unpatentable;

FURTHER ORDERED that Patent Owner’s Motion to Strike (Paper 29) is denied;

FURTHER ORDERED that Patent Owner’s Motion to Exclude (Paper 32) is denied; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2022-01400
Patent 11,149,306 B2

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