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Paper 11
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWINSTRAND BIOSCIENCES, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

IPR2022-01152
Patent 11,118,221 B2

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

VALEK, *Administrative Patent Judge*.

DECISION
Denying 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 1–30 of U.S. Patent No. 11,118,221 B2 (Ex. 1001, "the '221 patent"). Paper 2 ("Pet."). Guardant Health, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 9) and Patent Owner filed a Sur-reply to the Reply (Paper 10).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the argument and evidence presented by the parties, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we decline to institute an *inter partes* review of any claim of the '221 patent on any ground.

A. Related Proceedings

The parties state that the '221 patent has been asserted in *TwinStrand Biosciences, Inc. et al. v. Guardant Health*, *Inc.*, 1-21-cv-01126 (D. Del.). Pet 70; Paper 3, 1. The parties state that the '221 patent is also the subject of *Illumina, Inc. v. Guardant Health, Inc.; Helmy Eltoukhy; and Amirali Talasaz*, 22-cv-00334 (D. Del.) (March 17, 2022). *Id.*

The parties identify the following IPRs involving patents related to the '221 patent: IPR2022-00746, IPR2022-01115, IPR2022-00747, IPR22-01116. Pet. 70; Paper 3, 2. Patent Owner additionally identifies IPR2022-

00449, IPR2022-00450, IPR2022-00816, IPR2022-00817, and IPR2022-00935 as related matters. Paper 3, 1–2.

B. The '221 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 '221 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 '221 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 '221 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 '221 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 '221 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 1–30 of the '221 patent. Claims 1 and 18 are the only independent claims. These claims are reproduced below:

> 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 of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein duplex tags from the set of duplex tags are attached at both ends of a molecule of the plurality of the cfDNA molecules;
>
> (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 in the set of sequence reads using at least sequence information from the molecular barcodes to generate a plurality of consensus sequences representative of original cfDNA molecules from among the tagged parent polynucleotides, wherein the plurality of consensus sequences is generated from (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand

derived from a cfDNA molecule from among the tagged parent polynucleotides, and (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from a cfDNA molecule from among the tagged parent polynucleotides.

18. A method, comprising:

(a) providing a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) non-uniquely tagging a plurality of the doublestranded cfDNA molecules of the population with a set of duplex tags comprising molecular barcodes from a set of molecular barcodes to produce non-uniquely tagged parent polynucleotides,

wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of the double-stranded cfDNA molecules that map to the mappable base position;

(c) amplifying a plurality of the non-uniquely 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;

(e) reducing or tracking redundancy in the set of sequence reads using at least sequence information from the molecular barcodes;

(f) sorting the set of sequence reads into paired reads and unpaired reads, wherein (i) a paired read corresponds to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides, and (ii) an unpaired read corresponds to sequence reads generated from a first tagged strand having no second tagged complementary strand

derived from a double-stranded cfDNA molecule from among the non-uniquely tagged parent polynucleotides; and

(g) determining, at one or more loci of a reference sequence, quantitative measures of at least two of (i) the paired reads, (ii) the unpaired reads, (iii) read depth of the paired reads, and (iv) read depth of the unpaired reads.

Ex. 1001, 61:9–38 (claim 1), 62:50–63:21 (claim 18).

D. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

Claims Challenged	35 U.S.C. §[1]	References/Basis
1–4, 6, 7, 9–15, 18–22, 24–28	103	Narayan[2] and Schmitt[3]
5	103	Narayan, Schmitt, and Meyer[4]
8, 23	103	Narayan, Schmitt, and Craig[5]

[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 '221 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 '221 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").

Claims Challenged	35 U.S.C. §[1]	References/Basis
16, 17, 29, 30	103	Narayan, Schmitt, and Kivioja[6]

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

II. ANALYSIS

A. 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. 19 (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))).

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

B. 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) (2021). 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).

Regarding the phrase "a number of double-stranded cfDNA molecules that map to the mappable base position" in claims 6 and 18, Petitioner contends a "POSA would understand that the number of double-stranded cfDNA molecules that map to the mappable base position will vary, depending on the number of haploid genome equivalents (HGEs) in the sample" and generally be equal to the amount of HGEs. Pet. 20, (citing Ex. 1002 ¶¶ 133–136). Patent Owner does not dispute Petitioner's understanding, but contends no construction is necessary at this stage. *See* Prelim. Resp. 30

We agree with Patent Owner that it is unnecessary to expressly construe any claim terms 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))).

C. Obviousness over Narayan and Schmitt

Petitioner asserts that claims 1–4, 6, 7, 9–15, 18–22, and 24–28 are unpatentable as obvious over Narayan and Schmitt. Pet. 27–61. Patent Owner opposes Petitioner's assertions. Prelim. Resp. 30–56. On this record,

we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the challenged claims are unpatentable as obvious over the cited references.

1. Legal Standard

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of 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).

2. Cited References

a) Narayan

Narayan is a journal article entitled "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 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.*

b) 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 provisional application 61/625,623 ("Schmitt-623" (Ex. 1083)). Pet. 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.[8]

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

[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

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 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

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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.

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 αβ or βα 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. Analysis of Claims 1–17

Claims 2–17 depend from claim 1, which is representative for purposes of our analysis of these claims. Below we focus on the Petition's showing for claim element 1(e) and, in particular, that element's requirement

that "a plurality of consensus sequences representative of original cfDNA molecules" be generated "wherein the plurality of consensus sequences is generated from (i) paired reads . . . and (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand." Ex. 1001, 61:24–38. As explained below, after reviewing the arguments and evidence presented, we determine that Petitioner has not met its burden with respect to element 1(e).

Petitioner contends that claim 1 is rendered obvious by the application of Schmitt's DCS method to the cfDNA taught in Narayan. *See* Pet. 33. Petitioner argues that "Schmitt alone" discloses all of the steps of claim 1 and "a POSA would have had several reasons to combine Narayan's cfDNA with Schmitt's DCS." *Id.* 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 33–34 (citing Ex. 1002 ¶¶ 182–186). 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 (internal quotations omitted).

Regarding element 1(e), the Petition relies solely on the teachings in Schmitt. *See* Pet. 31–33. According to Petitioner, Schmitt discloses tracking and reducing redundancy in sequence reads because it teaches grouping "members of the same PCR family . . . by virtue of having a common (i.e., the same) SMI tag sequence" and "generating a plurality of consensus sequences from the families ('collapsing') into [sic] 'single strand consensus sequences (SSCSs).'" *Id.* at 31–32 (quoting Ex. 1083 ¶¶ 60, 63). The Petition relies on 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 generated consensus sequences from sequence reads of a first tagged strand having no second tagged complementary strand – i.e., unpaired reads, as recited in claim 1(e)(ii). For example, Schmitt discusses the number of unpaired reads (more than 99%) in one of its working examples.

Id. at 33 (citing Ex. 1002 ¶¶ 180–81; Ex. 1083 ¶ 68).

Patent Owner argues that Schmitt does not disclose generating a plurality of consensus sequences representative of original cfDNA molecules from unpaired reads because "DCS only generates consensus sequence for original molecules when the sequence information for ***both strands*** of the original duplex is in agreement." Prelim. Resp. 46–47 (citing Ex. 1083 ¶¶ 10, 13, 14, 60, 63, 68). According to Patent Owner, Schmitt's grouping of families of reads that share a common SMI tag "is agnostic to whether reads are paired or unpaired" and the passages the Petition relies on from the 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 47–50 (quoting Ex. 1083 ¶¶ 60, 68). Accordingly, Patent Owner urges that "[u]npaired reads are not discussed or contemplated in Schmitt, nor could they even be utilized to generate a duplex consensus sequence" and thus Schmitt "does not render obvious claims directed to using such reads to generate consensus sequences representative of original molecules." *Id.* at 51.

Patent Owner also disputes Petitioner's conclusion that "'Schmitt discusses the number of unpaired reads (more than 99%)'" in its working example. Prelim. Resp. 49 (quoting Pet. 33). According to Patent Owner, the fact "[t]hat fewer than 1% of tags could meet" the "stringent filtering step" taught in Schmitt "is not evidence that 99% of tags are inherently or necessarily 'unpaired' as that term is specifically used in claims 1–17." *Id.* In particular, Patent 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).

On the current record, we determine that Patent Owner has the better argument. 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 consensus sequences, Petitioner has 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).

The Petition frames Ground 1 as the combination of Schmitt's DCS with Narayan's cfDNA. *See* Pet. 33–36. It relies on Schmitt's "methods of error correction for NGS by generating duplex consensus sequences (i.e., reducing or tracking redundancy in sequence reads)" as Petitioner's alleged motivation for that combination. *Id.* at 33–34; *see also id.* at 37 (arguing that a POSA would have had a reasonable expectation of success because "the prior art expressly taught that DCS could enhance accuracy when sequencing cfDNA") (internal quotations omitted). According to Schmitt, the error correction and improved accuracy of DCS results from grouping reads into paired families in order to "capitalize[] on the redundant information stored in double-stranded DNA, thus overcoming technical limitations of prior methods utilizing data from only one of the two strands." Ex. 1083, 47 (Abstract); *see also id.* ¶¶ 7, 43. Thus, Petitioner's theory of unpatentability is inextricably tied to DSC's use of paired reads, as opposed to unpaired reads, to generate consensus sequences.

To the extent Petitioner contends that the collapsing of reads into SSCSs prior to the formation of Schmitt's double-stranded consensus sequences discloses the use of unpaired reads, such a theory is not sufficiently supported on the current record. The portions of Schmitt the Petition relies on for element 1(e) describe the use of paired families to generate a double-stranded consensus sequence. *See* Pet. 31–33 (citing Ex. 1083 ¶¶ 13, 60, 68, Fig. 3). For example, Petitioner points to the

"schematic of family groupings in Figure 3" of Schmitt. *See* Pet. 31–32. But according to 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). Figure 3 of Schmitt does not depict "unpaired reads . . . having no second tagged complementary strand" as recited in element 1(e), nor does it show any consensus sequence generated from such reads.

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 number 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. Pet. 33; *see also* Reply 2–3 (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 generation of consensus sequences from reads lacking a complementary strand. 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 1(e). But neither the Petition,

nor the testimony it cites from Dr. Spellman, provides sufficient explanation to support that assumption. *See* Pet. 33 (citing Ex. 1002 ¶¶ 180–81).

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, and thus the SSCS would not have been generated from "unpaired reads . . . having no second tagged complementary strand" as recited in element 1(e). This undermines Patent Owner'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 also result from sequencing errors in the SMI or barcode. *See* Prelim. Resp. 50 (Ex. 1063, 2; Ex. 2013, 5–6). Patent Owner relies on Stoler,[9] 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, Petitioner acknowledges that "sequencing errors in the barcode itself" were known to occur and "can result in a sequencing read being erroneously assigned to the wrong barcode family." Pet. 63–64. "Such sequencing errors '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'" *Id.* at 64

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

(quoting Ex. 1063, 2). 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 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." *See* Reply. 2–3.[10]

Accordingly, having considered the parties' respective arguments and evidence, we determine that Petitioner has not sufficiently shown that the cited references teach or suggest element 1(e). For this reason, Petitioner has not established a reasonable likelihood of prevailing on its assertion that independent claim 1, and therefore dependent claims 2–17 as well, would have been obvious over Narayan and Schmitt.

4. Analysis of Claims 18–30

Claims 19–30 depend from claim 18. Claim 18 is representative for purposes of our analysis of these claims. Herein, we focus on the Petition's showing for claim element 18(f) and, in particular, that element's requirement of "sorting the set of sequence reads into paired reads and unpaired reads, wherein . . . (ii) an unpaired read corresponds to sequence

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[10] 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. 3. But element 1(e) requires "consensus sequences *representative of original cfDNA molecules*" that are generated from "unpaired reads corresponding to sequence reads generated from a first tagged strand *having no second tagged complementary strand*." Ex. 1083, 61:26–28 (emphases added). We agree with Patent Owner that 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 2–3 (urging that "[e]rrors in the barcode may prevent pairing, but not describe an unpaired read *as claimed*").

reads generated from a first tagged strand having no second tagged complementary strand." Ex. 1001, 63:6–16. As explained below, after reviewing the arguments and evidence of record, we determine that Petitioner has not met its burden with respect to element 18(f).

Petitioner argues that "[c]laim 18(f) is similar to claim 1(e) in that they both entail identifying the sequence reads as either a paired read (i.e., one that has a complementary strand-mate) or an unpaired read (one that does not have a complementary strand-mate)." Pet. 43. Thus, Petitioner asserts that "Schmitt discloses claim 18(f) for the same reasons" it discloses element 1(f). *Id.* at 43–44. Moreover, Petitioner contends "a POSA would have known that Schmitt discloses 'sorting' the reads into paired and unpaired reads, as recited in claim 18(f), because Schmitt discloses generating duplex consensus sequence reads (paired reads), which requires 'sorting' the reads into paired reads and unpaired reads." *Id.* at 44. 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).

Patent Owner argues that Schmitt does not disclose element 18(f). *See* Prelim. Resp. 53–55. 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 54. Patent Owner argues that "Schmitt describes grouping as forming families of reads that share a common SMI tag" and this process is "agnostic to whether the reads are paired or unpaired." *Id.* (quotations omitted). Patent Owner also argues that "Schmitt describes generating duplex consensus sequences from consensus sequences **not** distinguishing between paired and unpaired sequence reads." *Id.*

On the current record, we determine that Patent Owner again has the better argument. The Petition points to two steps in Schmitt's DCS method for element 18(f): (1) the grouping of reads into families based on their SMI tag; and (2) the subsequent grouping of those families into paired families based on the orientation of their tag. *See* Pet. 45. 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 18(f). In the second of these steps, paired families comprising complementary sequences are formed. While this may result in the sorting of SSCSs into paired reads, Petitioner has not shown that it teaches or suggests that reads are also sorted into "unpaired reads" as recited in element 18(f). The figures and disclosures cited in the Petition merely show the grouping of families of reads with the same SMI into paired families.[11] They do not depict or describe reads that lack a complementary strand, i.e., much less the sorting of such reads.

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. 44. 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, there is no corollary disclosure suggesting the identification or sorting of reads that lack a complementary strand. Moreover, as explained above, while the results in Schmitt Example 1 note that some tags lacked a

[11] The Petition also cites paragraphs 231–236 of Dr. Spellman's Declaration. The testimony in these paragraphs is substantially the same as the argument in the Petition and cites the same figures and disclosure in Schmitt. *See* Ex. 1002 ¶¶ 231–236.

corresponding partner tag, that does not mean those tags necessarily correspond to "unpaired reads . . . having no second tagged complementary strand" as recited in element 18(f). *See supra* § C(3) (discussing evidence suggesting that sequencing errors in the barcode and imperfect agreement between strands result in reads comprising complementary strands that nonetheless do not form DCS partner pairs). Thus, even if Schmitt could be said to disclose sorting between reads with tags that have a corresponding partner tag and those that do not, Petitioner has not sufficiently shown that Schmitt teaches or suggests sorting between "paired reads" and "unpaired reads" as recited in element 18(f).

Accordingly, having considered the parties' respective arguments and evidence, we determine that Petitioner has not sufficiently shown that the cited references teach or suggest element 18(f). For this reason, Petitioner has not established a reasonable likelihood of prevailing on its assertion that independent claim 18, and therefore dependent claims 19–30, would have been obvious over Narayan and Schmitt.

D. Remaining Grounds

In Grounds 2–4, Petitioner asserts dependent claim 5 would have been obvious over Narayan, Schmitt, and Meyer, dependent claims 8 and 23 would have been obvious over Narayan, Schmitt, and Craig, and dependent claims 16, 17, 29, and 30 would have been obvious over Narayan, Schmitt, and Kivioja. Pet. 61–69. In Petitioner's analysis of the additional limitations recited in these dependent claims, the Petition cites Meyer's disclosure regarding ligating sequencing adapters to double-stranded DNA molecules (*id.* at 61–63), Craig's disclosure of 6-mer barcodes (*id.* at 63–65) and Kivioja's methods for calculating unseen molecules (*id.* at 67–69). However, for each of these grounds, the Petition relies on the same showing for

elements 1(e) and 18(f) as in Ground 1. *See* Pet. 61–19. Because Petitioner does not rely on Meyer, Craig, or Kivioja to teach or suggest elements 1(e) and 18(f) of the independent claims, we determine Petitioner has not shown a reasonable likelihood of prevailing on these grounds for the same reasons stated above for Ground 1.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established a reasonable likelihood of prevailing on its assertions that claims 1–30 of the '221 patent are unpatentable over the cited art.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all challenged claims of the '221 patent and no trial is instituted.

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