UNITED STATES PATENT AND TRADEMARK OFFICE
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BEFORE THE PATENT TRIAL AND APPEAL BOARD
_____

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.
_____

Case IPR2019-00652
Patent No. 9,834,822
_____

PATENT OWNER'S NOTICE OF APPEAL

Pursuant to 37 C.F.R. § 90.2(a) and 35 U.S.C. §§ 141(c), 142, and 319,

Guardant Health, Inc. ("Patent Owner") respectfully gives notice that it appeals to

the United States Court of Appeals for the Federal Circuit from the Patent Trial

and Appeal Board's Final Written Decision entered on August 18, 2020 (Paper 47),

and from all other underlying orders, decisions, rulings, and opinions. Foundation

Medicine, Inc. ("Petitioner") filed a Notice of Appeal on October 20, 2020.

For the limited purpose of providing the Director of the United States

Patent and Trademark Office with the information specified in 37 C.F.R.

§ 90.2(a)(3)(ii), the issues on appeal include the Board's determination that claims

1-11, 13, and 17-20 of U.S. Patent No 9,834,822 B2 were shown to be

unpatentable in view of the grounds of unpatentability on which trial was instituted

(Paper 12). The issues on appeal also include any finding or determination

supporting or related to these issues, as well as all other issues decided adversely to

Patent Owner in any order, decision, ruling, or opinion.

Simultaneous with this filing and in accordance with 37 C.F.R.

§ 90.2(a)(1), this Notice of Appeal is being filed with the Director and served on

Petitioner in accordance with 37 C.F.R. § 42.6(e). This Notice of Appeal, along

with the required fees, is also being filed with the Clerk's Office for the United

States Court of Appeals for the Federal Circuit in accordance with Fed. Cir. R.

15(a)(1).

Respectfully Submitted,

Dated: October 20, 2020

/ Michael T. Rosato /

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CERTIFICATES OF FILING AND SERVICE

I hereby certify that, in addition to being filed electronically through the Patent Trial and Appeal Board's End to End system, the foregoing Notice of Appeal was filed by Express Mail on this 20th day of October, 2020, with the Director of the United States Patent and Trademark Office, at the following address:

> Director of the U.S. Patent and Trademark Office
> c/o Office of the General Counsel
> P.O. Box 1450
> Alexandria, Virginia 22313-1450

I hereby certify that a true and correct copy of the foregoing Notice of Appeal was filed electronically by CM/ECF on this 20th day of October, 2020, with the Clerk's Office of the United States Court of Appeals for the Federal Circuit.

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served a true and correct copy of the foregoing Notice of Appeal on the Petitioner at the electronic service addresses of the Petitioner as follows:

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Dated: October 20, 2020   / Michael T. Rosato /
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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

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IPR2019-00652
Patent 9,834,822 B2

———————

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

SAWERT, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining Some Claims Unpatentable
Dismissing in Part and Denying in Part Petitioner's Motion to Exclude
Dismissing in Part and Denying in Part Patent Owner's Motion to Exclude
35 U.S.C. § 318(a)

I.   INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–13 and 17–20 ("the challenged claims") of U.S. Patent No. 9,834,822 B2 (Ex. 1001, "the '822 patent"). We have jurisdiction under 35 U.S.C. § 6 and enter this Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–11, 13, and 17–20 are unpatentable. We determine that Petitioner has not shown, by a preponderance of the evidence, that claim 12 is unpatentable. *See* 35 U.S.C. § 316(e) (2012).

A.   Procedural History

Foundation Medicine, Inc. ("Petitioner") filed a Petition for an *inter partes* review under 35 U.S.C. § 311. Paper 2 ("Pet."). Petitioner supported its Petition with the Declaration of Stacey Gabriel, Ph.D. Ex. 1002. Guardant Health, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6. On our authorization (Paper 9), Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 11).

On August 19, 2019, pursuant to 35 U.S.C. § 314(a), we instituted trial to determine whether any challenged claim of the '822 patent is unpatentable based on the grounds raised in the Petition:

IPR2019-00652
Patent 9,834,822 B2

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–13, 17–20	103(a)[1]	Schmitt,[2] Schmitt 2012,[3] and Fan[4] or Forshew[5]

Paper 12, 7, 36 ("Institution Decision" or "Inst. Dec.").

Patent Owner filed a Response. Paper 26 ("PO Resp."). Patent Owner supported its Response with the Declaration of Jay Shendure, M.D., Ph.D., Ex. 2023, and the Declaration of John Quackenbush, Ph.D., Ex. 2025. Petitioner filed a Reply to Patent Owner's Response. Paper 32 ("Pet. Reply"). Petitioner supported its Reply with a Reply Declaration of Dr. Gabriel. Ex. 1104. Patent Owner filed a Sur-Reply. Paper 34 ("PO Sur-Reply"). Patent Owner supported its Sur-Reply with a Supplemental Declaration of Dr. Quackenbush. Ex. 2042.

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[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the challenged claims have an effective filing date before this date, the pre-AIA version of § 103 applies.

[2] Michael Schmitt et al., U.S. Patent No. 9,752,188 B2, issued Sept. 5, 2017 (Ex. 1011, "Schmitt").

[3] Michael W. Schmitt et al., *Detection of Ultra-rare Mutations by Next-generation Sequencing*, 109(36) PROC. NATL. ACAD. SCI. 14508–513 (2012) (Ex. 1047, "Schmitt 2012").

[4] Christina Fan et al., *Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood*, 105(42) PROC. NATL. ACAD. SCI. 16266–271 (2008) (Ex. 1048, "Fan")

[5] Tim Forshew et al., *Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA*, 4(136) SCI. TRANSL. MED. 1–34 (2012) (Ex. 1004, "Forshew").

Petitioner and Patent Owner each filed respective Motions to Exclude Evidence. *See* Paper 38 ("Pet. Mot."); Paper 39 ("PO Mot."). Petitioner filed an Opposition to Patent Owner's Motion, Paper 40 ("Pet. Opp."), to which Patent Owner filed a Reply, Paper 42 ("PO Reply"). Patent Owner filed an Opposition to Petitioner's Motion, Paper 41 ("PO Opp."), to which Petitioner filed a Reply, Paper 43 ("Pet. Reply Opp.").

An oral hearing was held on May 13, 2020. A transcript of the hearing is included in the record. Paper 46 ("Tr.").

B. Real Parties in Interest

Petitioner identifies Foundation Medicine, Inc., Roche Holdings, Inc., Roche Finance Ltd., and Roche Holding Ltd. as the real parties-in-interest. Pet. 73. Patent Owner identifies Guardant Health, Inc., as the real party-in-interest. Paper 4, 2.

C. Related Matters

Patent Owner has asserted the '822 patent against Petitioner in *Guardant Health, Inc. v. Foundation Medicine, Inc.*, Case No. 17-cv-1616 (D. Del.) ("the co-pending litigation"). Pet. 74; Paper 4, 2. Patent Owner has also asserted the '822 patent against Personal Genome Diagnostics, Inc. ("PGDx") in *Guardant Health, Inc. v. Personal Genome Diagnostics, Inc.*, Case No. 17-cv-1623 (D. Del.). Pet. 74; Paper 4, 2.

Petitioner filed a second petition seeking *inter partes* review of the '822 patent, designated IPR2019-00653. Paper 4, 2. A Decision denying institution in that case was issued on August 19, 2019 (Paper 12), and a Decision denying Petitioner's request for rehearing issued on January 22, 2020 (Paper 14).

Petitioner also filed several petitions seeking *inter partes* review of patents related to the '822 patent, including: IPR2017-01170, IPR2017-

01447, and IPR2017-01448 (challenging U.S. Patent No. 9,340,830);

IPR2019-00130 (challenging U.S. Patent No. 9,598,731); IPR2019-00634

(challenging U.S. Patent No. 9,840,743); and IPR2019-00636 and IPR2019-

00637 (challenging U.S. Patent No. 9,902,992). Of these cases, only

IPR2019-00634 is pending.

PGDx also filed petitions seeking post-grant review of the '822

patent, designated PGR2018-00058, and of U.S. Patent No. 9,840,743,

designated PGR2018-00057. *Id.* at 2. Both petitions were dismissed before

a decision on institution.

D. *Summary of the '822 Patent*

The '822 patent relates to methods for detecting rare mutations and

copy number variations in cell free polynucleotides. Ex. 1001, code (57).

The '822 patent states that cell-free DNA ("cfDNA"), found in different

types of bodily fluids, may be used to detect and monitor disease. *Id.* at

1:29–45. For instance, cfDNA may contain genetic aberrations—like a

change in copy number variations and/or single or multiple sequence

variations associated with a particular disease—that can be used to detect or

monitor such disease. *Id*. at 1:29–41, 30:8–14. The '822 patent states that

"there is a need in the art for improved methods and systems for using cell

free DNA to detect and monitor disease." *Id.* at 1:41–45.

The '822 patent states that the disclosed methods generally "comprise

sample preparation, or the extraction and isolation of cell free polynucleotide

sequence[s] from a bodily fluid; subsequent sequencing of cell free

polynucleotides by techniques known in the art; and application of

bioinformatics tools to detect rare mutations and copy number variations as

compared to a reference." *Id*. at 30:4–14. The '822 patent states that

"[s]ample preparation typically involves converting polynucleotides in a

sample into a form compatible with the sequencing platform used." *Id.* at 32:58–61. "This conversion [c]an involve tagging polynucleotides" with "polynucleotide sequence[s]." *Id.* at 32:61–63. The '822 patent refers to these polynucleotide sequences as "identifiers." *Id.* at 38:3–6. The identifier may be a molecular barcode. *Id.* at 38:6–7.

The '822 patent explains that "the efficient conversion of individual polynucleotides in a sample of initial genetic material into sequence-ready tagged parent polynucleotides" is an important tool "for detecting with high sensitivity genetic variation in a sample of initial genetic material." *Id.* at 32:33–39. According to the '822 patent, efficient conversion "increase[s] the probability that individual polynucleotides in a sample of initial genetic material will be represented in a sequence-ready sample" and "can produce sequence information about more polynucleotides in the initial sample." *Id.* at 32:39–42.

The '822 patent states that the parent polynucleotides may be tagged with either unique or non-unique identifiers. *Id*. at 37:44–49; *see also id.* at 3:10–15 (stating that, in some embodiments, the barcodes are unique, but in other embodiments, the barcodes are not unique); *see also id.* at 6:26–28 (stating that, in some embodiments, "each tagged parent polynucleotide in the set is uniquely tagged," whereas in other embodiments, "the tags are non-unique"). In the case of non-uniquely tagged parent polynucleotides, the '822 patent explains that "the use of non[-]unique barcodes, in combination with sequence data at the beginning (start) and end (stop) portions of individual sequencing reads and sequencing read length may allow for the assignment of a unique identity to individual sequences." *Id.* at 37:43–48.

E. Illustrative Claim

Claim 1 is the only independent claim. Claims 2–13 and 17–20 depend directly from claim 1. *See* Ex. 1001, 62:51–64:22. Claim 1 is illustrative and reproduced below:

1. A method, comprising:

a) providing a population of cell-free DNA ("cfDNA") molecules obtained from a bodily sample from a subject;

b) converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a cfDNA molecule of the population of cfDNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes;

c) amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides;

d) sequencing the population of amplified progeny polynucleotides to produce a set of sequence reads;

e) mapping sequence reads of the set of sequence reads to one or more reference sequences from a human genome;

f) grouping the sequence reads into families, each of the families comprising sequence reads comprising the same identifier sequence and having the same start and stop positions, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;

g) at each genetic locus of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus;

> h) determining a frequency of one or more bases called at the
> locus from among the families.

Ex. 1001, 62:18–48.

II. PETITIONER'S MOTION TO EXCLUDE

Petitioner moves to exclude Exhibits 2002, 2032, 2036, 2037, 2038, 2039, 2040, and 2041 in their entirety and Exhibits 2023 and 2025 in whole or in part. Pet. Mot. 1.

We *dismiss as moot* Petitioner' Motion to Exclude as it relates to Exhibits 2002, 2032, 2036, 2037, 2038, 2039, 2040, and 2041, for the following reasons. *First*, we do not rely on or cite to Exhibits 2032, 2036, 2037, or 2038 in this Decision. *Second*, Patent Owner cites to Exhibits 2002, 2039, 2040, and 2041 as support for its arguments about reasonable expectation of success. To the extent we refer to these exhibits herein, we determine that the record as a whole supports Petitioner's position as to reasonable expectation of success. *Infra* § IV.E.2.b. *Third*, Exhibit 2023 is the Declaration of Dr. Shendure that is limited in scope to the applicability of Schmitt to cfDNA. Ex. 2023 ¶¶ 16–37. Again, to the extent we refer to Exhibit 2023, we determine that the record as a whole supports Petitioner's position as to motivation to combine the Schmitt references with Fan or Forshew and as to reasonable expectation of success. *Infra* § IV.E.2.a–b. Thus, as to Exhibits 2002, 2023, 2032, 2036, 2037, 2038, 2039, 2040, and 2041, on which we do not rely to support our decision, Petitioner's Motion to Exclude is *dismissed as moot*.

Exhibit 2025 is the Declaration of Dr. Quackenbush. Petitioner contends that Dr. Quackenbush's Declaration should be excluded under Federal Rules of Evidence 702, 703, 705, and 401–403. Pet. Mot. 5–7.

Specifically, Petitioner contends that we should exclude at least certain paragraphs of Dr. Quackenbush's Declaration because "they lack a disclosed basis of sufficient facts or data," "are not based on sufficient facts or data, the product of reliable principles and methods, and/or a reliable application of the principles and methods to the facts," and "are misleading, confusing, and/or needlessly cumulative." *Id.* at 5.

We have considered Petitioner's arguments but are not persuaded that Exhibit 2025 should be excluded in whole or in part. Patent Owner has shown, and Petitioner does not dispute, that Dr. Quackenbush is qualified to opine as to the perspective of an ordinarily skilled artisan at the time of the invention. PO. Opp. 5–93; *see also infra* § IV.B. As such, Dr. Quackenbush's testimony is highly relevant about how an ordinarily skilled artisan would have interpreted the prior-art references, as well as to the general knowledge in the field at the time the invention was made. Any deficiencies in Dr. Quackenbush's Declaration go to the weight that we should afford his testimony and do not support a motion to exclude. *See, e.g., Yorkey v. Diab*, 601 F.3d 1279, 1284 (Fed. Cir. 2010) (holding that the Board has discretion to give more weight to one item of evidence over another "unless no reasonable trier of fact could have done so"); *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) ("[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations."). Thus, as to Exhibit 2025, Petitioner's Motion is Exclude is *denied*.

III. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude Exhibits 1002, 1007, 1013, 1016–1020, 1022, 1036, 1037, 1055, 1080, 1082, 1084–1093, 1100, 1101, 1104,

1110, and 1111. PO Mot. 1. We do not rely on Exhibits 1007, 1013, 1016–1020, 1022, 1036, 1037, 1055, 1080, 1082, 1084–1093, 1100, 1110, or 1111 in this Decision. Thus, we *dismiss as moot* Patent Owner's Motion to Exclude as it relates to Exhibits 1007, 1013, 1016–1020, 1022, 1036, 1037, 1055, 1080, 1082, 1084–1093, 1100, 1110, and 1111.

Exhibits 1002 and 1104 are the first and second Declarations of Dr. Gabriel, respectively. PO Mot. 1–8. Patent Owner argues that Exhibit 1002 should be excluded in its entirety because the "entire declaration is premised on an impossible standard to be met by a person of ordinary skill in the art" and "Dr. Gabriel uses this impossible perspective to support a hindsight-based obviousness analysis." *Id.* at 1–3. We agree with Petitioner, however, that Patent Owner's arguments constitute a disagreement about a question of fact (i.e., the proper definition of an ordinarily skilled artisan), and "[a] motion to exclude is not the proper mechanism to direct [its] attention to differences in the evidence." Pet. Opp. 2 (quoting *Google Inc. v. Visual Real Estate, Inc.*, IPR2014-01339, Paper 39 at 37 (PTAB Jan. 25, 2016)). Moreover, we note that Dr. Gabriel applies in her Declarations the same definition of an ordinarily skilled artisan as that we adopted in our Institution Decision and reaffirm here. Inst. Dec. 7–8; *infra* § IV.B. Thus, we are not persuaded that we should exclude Dr. Gabriel's Declarations Exhibits 1002 and 1104 for this reason.

Patent Owner also argues that Dr. Gabriel's second Declaration (Exhibit 1104) should be excluded because it attempts to "fill[] a gap in [Petitioner's] *prima facie* case," relies on "new theories regarding the teachings of Schmitt," and "presents an entirely different theory of obviousness with respect to the 'non-uniquely tagged' limitation." PO Mot. 3–8. We are not persuaded, however, that Exhibits 1002 and 1104

should be excluded. "A motion to exclude is not a mechanism to argue that a reply contains new arguments or relies on evidence necessary to make out a prima facie case." *Vibrant Media, Inc. v. General Elec. Co.*, IPR2013-00170, Paper 56 at 31 (PTAB June 26, 2014). Thus, Patent Owner's arguments in this regard are improper.

In any event, Petitioner has shown, and Patent Owner does not dispute, that Dr. Gabriel is qualified to opine as to the perspective of an ordinarily skilled artisan at the time of the invention. Pet. Opp. 2–3; *see also infra* § IV.B. As with Dr. Quackenbush's testimony above, Dr. Gabriel's testimony is highly relevant about how an ordinarily skilled artisan would have interpreted the prior-art references, as well as to the general knowledge in the field at the time the invention was made. And any deficiencies in Dr. Gabriel's Declaration go to the weight that we should afford her testimony and do not support a motion to exclude.

For these reasons, as to Exhibits 1002 and 1104, Patent Owner's Motion to Exclude is *denied*.

IV. ANALYSIS

We have reviewed the parties' respective briefs as well as the relevant evidence discussed in those papers. For the reasons discussed in detail below, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–11, 13, and 17–20 of the '822 patent are unpatentable under 35 U.S.C. § 103 as having been obvious, but not that claim 12 would have been unpatentable as obvious.

A. *Principles of Law*

To prevail in its challenges to the patentability of all claims of the '822 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e) (2012); 37 C.F.R.

§ 42.1(d) (2018). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including the scope and content of the prior art, any differences between the claimed subject matter and the prior art, the level of ordinary skill in the art, and objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements." *Magnum Oil*, 829 F.3d at 1380. Moreover, a decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

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

B. *Level of Ordinary Skill in the Art*

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art and, thus, begin with the level of ordinary skill in the art. The level of ordinary skill in the art is "a prism or lens through which . . . the Board views the prior art and the claimed invention" to prevent hindsight bias. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Relying on the declaration testimony of its declarant, Dr. Gabriel, Petitioner contends that a person of ordinary skill in the art for the '822 patent "would have had a Ph.D. in genetics, molecular biology, bioinformatics or a related field, and at least five years of research in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics." Pet. 20 (citing Ex. 1002 ¶ 72). In response, Patent Owner does not appear to dispute the type of experience Petitioner proposes for the level of ordinary skill in the art. *See generally* PO Resp. We observe, however, that Patent Owner's declarants, Dr. Shendure and Dr. Quackenbush, contend that Petitioner's definition of an ordinarily skilled artisan relates more to an artisan with "extraordinary," rather than "ordinary," skill. *See* Ex. 2023 ¶ 15, Ex. 2025 ¶ 23.

In our Institution Decision, we preliminarily adopted Petitioner's proposed level of ordinary skill. Inst. Dec. 7–8. We also determined that the prior art itself was sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. Inst. Dec. 8. For this Decision, we maintain that the prior art demonstrates the appropriate level of ordinary skill in the art. *See Okajima*, 261 F.3d at 1355 (the prior art, itself, can reflect appropriate level of ordinary skill in art).

Nevertheless, for further clarity, we set forth the definition of an ordinarily skilled artisan as follows. As to level of education, because of the nature of the subject matter of the '822 patent, we agree with Petitioner that an ordinarily skilled artisan would have had a doctorate degree (Ph.D.) in genetics, molecular biology, bioinformatics, or a related field. Ex. 2023 ¶¶ 28–29; Ex. 1002 ¶ 25. We also agree with Petitioner that an ordinarily skilled artisan would have had five years' research experience in industry or academia, including at least two to three years of research experience in the field of cancer genomics.

We acknowledge Petitioner's contention that an ordinarily skilled artisan "would have had knowledge of DNA sequencing, including NGS [next-generation sequencing] and related sequencing methods, and related sample preparation techniques, bioinformatics methods for grouping and comparing sequence reads and mapping sequence reads onto genomes, and methods for identifying genetic variants in a sample." Pet. 20. But we conclude that these statements more aptly apply to the scope and content of the prior art under *Graham* and, thus, are best addressed in relation to Petitioner's asserted grounds of unpatentability based on obviousness.

Finally, we have considered the qualifications of Dr. Gabriel, Dr. Shendure, and Dr. Quackenbush and find that each is qualified to opine as to the perspective of an ordinarily skilled artisan at the time of the invention. *See* Ex. 1003 (Dr. Gabriel's *curriculum vitae*); Ex. 2024 (Dr. Shendure's *curriculum vitae*); Ex. 2026 (Dr. Quackenbush's *curriculum vitae*).

C. Claim Construction

The instant Petition was filed on February 2, 2019. Thus, the new rules amending the claim construction standard apply here because the

Petition was filed after the November 13, 2018, effective date of the amendment. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,358 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)). Accordingly, for this *inter partes* review, the Board applies the same claim construction standard as that applied in federal courts.

Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (stating that claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art in question at the time of the invention). Only terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).

1. Overview

At the close of trial, the only claim-construction dispute remaining in this proceeding concerns the meaning of "non-uniquely tagged" in the context of a population of parent polynucleotides, as recited in claim 1. *See* Ex. 1001, 62:22–24 (reciting "converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides"). Petitioner contends that "non-uniquely tagged" "means that the number of different identifiers attached to the polynucleotides is at least 2 and fewer than the number of polynucleotides." Pet. 21. Patent

Owner argues that "non-uniquely tagged" means "the number of different identifiers is at least 2 and fewer than the number of polynucleotides *that map to the mappable base position*."[6] PO Resp. 16.

As an initial matter, we acknowledge that, in our Institution Decision, we referred to "non-uniquely tagged" as both "the number of different identifiers attached to the polynucleotides is at least 2 and fewer than the number of polynucleotides" and "the number of different identifiers attached to the polynucleotides is at least 2 and fewer than the number of polynucleotides that map to the mappable base position." *Compare* Inst. Dec. 9 ("Petitioner contends that '[t]he term "non-uniquely tagged" means that the number of different identifiers attached to the polynucleotides is at least 2 and fewer than the number of polynucleotides.' We agree." (quoting Pet. 21)), *with id.* (stating, "In the context of 'non-unique' identifiers, the '822 patent follows the words 'non-uniquely tagged' with '*that is*, the number of different identifiers can be at least 2 and fewer than the number of polynucleotides that map to the mappable base position.'" (quoting Ex. 1001, 41:42–46)). As a result, both parties claim that the Board adopted their respective construction of "non-uniquely tagged." *See* PO Resp. 15–16 (stating that "[t]here is no dispute as to the express definition of 'non-uniquely tagged' in the '822 patent"); Pet. Reply 3 (stating that "[t]he Board should reject Patent Owner's arguments and reaffirm its construction, which is identical to the District Court's").

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[6] The Declarants for both parties agree that an ordinarily skilled artisan would understand that "mappable base position" means a position in the reference sequence to which polynucleotide molecules can be confidently mapped. *See* Ex. 2027 ¶ 67; Ex. 2022, 23:22–24:13, 30:4–18, 35:5–7; Ex. 2025 ¶ 65. We apply that understanding for this Decision.

To be clear, we have considered the totality of the arguments and evidence anew at the close of trial, as well as the reasoning set forth in our Institution Decision, and determine, for the reasons discussed below, that "non-uniquely tagged" should be construed to mean that "the number of different identifiers is at least 2 and fewer than the number of polynucleotides" in a sample, without the additional phrase "that map to a mappable position."

At the heart of the parties' dispute is the following passage from the '822 patent:

> Accordingly, this invention also provides compositions of tagged polynucleotides. The polynucleotides can comprise fragmented DNA, e.g. cfDNA. *A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be [] at least 2 and fewer than the number of polynucleotides that map to the mappable base position.*

Ex. 1001, 41:42–47 (emphasis added).

The parties agree that "non-uniquely tagged" means that "the number of different identifiers [i.e., the tag count[7]] can be at least 2 and fewer than the number of polynucleotides," but disagree whether the phrase "that map to the mappable base position" should be included in the construction of "non-uniquely tagged." Put differently, the parties agree that, to be "non-uniquely tagged," the *lower limit* for the tag count is two, but disagree on the *upper limit* for the tag count.

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[7] As relevant here, the '822 patent refers to the "number of unique identifiers" as the "tag count." Ex. 1001, 40:63. For clarity, we use these terms interchangeably in this Decision.

2. Patent Owner's Arguments

Patent Owner argues that the upper limit on the tag count is "fewer than the number of polynucleotides that map to the mappable base position." PO Resp. 15; *see also* PO Sur-Reply 6 (arguing that "the '822 patent expressly defines 'non-uniquely tagged' as limited by the number of polynucleotides that map to the mappable base position"). Relying on Dr. Quackenbush's Declaration, Patent Owner offers the following schematic distinguishing between (a) the total polynucleotide fragments in a sample, (b) the number of polynucleotides that map to a given mappable base position, and (c) cognates.[8] PO Resp. 13.
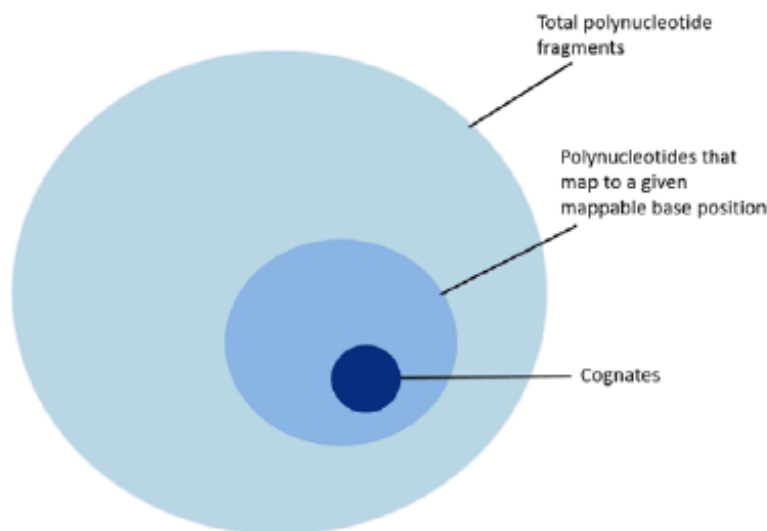
Schematic submitted by Patent Owner distinguishing between the polynucleotides in a sample. PO Resp. 13.

According to Patent Owner, the upper limit on the number of different identifiers does *not* depend on the total polynucleotide fragments in a sample (shown by the light blue circle). *Id.* at 14. Instead, the tag count "depends

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[8] The '822 patent defines "cognates" (or "duplicates") as "more than one polynucleotide from different genomes [that] have the same start and stop positions." Ex. 1001, 40:4–8.

. . . on a subpopulation of fragments that map to a given position in the reference genome" (shown by the medium blue circle) "and the expected number of cognates" (shown by the dark blue circle). *Id.* (citing Ex. 1001, 41:6–13). Patent Owner argues that the '822 patent expressly defines "non-uniquely tagged" as limited by the number of polynucleotides that map to the mappable base position, and that any argument otherwise "strains credulity." PO Sur-Reply 5–6; *see also* PO Reply 15.

3. *Petitioner's Arguments*

Petitioner contends that the upper limit on the number of different identifiers is "fewer than the number of polynucleotides" in a sample. Pet. 21. Specifically, Petitioner contends that, when "fewer barcodes than original DNA fragments" are used, "not every fragment has a unique barcode," and thus the population of polynucleotides are "non-uniquely tagged." *Id.* at 11–12. As an example, Petitioner contends that "if there are 1000 DNA fragments and only 500 different barcodes, [then] each fragment does not have its own unique barcode," and thus the population of polynucleotides is "non-uniquely tagged" in the context of claim 1. *Id.* at 12 (citing Ex. 1002 ¶ 51). Conversely, "if there are 1000 original DNA fragments and at least 1000 different barcodes, [then] each fragment will have its own unique barcode." *Id.* at 11 (citing Ex. 1002 ¶ 50). Petitioner contends that we should not include "that map to the mappable base position" in the construction of "non-uniquely tagged" because that phrase represents "a single embodiment" of the '822 patent and because that construction "is inconsistent" with Patent Owner's arguments in District Court about the meaning of "non-uniquely tagged." Pet. Reply 3–10.

4. *Analysis*

We begin with the words of claim 1. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1301 (Fed. Cir. 2006) ("claim construction must begin with the words of the claims themselves"). The first step of claim 1 recites "providing *a population* of cell free DNA ('cfDNA') molecules," and the second step recites "converting *the population* of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides." Ex. 1001, 62:19–24 (emphases added). We observe that nothing in the plain language of claim 1 requires the population of cfDNA molecules that undergoes tagging (i.e., the population that is converted into a population of "non-uniquely tagged parent polynucleotides") to be limited to a population where each polynucleotide maps to a mappable base position. Instead, claim 1 recites that *the* population (i.e., not necessarily the mappable population) is converted into non-uniquely tagged parent polynucleotides. *Id.* For these reasons, we determine that the words of claim 1 do not support Patent Owner's argument that the tag count is limited by the number of polynucleotides that map to a mappable base position.

We now turn to the intrinsic record. Starting with the passage reproduced above that we identified as the heart of the parties' dispute (Ex. 1001, 41:42–47), we acknowledge that the use of "that is" (or "i.e.") typically "signals an intent to define the word to which it refers." *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1334 (Fed. Cir. 2009). Here, however, we agree with Petitioner that the use of "non-uniquely tagged" in this passage of the written description refers to a specific embodiment of the '822 patient—that is, an embodiment where *the set* of polynucleotides map to a mappable base position. *See* Pet. 4–5. The '822 patent describes various "sets" of polynucleotides and states that, "[*i*]*n some embodiments*

each polynucleotide in a set is mappable to a reference sequence." Ex. 1001, 6:1–2 (emphasis added). The '822 patent also states that, "*[i]n some embodiments*, each set of parent polynucleotides is mappable to a position in a reference sequence, and the polynucleotides in each set are not uniquely tagged." *Id.* at 18:39–42 (emphasis added). That each polynucleotide in a set is mappable *in some embodiments* necessarily implies that, in other embodiments, not every polynucleotide is mappable. Moreover, that each parent polynucleotide is mappable and non-uniquely tagged *in some embodiments* suggests that mappability and non-unique tagging are not necessarily concomitant. *See WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1323–24 (Fed. Cir. 2018) ("It is well established that claims are not limited to preferred embodiments, unless the specification clearly indicates otherwise.").

Next, we determine that other portions of the '822 patent do not support Patent Owner's argument that the upper limit of the tag count depends on the number of polynucleotides that map to a mappable base position. PO Resp. 13–14. The '822 patent explains that, when polynucleotides have a tag count equal to 1 ("equivalent to having no unique tags or not tagging"), "it may not be possible to determine which sequence reads are derived from which parent molecules." *Id.* at 40:34–61. The '822 patent further explains that "[t]his problem can be diminished by tagging parent molecules with a sufficient number of unique identifiers." *Id.* at 40:61–63. According to the '822 patent, the methods of the prior art "uniquely tag[ged] every, or nearly every, different parent molecule in the sample." *Id.* at 40:67–41:2. But, these prior art methods were "cumbersome and expensive," because they required "billions of different unique identifiers." *Id.* at 41:2–6.

The '822 patent explains that "[t]his invention" solves the problem of distinguishing polynucleotides by tagging a population of DNA "with n different unique identifiers, wherein n is at least 2 and no more than 100,000*z, wherein z is a measure of the central tendency (e.g., mean, median, mode) of an expected number of duplicate molecules having the same start and stop positions" (i.e., cognates). *Id.* at 41:6–13. The '822 patent describes embodiments where the lower limit of the tag count is between 2*z to 20*z, and other embodiments where the upper limit of the tag count is between 100*z to 100,000*z. *Id.* at 41:13–18.[9] The '822 patent then expressly states that "n can range from any combination of these upper and lower limits." *Id.* at 41:18–19.

Thus, the '822 patent clearly teaches the ordinarily skilled artisan that the number of different identifiers—that is, the tag count "n"—is based on the number of expected cognates in a sample ("z"), which in turn "is a function of the number of haploid genome equivalents in a sample and the distribution of fragment sizes." Ex. 1001, 40:8–11; 41:6–39; *see also* PO Resp. 12 ("The inventor of the '822 patent determined empirically that the number of cognates in a sample is proportional to the size distribution of the polynucleotide fragments and the number of genomic equivalents—that is, the number of haploid genome copies present in the sample.").

Patent Owner does not persuasively point us to any teaching in this description—which Dr. Quackenbush admits describes a "non-uniquely

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[9] The '822 patent's reference to "1000,000*z" at column 41, line 17, appears to be a typographical error. *See* Ex. 2001 (Patent Owner's claim-construction brief quoting the same passage from the '822 patent as "2 and no more than 100,000*z"). For this Decision, we read that term as "100,000*z."

tagged" embodiment of the '822 patent—that instead correlates the upper limit of the tag count to a *subpopulation* of polynucleotides in a sample that map to a mappable base position. *See* Ex. 2025 ¶ 58 (citing Ex. 1001, 41:6–13); Ex. 1103, 36:18–21, 37:7–11, 14–16.[10] Rather, according to the '822 patent—in an embodiment described as "[t]his invention"—the tag count can encompass up to 100,000*z different identifiers. Ex. 1001, 41:6–13. The '822 patent also teaches that, "in a sample of about 10,000 haploid genome equivalents of human DNA, there are about 3 duplicate polynucleotides beginning at any given position." *Id.* at 40:24–27, 41:10–13. Thus, for a sample comprising 10,000 haploid copies of polynucleotides, z=3, the sample can be tagged with up to 100,000*3 (300,000) identifiers and still be considered "non-uniquely tagged." *Id.* at 41:6–13. This number of unique identifiers (300,000) is far greater than the number of polynucleotides that would map to a given mappable base position (10,000) in a sample of 10,000 haploid genome equivalents under Patent Owner's construction. *See* PO Resp. 17–19 (arguing that for "for non-uniquely tagged," a single copy of the genome would produce 1 polynucleotide that maps to a mappable base position, and five haploid genome equivalents would produce 5 polynucleotides that map to a mappable base position).

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[10] Indeed, claim 12 contrasts the expected number of duplicate molecules with the population of polynucleotides *in the sample*. *See* Ex. 1001, 63:15–19 (Claim 12, reciting "The method of claim 1, wherein *the population of polynucleotides* is tagged with n different unique identifiers, wherein n is no more than 100*z, wherein z is a mean of an expected number of duplicate molecules having the same start and stop positions *in the sample*." (emphases added)).

Patent Owner appears to acknowledge that this embodiment would be outside the scope of claim 1, but nevertheless argues that this "is of no moment" because it "is not required to claim all that it discloses." PO Sur-Reply 6–7. Even so, we find that Patent Owner has not provided an adequately persuasive reason, based on either the claim language or the '822 patent, for doing so here. *See SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1378–79 (Fed. Cir. 2013) ("A claim construction that excludes the preferred embodiment is rarely, if ever, correct and would require highly persuasive evidentiary support." (quotation marks and citation omitted)); *see also In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1324 (Fed. Cir. 2011) ("there is a strong presumption against a claim construction that excludes a disclosed embodiment").

Turning to the extrinsic evidence, we note that Patent Owner argued in its Opening Brief on Claim Construction to the District Court in the co-pending litigation that, as to the construction of "non-uniquely tagged," "[t]he dispute between the parties is whether the number of 'non-unique' barcodes can approach the total number of polynucleotides." Ex. 2001, 7. This accords with the dispute between the parties in this proceeding as well. But before the District Court, unlike here, Patent Owner argued that "the total number of barcodes must plainly be less than the *total number of polynucleotides*." *Id.* at 9 (emphasis added). Patent Owner also argued that "in describing the embodiments that use 'non-unique' barcoding, the specification explains that they use between '2 and no more than 100,000*z' barcodes 'wherein z is a measure of central tendency (e.g., mean, median, mode) of an expected number of duplicate molecules.'" *Id.* at 8 (quoting Ex. 1001, 41:10–13). Thus, unlike here, Patent Owner did not rely on the

"number of polynucleotides that map to the mappable base position" as setting forth the upper limit for the number of different identifiers. *Id.*

Patent Owner argues that its previous statements to the District Court were made simply to distinguish the claims over the prior art at issue in the co-pending litigation and are not inconsistent with its construction of "non-uniquely tagged" here. PO Sur-Reply 6. We disagree. In its claim-construction brief, Patent Owner criticized the opposing parties' proposed constructions as "uniformly at odds with the *intrinsic* record," Ex. 2001, 1 (emphasis added), and argued that its own construction of "non-uniquely tagged" was most consistent with the specification and the plain meaning of "non-uniquely tagged," *id.* at 7–9. Although we do not consider Patent Owner's arguments in the co-pending litigation dispositive, we find that they nonetheless further support our construction of "non-uniquely tagged" here.

For all the above reasons, we determine that "non-uniquely tagged" means that "the number of different identifiers can be at least 2 and fewer than the number of polynucleotides" in a sample. Thus, a population of parent polynucleotides is "non-uniquely tagged" in the context of claim 1 when the number of different identifiers (the tag count) is at least 2 but fewer than the number of parent polynucleotides in the sample.

D. *Asserted References*

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. *Schmitt (Ex. 1011)*

Schmitt relates to a method for sequencing target DNA fragments called Duplex Consensus Sequencing ("DCS"). Ex. 1011, code (57). According to Schmitt, the DCS method greatly reduces sequencing errors by independently tagging and sequencing each of the two strands of a target

DNA fragment. *Id.* Because the two strands of DNA are complementary, true mutations can be found at the same position on both strands, as opposed to on a single strand if PCR or sequencing errors occur. *Id.*

Schmitt's DCS methods utilize "a single molecule identifier (SMI) adaptor molecule for use in sequencing a double-stranded target nucleic acid molecule." Ex. 1011, 2:66–3:1. Schmitt teaches that the SMI adaptor molecule comprises an SMI sequence or "tag" (which is a degenerate or semi-degenerate n-mer sequence[11]) and an SMI ligation adaptor (which allows the SMI adaptor molecule to be ligated to the target DNA fragment). *Id.* at 3:1–9; *see also id.* at 5:57–59 (providing that the "SMI adaptor molecule is double stranded, and may include a single molecule identifier (SMI) sequence, and an SMI ligation adaptor"); *id.* at 6:46–47 (referring to the SMI sequence as a "tag"). The DCS method includes the steps of:

> ligating a double-stranded target nucleic acid molecule to at least one SMI adaptor molecule to form a double-stranded SMI-target nucleic acid complex; amplifying the double-stranded SMI-target nucleic acid complex, resulting in a set of amplified SMI-target nucleic acid products; and sequencing the amplified SMI-target nucleic acid products.

Id. at 3:12–20.

In one embodiment, the SMI sequence is "a unique, double-stranded, complementary n-mer random tag," such that every DNA fragment becomes labeled with two distinct SMI sequences. *Id.* at 3:47–53. In this embodiment, the "nucleotide n-mer sequences may be any suitable length to produce a sufficiently large number of unique tags to label a set of sheared

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[11] It is well known in the art that an "n-mer" is a short sequence comprising "n" number of nucleotides. For example, a "4-mer" polynucleotide is a short sequence of four nucleotides in a DNA sequence.

DNA fragments from a segment of DNA." *Id.* at 6:59–63. Schmitt provides

as an example a "nucleotide n-mer sequence which is 12 nucleotides in

length" that, once ligated to each end of the target DNA fragment, "results in

the generation of up to 4^{24} (i.e., 2.8×10^{14}) distinct tag sequences." *Id.* at

6:66–7:5.

In another embodiment, referred to as the "hybrid method," the SMI

sequence comprises "a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more

degenerate or semi-degenerate bases)." *Id.* at 9:9–13. In this embodiment,

the SMI adaptor molecules "serve as unique molecular identifiers" by

combining information from the sheared ends of the target DNA fragment

and the short n-mer tag. *Id.*

Schmitt teaches that, for error correction through DCS, sequence

reads sharing a unique set of SMI tags are grouped into paired families, each

pair reflecting one double-stranded DNA fragment. *Id.* at 4:4–10.

Mutations present in only one or a few family members, or mutations

occurring in only one of the two strands, represent sequencing mistakes or

PCR-introduced errors. *Id.* at 4:10–18. True mutations are present on both

strands and appear in all members of a family pair. *Id.* at 4:18–20.

2. *Schmitt 2012 (Ex. 1047)*

Schmitt 2012 also relates to the DCS method and uses the same

library-preparation techniques and sequencing methods disclosed in Schmitt.

Ex. 1047, Abstract, 14509 (Fig. 1). Schmitt 2012 discloses a "data

processing" workflow comprising the steps of filtering sequence reads,

aligning reads to a reference genome, grouping reads containing identical tag

sequences to form single-strand consensus sequence reads ("SSCS"), re-

aligning reads to the reference genome, and identifying and comparing

partner strands among SSCS reads compared to form DCS reads. *Id.* at
14513, SI1–SI2; *see also* Ex. 1002 ¶ 91.

3. *Fan (Ex. 1048)*

Fan relates to a method for diagnosing fetal aneuploidy by directly
sequencing cfDNA from the plasma of pregnant women with high-
throughput shotgun sequencing technology. Ex. 1048, Abstract. In doing
so, Fan was able to measure the over- and under-representation of
chromosomes from an aneuploidy fetus. *Id.*

4. *Forshew (Ex. 1004)*

Forshew relates to a method for identifying cancer mutations present
in cfDNA using tagged-amplicon deep sequencing ("TAm-Seq"). Ex. 1004,
Abstract. Tagged-amplicon deep sequencing allows amplification and deep
sequencing of genomic regions spanning thousands of bases. *Id.* at 1.
Forshew applied the technique to both abundant and rare mutations in
circulating DNA from blood plasma of ovarian and breast cancer patients.
Id. at 1–2.

E. *Obviousness over Schmitt in View of Schmitt 2012, and Further in View of Fan or Forshew*

Petitioner contends that claims 1–13 and 17–20 of the '822 patent are
unpatentable as obvious over Schmitt, Schmitt 2012, and Fan or Forshew.
Pet. 30–70. Patent Owner opposes. PO Resp. 19–62; PO Sur-Reply 3–26.
Having considered the totality of the arguments and evidence, we find that
Petitioner has shown by a preponderance of the evidence that claims 1–11,
13, and 17–20 are unpatentable as having been obvious over Schmitt,
Schmitt 2012, and Fan or Forshew, but has not shown that claim 12 would
have been obvious.

1.   Limitations of the challenged claims

Petitioner contends that the combination of Schmitt, Schmitt 2012, and Fan or Forshew discloses or suggests each element of the challenged claims. Petitioner presents arguments mapping the language of claims 1–13 and 17–20 to the disclosures of each reference. Pet. 41–71.

a.   *Independent Claim 1*

Step (a) of claim 1 recites "providing a population of cell-free DNA ('cfDNA') molecules obtained from a bodily sample from a subject." Ex. 1001, 62:19–21. We agree with Petitioner that Fan and Forshew teach this limitation. Pet. 41–42. Fan describes extracting cfDNA from the plasma of pregnant women to detect fetal aneuploidy. *See* Ex. 1048, 16266 ("We directly sequenced cell-free DNA with high-throughput shotgun sequencing technology form plasma of pregnant women . . . ."), 16270 (stating that "DNA was extracted from cell-free plasma"). Specifically, Fan extracted between 1.2 and 8 ng of cfDNA from plasma samples ranging from 1.3 to 3.2 ml. *Id.* at SI7 (Table S1); *see also* Ex. 1002 ¶ 122. Similarly, Forshew describes extracting cfDNA from plasma samples to identify mutations in cancer patients. *See* Ex. 1004, 1 (stating that "[p]lasma of cancer patients contains cell-free tumor DNA"), 10 (stating that "[c]irculating DNA was extracted from between 0.85 and 2.2 ml of plasma"). As shown in Table S6, Forshew obtained amounts ranging from 0.9 to 19.7 ng of cfDNA from plasma samples of cancer patients. *Id.* at 32 (Table S6); *see also* Ex. 1002 ¶ 23.

Turning to step (b) of claim 1, the first portion of this step recites "converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides." Ex. 1001, 62:22–24. We agree with Petitioner that Schmitt in combination with Fan or Forshew teaches this

limitation. Pet. 42–46. Schmitt teaches that, in the DCS method, SMI adaptor molecules comprising an "SMI sequence (or 'tag') of nucleotides" and an SMI ligation adaptor are ligated to the ends of target DNA polynucleotides. *See* Ex. 1011, 3:1–9, 5:57–59, 6:46–51. Schmitt refers to the SMI sequences as a "nucleotide n-mer" sequence. *Id.* at 6:46–66.

   As explained above, we construe "non-uniquely tagged" to mean that the number of different identifiers attached to the parent polynucleotides is at least 2 but fewer than the number of polynucleotides in the sample. *Supra* § IV.C.4. Schmitt discloses a DCS "hybrid method" tagging target DNA polynucleotides that uses "a combination of sheared ends 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. 1011, 9:9–11 (emphasis added); *see also* Pet. 43–46; Ex. 1002 ¶¶ 126–127. Schmitt also expressly discloses examples of 4-mer tags. *See* Ex. 1011, 4:30–54; *id.* at 9:9–13. Dr. Gabriel testifies without rebuttal that using a 4-mer tag yields 4^4, or 256, different tag sequences—which when ligated at both ends of a parent polynucleotide—yields 256^2, or 65,536 different or "unique" identifiers. *See* Ex. 1002 ¶ 127 & n.7; Pet. 44–45; *see also* Ex. 2025 ¶ 69 (testimony of Dr. Quackenbush as to "[t]he 65,536 possible unique tags from a 4-mer sequence"); PO Resp. 18 (accord).

   We agree with Petitioner that the use of n-mer tags in the hybrid DCS method results in a population of "non-uniquely tagged parent polynucleotides," because the n-mer tags are not "unique" for each parent polynucleotide. That is, the number of different n-mer tags is fewer than the number of polynucleotides in the sample because Schmitt explicitly distinguishes the hybrid method from embodiments in which every polynucleotide in the sample is tagged with a unique SMI identifier. *See* Ex. 1011, 9:1–4 (stating that the DCS method "does *not strictly require the*

use of an SMI tag, as the sheared ends can be used as identifiers to differentiate unique individuals molecules from PCR duplicates" (emphasis added)); *see also id.* at 6:59–63 (stating that, in the main embodiment, the "nucleotide n-mer sequences may be any suitable length to produce a sufficiently large number of unique tags to label a set of sheared DNA fragments from a segment of DNA"). Finally, although Schmitt does not expressly teach that the target polynucleotide is cfDNA, both Fan and Forshew teach the extraction and analysis of cfDNA as described immediately above.

The second portion of step (b) provides that "each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a cfDNA molecule of the population of cfDNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes." Ex. 1001, 62:24–28. We again agree with Petitioner that Schmitt teaches this limitation. Pet. 45. Schmitt describes embodiments (a–c) in Figure 3, in which sequence reads are derived from parent polynucleotides comprising both a "strand identifier" and a sequence derived from the parent DNA molecule. Ex. 1011, 4:4–54; *see also* Ex. 1002 ¶ 129.

Turning to the remaining limitations of claim 1, we agree with Petitioner's contentions and supporting evidence about steps (c) through (h) of the claimed method. *See* Pet. 47–56. In particular, we agree with Petitioner's contentions that Schmitt, either alone or in combination with Schmitt 2012, discloses:

- amplifying the tagged polynucleotides and sequencing the amplified progeny (steps (c) and (d) of claim 1), *see* Pet. 47; Ex. 1011, 3:10–20 (disclosing "amplifying the double-stranded SMI-target nucleic acid complex, resulting in a set of amplified SMI-target nucleic acid

products; and sequencing the amplified SMI-target nucleic acid products"); *see also id.* at 21:55–57; Ex. 1002 ¶¶ 132–133;

- mapping the sequence reads to a reference sequence (step (e) of claim 1), *see* Pet. 47–49; Ex. 1011, 20:39–64 (teaching aligning sequence reads "to the human genome with the Burrows Wheeler Aligner (BWA)"); *id.* at 23:10–14, 24:33–37; Ex. 1047, SI1 ("Reads were then aligned to the reference genome with the Burrows Wheeler aligner (BWA) and nonmapping reads were discarded. . . . Reads sharing identical tag sequences were then grouped together and collapsed to consensus reads."); *see also* Ex. 1002 ¶¶ 134–137, 139;

- grouping the sequence reads into families (step (f) of claim1), *see* Pet. 40–51; Ex. 1011, 4:9–10, 9:9–14, 17:61–18:2, 20:39–64, 21:55–61; *see also* Ex. 1002 ¶¶ 140–144;

- collapsing sequence reads in each family to yield a "base call" (step (g) of claim 1), *see* Pet. 51–55; Ex. 1011, 4:20–29, 4:55–66, 18:44–61, 20:50–56; 22:50–53, 23:19–22, 23:61–24:1, 25:20–30, Figures 3 and 5C; *see also* Ex. 1002 ¶¶ 145–152; and

- determining the frequency of bases called at the locus from among the families (step (h) of claim 1), *see* Pet. 55–56; Ex. 1011, 4:25–29, Figure 3; *see also* Ex. 1002 ¶¶ 154–155.

  b. *Analysis of Patent Owner's Arguments*

We are not persuaded by Patent Owner's arguments that the combination of Schmitt, Schmitt 2012, and Fan or Forshew fails to teach or suggest all the limitations of claim 1. PO Resp. 19–56; PO Sur-Reply 3–26. Patent Owner first argues that Schmitt fails to disclose "non-uniquely tagged parent polynucleotides" as this phrase should be correctly construed, and that the Petition fails because Petitioner never applied the correct

construction of "non-uniquely tagged" to the prior art in the Petition.
PO Resp. 20–23; PO Sur-Reply 3–4. But, as explained in detail above, we
do not read "non-uniquely tagged" as limiting the tag count to a
subpopulation of polynucleotides that map to a mappable base position.
Supra § IV.C.4. Thus, we disagree with Patent Owner that Petitioner failed
to apply the correct construction of "non-uniquely tagged parent
polynucleotides" in its Petition.

Patent Owner's next argument, that "Petitioner's contrived scenario
does not support its assertion that Schmitt teaches non-uniquely tagged
parent polynucleotides," PO Resp. 23–27, also relies on its unduly narrow
construction of "non-uniquely tagged parent polynucleotides." In this
regard, Patent Owner argues that "Schmitt is silent regarding a sub-
population of fragments in a sample that map to a given mappable base
position," *id.* at 20–21, and that an ordinarily skilled artisan would not have
been able to determine the number of polynucleotides that map to a
mappable base position from Schmitt's disclosure, *id.* at 23 (citing Ex. 2025
¶ 72). But, again, we do not read "non-uniquely tagged parent
polynucleotides" as limiting the tag count to a subpopulation of
polynucleotides that map to a mappable base position. *Supra* § IV.C.4.
Patent Owner's argument therefore fails, and its follow-on arguments about
Dr. Quackenbush's testimony and Dr. Gabriel's cross-examination
testimony as to the tagging and sequencing of one haploid human genome
equivalent, *see* PO Resp. 24–26, are irrelevant.[12]

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[12] Similarly, Patent Owner's argument that "Schmitt does not disclose
sequencing targets as large as the entire 3 billion base pair haploid human
genome," PO Resp. 26, is unpersuasive because nothing in claim 1 limits the
size of the sequencing target. *See* Ex. 1001, 62:18–48; *see also In re Hiniker*

We also disagree with Patent Owner's argument that Schmitt fails to disclose "non-uniquely tagged parent polynucleotides." PO Resp. 27–33 (arguing that "Schmitt exclusively teaches unique tagging methods"). As explained above, *supra* § IV.D.1., Schmitt discloses methods for sequencing target parent polynucleotides that utilize SMI sequences as tags. Ex. 1011, 2:66–3:1. In the main embodiment, the SMI sequence is "a *unique*, double-stranded, complementary n-mer random tag," and every target polynucleotide is labeled with two distinct SMI sequences. *Id.* at 3:47–53 (emphasis added). In this embodiment, Schmitt teaches that the "nucleotide n-mer sequences may be any suitable length to produce a sufficiently large number of unique tags to label a set of sheared DNA fragments from a segment of DNA." *Id.* at 6:59–63. Schmitt provides as an example a "nucleotide n-mer sequence which is 12 nucleotides in length," that, once ligated to each end of the target DNA fragment, "results in the generation of up to 4^{24} (i.e., 2.8×10^{14}) distinct tag sequences." *Id.* at 6:66–7:5. There is no dispute that this embodiment of Schmitt is directed to a *unique* tagging method because the number of SMI tags exceeds the number of parent polynucleotides in the sample. *See* Ex. 1002 ¶ 126 (testimony of Dr. Gabriel that "[i]n some embodiments, Schmitt describes the use of a large number of *unique* barcode sequences such that there is a high probability that a different barcode sequence is ligated to each parental DNA template").

But, contrary to Patent Owner's arguments otherwise, Schmitt also teaches an alternative "hybrid" method that we conclude results in the generation of "non-uniquely tagged parent polynucleotides" as claimed.

Co., 150 F.3d 1362, 1369 (Fed. Cir. 1998) ("the name of the game is the claim").

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Specifically, Schmitt teaches that the DCS method "does not strictly require the use of an SMI tag" because the sheared ends of the target parent DNA polynucleotides "can be used as identifiers to differentiate unique individual molecules from PCR duplicates." Ex. 1011, 9:1–4. Schmitt acknowledges, however, that "there are a limited number of shear points flanking any given genomic position and thus the power to sequence deeply is increased via inclusion of the SMI tag." *Id.* at 9:6–9. Schmitt thus proposes a solution that utilizes both the sequence information from the sheared ends and an n-mer: the "hybrid" method. *Id.* at 9:9–13. Specifically, Schmitt teaches that the hybrid method uses "a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases)" in combination with the sheared ends of the target DNA fragment to "serve as unique molecular identifiers." *Id.*

We find credible, and supported by preponderant record evidence, Dr. Gabriel's testimony that the *combination* of the sheared ends and a *non-unique* short n-mer tag results in a "*unique* molecular identifier[]." Ex. 1002 ¶ 126 (emphasis added); *see also* Ex. 1011, 9:1–13. Specifically, we are persuaded by Dr. Gabriel's testimony that the short n-mer tag used in Schmitt's hybrid method is itself *not unique* for each parent polynucleotide in the sample. Ex. 1002 ¶ 127. Schmitt expressly teaches that the "shorter n-mer tag" may comprise 4 or fewer nucleotide bases. Ex. 1011, 9:10–12. From this disclosure—as Dr. Gabriel persuasively testifies and we agree— an ordinarily skilled artisan would have readily recognized that a 4-mer, for example, yields 4^4, or 256, different tag sequences, which when ligated at both ends of a parent polynucleotide, would yield 256^2, or 65,536 different or "unique" identifiers. Ex. 1002 ¶ 127 & n.7; *see also* Pet. 44–45. Indeed, Dr. Quackenbush acknowledges that "65,536 possible unique tags [result] from a 4-mer tag sequence." Ex. 2025 ¶ 69.

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An ordinarily skilled artisan would have readily recognized that this number of unique identifiers is far less than the millions or more parent polynucleotides that would result from Schmitt's size selection for DNA fragments in the range of 200 to 500 base pairs. Ex. 1002 ¶ 127 (citing Ex. 1011, 22:43–46 (stating that "DNA for sequencing was sheared and end-repaired by standard methods, with size-selection for fragments in the range of ~200–500 bp by size-selecting binding")). Thus, as Dr. Gabriel testifies and we agree, more than one parent polynucleotide would necessarily share the same short n-mer tag in Schmitt's hybrid method, because the number of unique identifiers (i.e., a tag count of 65,536) is at least 2 but fewer than the number of parent polynucleotide fragments in the sample (i.e., millions or more), as we have construed "non-uniquely tagged parent polynucleotides." *Id.*

Patent Owner argues that Petitioner was wrong to "assume a combination of more fragments in a sample (i.e., millions of fragments) than SMI tags (i.e., 65,536 tags) in order to conclude that the number of fragments is greater than the number of tags." PO Resp. 28. In this regard, Patent Owner argues that "Schmitt discloses applying DCS to much smaller targets—'ranging from ~300 bp to ~20 kb in size'" and that shearing those targets into 200 bp fragments would result in, at most, between 1 and 100 fragments, "far fewer fragments than 'millions of fragments'" Petitioner asserts would be in a sample. *Id.* at 29 (citing Ex. 1011, 19:65–66, 24:7–11, Ex. 2025 ¶ 85). Although we have carefully considered Patent Owner's argument, we find that it lacks evidentiary support in the disclosure of Schmitt and, therefore, is not persuasive.

Schmitt clearly discloses shearing 3 micrograms of DNA into fragments, ligating the SMI adaptor molecules to 750 ng of T-tailed DNA,

and amplifying (by PCR) 375 ng of the resulting adaptor-ligated (or tagged) DNA. Ex. 1011, 19:58–20:23. Then, for sequence analysis, Schmitt discloses that "an arbitrary 758 kb region of the genome consisting of both coding and noncoding sequences" was "targeted" and "capture[d]" using capture baits. *Id.* at 20:27–30. The much smaller fragments to which Patent Owner refers—i.e., DNA molecules ranging from ~300 bp to ~20 kb in size—represent DNA targets that would have been similarly captured for the purpose of sequence analysis *after* the process of shearing and tagging. *See id.* at 20:16–30 (describing the process of pre-capture amplification and DNA capture); 24:7–9 (describing the ~300 bp to ~20 kb DNA molecules as "vastly smaller *target* DNA molecules" (emphasis added)); Ex. 1104 ¶ 18 (explaining that "Schmitt discloses tagging DNA fragments *before* target capture, not after"). An ordinarily skilled artisan would have understood from Schmitt's disclosure, then, that these ~300 bp to ~20 kb DNA molecules would not have been subjected to shearing and ligation reactions, because those molecules would have been already tagged with the SMI sequence identifiers. Ex. 1104 ¶ 18. For these reasons, Patent Owner's argument (and Dr. Quackenbush's corresponding testimony) about the number of polynucleotide fragments that would result from *further shearing* of 300 bp to ~20 kb DNA molecules reflects a misreading of Schmitt's disclosure and is not persuasive. *See* Ex. 2025 ¶ 85 (Dr. Quackenbush's testimony "[a]ssuming" shearing of Schmitt's ~300 bp to ~20 kb DNA targets).

Moreover, we find that an ordinarily skilled artisan would have understood that the total number of polynucleotides in Schmitt's sample of T-tailed DNA would have far exceeded the 65,536 possible unique tags resulting from a 4-mer sequence, and thus reads on a "a population of non-

uniquely tagged parent polynucleotides." Dr. Quackenbush admits that, for "a sample comprised of five haploid copies of the human nuclear genome that are fragmented into 200 base pair polynucleotides," "[t]he entire sample comprises about *75 million* polynucleotide fragments," which is much more than "[t]he 65,536 possible unique tags from a 4-mer tag sequence." Ex. 2025 ¶ 69 (emphasis added). There can be no dispute that, if a sample of five haploid copies of DNA produces about 75 million polynucleotide fragments, then a sample of 750 ng T-tailed DNA in Schmitt would represent a much greater amount of polynucleotide fragments. Pet. Reply 11–12; Pet. 66; Ex. 1104 ¶ 19 (stating that a sample of 20 ng of DNA contains approximately 6,060 haploid genome equivalents, correlating to billions of polynucleotide fragments); Ex. 1001, 40:15–19 (stating that a sample of 30 ng of DNA contains approximately 10,000 haploid genome equivalents, while a sample of 100 ng of DNA contains approximately 30,000 haploid genome equivalents).

Patent Owner argues that the DCS method is different from the claimed subject matter in the '822 patent because "[t]he method of Schmitt expressly requires flooding a sample with 'SMI tags' or 'n-mers' to ensure that every DNA fragment in the sample is uniquely labeled." PO Resp. 5; *see also, e.g., id.* at 29–30 (arguing that "where Schmitt does relate the number of barcodes to polynucleotide fragments in a sample it instructs that the barcodes should be in excess of the sample fragments" (citing Ex. 1011, 3:47–53, 6:59–62; Ex. 2025 ¶ 86)). Although we agree with Patent Owner that the disclosure of Schmitt is directed, in the main, to the use of an excess number of *unique* SMI sequences for tagging, Schmitt's "hybrid" method utilizes shorter *non-unique* n-mer SMI sequences that produce, in substance, a population of "non-uniquely tagged" DNA fragments. *See* Pet. 44–45; *see*

also Ex. 1002 ¶¶ 126–127. Patent Owner's argument that "[l]imiting n-mer tags as suggested in the petition materials would be contrary to the express instruction of Schmitt," PO Resp. 31, is unpersuasive because it ignores Schmitt's express disclosure and examples of 4-mer tags. *See* Ex. 1011, 4:30–54; *id.* at 9:9–13. Figure 4a of Schmitt, reproduced below, "illustrates an example of how a SMI sequence with n-mers of 4 nucleotides in length (4-mers) are read by Duplex Consensus Sequencing." *Id.* at 4:30–32.

A

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5'     1-TAAC----------------------TCCG-2     3'   (top strand)
3'     2-ATTG----------------------AGGC-1     5'   (bottom strand)
```
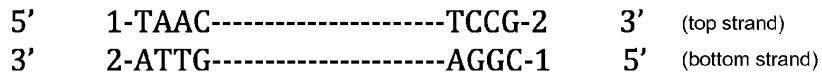
Figure 4a of Schmitt provides an example of an SMI sequence comprising an n-mer of 4 nucleotides in length (i.e., a 4-mer). Ex. 1011, 4:30–54.

And although Schmitt expressly labels the hybrid approach as providing a "*unique* molecular identifier," Ex. 1011, 9:12–13 (emphasis added), this is so only because the *combination* with the sequence information from the sheared ends with the short n-mer tag produces the "*unique* molecular identifier." The '822 patent similarly describes a "unique sequence" identifier that results from the combination of a non-unique barcode and sequence information at the ligation site:

> [A] plurality of barcodes may be used such that *barcodes are not necessarily unique to one another* in the plurality. In this example, the barcodes may be ligated to individual molecules such that the *combination of the bar code and the sequence it may be ligated to creates a unique sequence that may be individually tracked.* As described herein, detecting of non unique barcodes in combination with sequence data of beginning (start) and end (stop) portions of sequence reads may *allow assignment of a unique identity to a particular molecule.*

Ex. 1001, 39:13–22 (emphases added); *see also* Pet. 45–46; Ex. 1002 ¶ 130. Moreover, although claim 1 recites that the parent polynucleotides are "non-uniquely tagged," the parent polynucleotides are nevertheless uniquely identifiable because their amplified copies are grouped into families, "whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide." Ex. 1001, 62:40–42.

Finally, we disagree with Patent Owner that Schmitt's shearing process distinguishes over the method recited in claim 1 of the '822 patent. PO Resp. 33–35. Specifically, Patent Owner argues that "the hybrid method critically relies on sheared cellular DNA fragments" and that "shearing is incompatible with cfDNA samples." *Id.* at 33–34 (citing Ex. 1011, 9:9–13; Ex. 2020 ¶ 196; Ex. 2025 ¶¶ 93–95). Patent Owner's argument is unpersuasive because it treats the ordinarily skilled artisan like an automaton. "A person of ordinary skill is also a person of ordinary creativity . . . ." *KSR*, 550 U.S. at 421. And here, the record evidence supports Petitioner's contention that an ordinarily skilled artisan would have understood that cfDNA is already fragmented by nature and, thus, would have simply omitted the shearing step when tagging cfDNA with Schmitt's short 4-mer tags. Ex 1002 ¶¶ 118, 143; Ex. 1048, 16270–271 ("Library preparation was carried out according to the manufacturer's protocol with slight modifications. *Because cell-free plasma DNA was fragmented in nature, no further fragmentation by nebulization or sonication was done on plasma DNA samples.*" (emphasis added)); Ex. 1052,[13] 94 (describing plasma DNA library preparation and stating that "plasma DNA molecules

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[13] Gary J.W. Liao et al., *Targeted Massively Parallel Sequencing of Maternal Plasma DNA Permits Efficient and Unbiased Detection of Fetal Alleles*, 57(1) CLIN. CHEM. 92–101 (2011) (Ex. 1052).

[are] already fragmented in nature, so no additional fragmentation step [is] required").

Patent Owner's insinuation that an ordinarily skilled artisan would have found the shearing step to be an insurmountable obstacle to the combination of Schmitt and Fan or Forshew is therefore unpersuasive. *See ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1219 (Fed. Cir. 2016) ("The rationale of *KSR* does not support [the] theory that a person of ordinary skill can only perform combinations of a puzzle element A with a perfectly fitting puzzle element B."). Indeed, library generation, shearing (or not shearing), and ligating adaptors to DNA fragments were well known and routine steps in the art before the earliest priority date for the '822 patent. *See, e.g.*, Ex. 1011, 19:5–20:15 (Example 1); Ex. 1004, 16–34 (describing technical methods and design); Ex. 1048, 16270–271 (describing library preparation and adaptor ligation).

For all the above reasons, we agree with Petitioner and Dr. Gabriel that claim 1 does not distinguish over Schmitt's "hybrid" method. Pet. 45; Ex. 1002 ¶ 130. Although the '822 patent touts that "a sample comprising about 10,000 haploid human genome equivalents of cfDNA can be tagged with about 36 unique identifiers," Ex. 1001, 41:31–33, the tag count of claim 1 is not so limited. Indeed, dependent claim 11 recites tagging "with from 10 to 100,000 different identifiers," Ex. 1001, 63:11–13, thus suggesting that the number of non-unique tags in claim 1, from which claim 11 depends, is broader. *See AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). Thus, we are satisfied that Petitioner establishes by a preponderance of the evidence that the combination of

Schmitt, Schmitt 2012, and Fan or Forshew teaches or suggests each and every limitation of claim 1.

      c.   *Dependent Claims 3, 4, 6–8, 10, 11, and 17–20*

Having decided that the combination of Schmitt, Schmitt 2012, and Fan or Forshew teaches or suggests each and every limitation of claim 1, we turn to the remaining challenged claims of the '822 patent, which all directly depend from claim 1 (i.e., claims 1–13 and 17–20). Patent Owner presents separate arguments for dependent claims 2, 5, 9, 12, and 13. *See* PO Resp. 53–57. We address those claims individually below. *See infra* § IV.E.1.d–h.

As to dependent claims 3, 4, 6–8, 10, 11, and 17–20, we find that Petitioner also shows by a preponderance of the evidence that Schmitt, Schmitt 2012, and Fan or Forshew account for the limitations in these claims, or that certain limitations were well-known in the art as admitted in the '822 patent. Pet. 59–65, 67–70. We have also reviewed Dr. Gabriel's testimony and find that a preponderance of the evidence supports her contention that the cited references collectively disclose or suggest each and every limitation of claims 3, 4, 6–8, 10, 11, and 17–20. *See* Ex. 1002 ¶¶ 162–163 (claim 3) (citing Ex. 1011, 3:1–6, 3:44–62, 7:58–62, 15:21–38); *id.* ¶¶ 164–166 (claim 4) (citing Ex. 1011, 23:10–14; Ex. 1047, SI1); *id.* ¶¶ 168–169 (claim 6) (Ex. 1011, 4:25–29, 17:9–11, 29:57–30:10, Figure 3); *id.* ¶ 170 (claim 7) (citing Ex. 1011, 21:10–19, 23:10–14); *id.* ¶¶ 171–172 (claim 8) (citing Ex. 1004, Abstract, 3, SI1, Table S1 (as evidenced by Ex. 1081, 84, 87)); *id.* ¶¶ 174–176 (claim 10) (citing Ex. 1001, 32:16–19 (stating that "[m]ethods of reducing noise and/or distortion from a sequencing process are known" and such methods "include, for example, filtering sequences, e.g., requiring them to meet a quality threshold, or

reducing GC bias" (evidenced by Ex. 1079, 893; Ex. 1014, 446))); *id.* ¶ 177 (claim 11) (citing Ex. 1011, 9:1–13); *id.* ¶¶ 186–188 (claim 17) (citing Ex. 1011, 20:23–29, 22:50–67); *id.* ¶¶ 189–190 (claim 18) (citing Ex. 1004, 1, 3, SI1, Table S1); *id.* ¶¶ 191–192 (claim 19) (citing Ex. 1011, 20:65–21:19; Ex. 1047, SI2; Ex. 1001, 32:16–19 (as evidenced by Ex. 1079, 893; Ex. 1014, 446)); *id.* ¶¶ 193–194 (claim 20) (citing Ex. 1011, 9:1–13).

Again, Patent Owner does not present separate and specific arguments for any of these dependent claims. *See* PO Resp. 53–57 (presenting arguments only as to dependent claims 2, 5, 9, 12, and 13). We, therefore, adopt the teachings set forth in the Petition and in Dr. Gabriel's Declaration as mapped to the limitations of the challenged claims as our own findings. *See In re NuVasive, Inc.*, 841 F.3d 966, 974 (Fed. Cir. 2016) (explaining that the Board need not make specific findings about claim limitations that a patent owner does not dispute are disclosed in the prior art).

d. *Dependent Claim 2*

Claim 2 depends from claim 1 and recites "further comprising detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant." Ex. 1001, 62:49–51. We agree with Petitioner that Schmitt teaches or suggests detecting each of these types of genetic aberrations. Pet. 57–59.

Specifically, Schmitt teaches that the DCS method allows for the confirmation of "the presence of a true mutation (as opposed to a PCR error or other artifactual mutation) in a target nucleic acid sequence." Ex. 1011, 16:43–47. Schmitt also teaches that the DCS method has the "ability to indirectly infer that damage is present on the DNA," which is a useful biomarker for, e.g., cancer risk, cancer metabolic state, mutator phenotype related to defective damage repair, carcinogen exposure, chronic

inflammation exposure, individual-specific aging, and neurodegenerative diseases. *Id.* at 15:47–53. As an example, Schmitt teaches using DCS to detect "single base substitutions" in a series of M13mp2 variants. Ex. 1011, 29:57–30:10; *see also id.* at 5:3–6 (stating that "DCS analysis removes . . . strand bias and reveals the true mtDNA mutational spectrum to be characterized by an excess of transitions"). As another example, Schmitt teaches using DCS for the "accurate detection of altered genomic copy number (e.g., for sensitive diagnosis of genetic conditions such as trisomy 21)." Ex. 1011, 18:3–21 (footnote omitted); *see also* Ex. 1002 ¶¶ 158–159.

Patent Owner argues that Schmitt does not expressly disclose detecting genomic copy variation (as opposed to genomic copy number). PO Sur-Reply 23–24. But we agree with Petitioner that an ordinarily skilled artisan would have understood that Schmitt's reference to "true mutations" includes each type of genetic aberration recited in claim 2. Ex. 1002 ¶ 157; *see also Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016) (stating that we must "consider common sense, common wisdom, and common knowledge in analyzing obviousness").

e. *Dependent Claim 5*

Claim 5 depends from claim 1 and recites "wherein making the base call comprises voting, averaging, maximum a posteriori or maximum likelihood detection, dynamic programming, Bayesian methods, hidden Markov methods or support vector machine methods." Ex. 1001, 62:59–63. As Petitioner points out, the '822 patent states that "'voting, averaging, statistical, maximum a posteriori or maximum likelihood detection, dynamic programming, Bayesian, hidden Markov or support vector machine methods' for generating consensus sequences were 'known in the art.'" Pet. 60 (quoting Ex. 1001, 45:64–46:5). Patent Owner argues that Petitioner

fails to sufficiently point to a teaching *in Schmitt* for these base-calling methods. PO Resp. 564. But this argument merely attacks the references individually and ignores what Patent Owner's own written description provides as common knowledge in the art. Thus, Patent Owner's argument is not persuasive. *See Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) ("rejecting a blinkered focus on individual documents" in an obviousness analysis).

> f. *Dependent Claim 9*

Claim 9 depends from claim 1 and recites "wherein mapping the sequence reads comprises using information about a length of each of the sequence reads." Ex. 1001, 63:7–9. We agree with Petitioner that the references teach or suggest mapping sequence reads using information about the length of each sequence read. Pet. 64. Both Schmitt and Schmitt 2012 teach aligning (or mapping) sequence reads to a reference genome using the Burrows-Wheeler aligner (BWA). Ex. 1011, 20:57–58; Ex. 1047, SI1. Dr. Gabriel testifies that an ordinarily skilled artisan would have understood that the BWA uses information about a length of each of the sequence reads for mapping. Ex. 1002 ¶ 173. We find Dr. Gabriel's testimony credible as supported by preponderant record evidence. Specifically, Li and Durbin[14] provide an overview of the BWA and teach that "[d]etermining the allowed maximum number of differences" is based on "a read of length *m*." Ex. 1077, 1757. Patent Owner's argument to the contrary lacks specificity and is unpersuasive. *See* PO Resp. 55 (arguing that "[t]he petition does not

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[14] Heng Li and Richard Durbin, *Fast and accurate short read alignment with Burrows–Wheeler transform*, 25(14) BIOINFORMATICS 1754–1760 (2009) (Ex. 1077, "Li and Durbin").

explain what aspect of the BWA algorithm that allegedly provides this teaching").

        g. *Dependent Claim 12*

Claim 12 depends from claim 1 and recites "wherein the population of polynucleotides is tagged with n different unique identifiers, wherein n is no more than 100*z, wherein z is a mean of an expected number of duplicate molecules having the same start and stop positions in the sample."
Ex. 1001, 63:15–19. Petitioner contends that Fan and Forshew disclose cfDNA amounts between 1 and 20 ng. Pet. 66 (citing Ex. 1048, 16270, Table S1; Ex. 1004, Table S6). Relying on Dr. Gabriel's testimony, Petitioner contends that "[a] sample of 20 ng DNA contains about 6,060 haploid genome equivalents, which would have approximately 1–2 duplicate polynucleotides beginning at any given position." *Id.* (citing Ex. 1002 ¶ 179). Petitioner contends that, "when there are 6,060 haploid genome equivalents, $z \approx 1$–2 and $100*z \approx 10$–200," and thus "claim 12 requires tagging with no more than 100–200 different unique identifiers." *Id.* (citing Ex. 1002 ¶ 179). Petitioner contends that Schmitt teaches "the use of a small number of different tags," such as 1-mer tags, and "when considering 1-mer tags at both ends of a fragment, the number of different combinations is 16." *Id.* at 67 (citing Ex. 1011, 9:1–13; Ex. 1002 ¶ 180, n.12). "Accordingly," Petitioner contends, "Schmitt teaches the additional limitation of claim 12." *Id.* (citing Ex. 1002 ¶ 181).

Patent Owner argues that claim 12 is not unpatentable because "[n]one of the cited references disclose[s] the expected number of duplicate molecules in a sample much less a tagging scheme based on such a number." PO Resp. 55. Patent Owner argues that Petitioner's analysis of claim 12 is based on hindsight because Petitioner relies on the '822 patent's disclosure

of the empirical relationship between "z" and the number of tags, and that
Petitioner fails to provide any explanation "for selecting a 20 ng sample size
from the 1–20 ng range." *Id.* at 55–56 (citing Pet. 66).

In its Reply, Petitioner contends that "[c]laim 12 is directed to a
number of identifiers for non-unique tagging, *i.e.*, no more than 100*z," and
that the combination of prior-art references teaches this number. Pet.
Reply 16.

Upon review of the parties' respective arguments and evidence, we
determine that Patent Owner has the better position. As Patent Owner points
out and Petitioner does not dispute, the relationship between "z" and the
number of tags "n" in a sample was unknown prior to the '822 patent. PO
Resp. 55–56; *see also* Ex. 1001, 41:6–13 (expressly defining "z" as the
"measure of central tendency (e.g., mean, median, mode) of an expected
number of duplicate molecules having the same start and stop positions").
This is because the relationship was determined empirically and disclosed in
the '822 patent. *See* Ex. 1001, 40:24–27 ("It has been empirically
determined that in a sample of about 10,000 haploid genome equivalents of
human DNA, there are about 3 duplicate polynucleotides beginning at any
given position."). Petitioner has not explained adequately, nor provided
preponderant evidence, that the relationship between "100*z" and "n," as
recited in claim 12, was known in the art. *See In re Omeprazole Patent
Litigation*, 536 F.3d 1361, 1379–80 (Fed. Cir. 2008) (holding that even
where a general method that could have been applied to make the claimed
product was known and within the level of skill of the ordinary artisan, the
claim may nevertheless be nonobvious if the problem which had suggested
use of the method had been previously unknown). For example, Petitioner

does not rely on an inherency theory for a teaching or suggestion of the claimed subject matter in the prior art. Pet. 66–67; Pet. Reply 16.

We find that Petitioner's arguments and evidence as to claim 12 are conclusory and not persuasive. *See Magnum Oil*, 829 F.3d at 1380 (stating that a petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements"). In particular, Petitioner fails to specifically address the previously unknown relationship between "n" and "z" recited in the "wherein" clause of claim 12. Thus, we determine that Petitioner fails to show by a preponderance of the evidence that the prior art teaches or suggests the subject matter of claim 12.

      h. *Dependent Claim 13*

Claim 13 depends from claim 1 and recites "wherein no more than 100 nanograms of polynucleotides from the bodily sample are converted in b)." Ex. 1001, 63:20–22. We agree with Petitioner that both Fan and Forshew explicitly disclose providing no more than 100 ng of cfDNA molecules from the plasma of human subjects for sequencing. Pet. 67; *see also* Ex. 1002 ¶¶ 182–185. Specifically, Forshew extracted between 0.9 ng and 19.7 ng of DNA from cell-free plasma samples for sequence library preparation. Ex. 1004, Table S6. Similarly, Fan extracted between 1.2 ng and 8 ng of DNA from cell-free plasma for sequencing library construction. Ex. 1048, 16270, Table S1. These amounts fall within "no more than 100 nanograms of polynucleotides from the bodily sample" as recited in claim 13. Patent Owner argues that claim 13 "is not unpatentable" because "Schmitt discloses using 3 µg of human colonic mucosa DNA." PO Resp. 56–57. Again, this argument is unpersuasive because it attacks the references individually. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (attacking references individually is improper).

2. *Motivation to Combine/Reasonable Expectation of Success*

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). We address motivation to combine and reasonable expectation of success in turn below.

a. *Motivation to Combine*

Petitioner contends that an ordinarily skilled artisan, at the time of the '822 patent, would have been prompted to combine "the teachings of Schmitt and Schmitt 2012 regarding the DCS method" with "the teachings of either Fan or Forshew regarding sequencing and analysis of cell free DNA," with a reasonable expectation of success, based on the teachings of the art, the knowledge of an ordinarily skilled artisan, and the teachings of the Schmitt references. Pet. 32–41. In our Institution Decision, we determined that Petitioner had shown sufficiently for institution that an ordinarily skilled artisan would have been motivated to use Schmitt's DCS method to detect low-frequency genetic mutations in the cfDNA samples disclosed in Fan or Forshew. Inst. Dec. 24–25. Upon review of the complete record and the parties' respective arguments and evidence, we affirm our initial determination.

Specifically, we find that a preponderance of record evidence supports Petitioner's argument that Schmitt "provides explicit motivation to combine" its teachings with those of Fan, because Schmitt references Fan when discussing the state of the prior art and limitations thereof. Pet. 32 (citing Ex. 1011, 1:28–55; Ex. 1002 ¶ 99). When discussing the prior art, Schmitt states that "deep sequencing" technologies have "ushered in a new era of genomic exploration," because they "offer the unique ability to detect minor variants within heterogeneous mixtures." Ex. 1011, 1:28–37. Schmitt states that those technologies have been implemented in a variety of fields and that "[c]linical applications, such [as] prenatal screening for fetal aneuploidy . . . are rapidly being developed." Ex. 1011, 1:38–45. As an example of prenatal screening, Schmitt directly cites to Fan. *Id.* at 1:42–43 (citing reference "[9]"). Schmitt then discusses the limitations of the prior-art deep-sequencing techniques, such as limits on sensitivity and accuracy. *See id.* at 1:56–2:55 ("Although, in theory, DNA subpopulations of any size should be detectable when deep sequencing a sufficient number of molecules, a practical limit of detection is imposed by errors introduced during sample preparation and sequencing."). Schmitt states that the method disclosed in the '822 patent is "an approach for tag-based error correction, which reduces or eliminates artifactual mutations arising from DNA damage, PCR errors, and sequencing errors." *Id.* at 2:56–59. Schmitt states that the disclosed method is an improvement over the prior art because it "allows rare variants in heterogeneous populations to be detected with unprecedented sensitivity." *Id.* at 2:56–62.

We agree with Petitioner that an ordinarily skilled artisan would have had a reason to combine the disclosures of the Schmitt references with Fan: that is, to use Schmitt's DCS method to accurately detect prenatal genetic

mutations in cfDNA as taught by Fan. Pet. 36–37. Schmitt specifically

refers to "prenatal screening for fetal aneuploidy" and references Fan in

discussing the prior art and limitations thereof. Ex. 1011, 1:42–43; *see also*

Pet. 36. An ordinarily skilled artisan screening for fetal aneuploidy, as

described by Fan, Ex. 1048, Abstract, 16266, would have been prompted to

look to Schmitt's improved DCS method to "reduce[] or eliminate[]

artifactual mutations arising from DNA damage, PCR errors, and sequencing

errors." Ex. 1011, at 2:56–59; *see also* Pet. 36–37; Ex. 1002 ¶¶ 103–108.

We further agree with Petitioner that an ordinarily skilled artisan

screening cfDNA for cancer mutations, as described by Forshew, Ex. 1004,

Abstract, 1–2, would have also looked to Schmitt's DCS method for the

same reasons. Pet. 37; *see also* Ex. 1011, Abstract, 1:28–5; Ex. 1002

¶¶ 109–110. Specifically, in addition to discussing the use of deep-

sequencing techniques for prenatal screening for fetal aneuploidy, Schmitt

also refers to "early detection of cancer." Ex. 1011, 1:42–45. Thus, we

agree with Petitioner that an ordinarily skilled artisan screening for cancer

mutations in cell-free plasma DNA, as described by Forshew, Ex. 1004,

Abstract, would have been prompted to look to Schmitt's DCS method to

reduce amplification and sequencing errors and to improve detection of rare

genetic mutations. Ex. 1004, 1 (stating that "[s]ensitive methods for

detecting cancer mutations in plasma may find use in early detection

screening, prognosis, monitoring tumor dynamics over time, or detection of

minimal residual disease"); *see also* Pet. 36–37; Ex. 1002 ¶ 101.

We also find that the record supports, by a preponderance of the

evidence, Petitioner's contentions about the knowledge the "ordinarily

skilled artisan would have brought to bear when considering combinations

or modifications" of the prior-art references. *Randall Mfg. v. Rea*, 733 F.3d

1355, 1362 (Fed. Cir. 2013); *see* Pet. 32–35. Specifically, the record evidence shows that the ordinarily skilled artisan would have understood that genetic mutations in cfDNA occur at low frequencies compared to wild-type DNA and, thus, represent a small portion of the heterogeneous mixture of DNA in the plasma. Ex. 1002 ¶ 100; Ex. 1051, Abstract (discussing the low frequency of mutant adenomatous polyposis coli (APC) DNA molecules in the plasma of cancer patients compared to normal APC); Ex. 1052, 92 (stating that "the coexistence in maternal plasma of a minor population of fetal DNA within a major background of maternal DNA" poses challenges for non-invasive prenatal diagnosis of fetal genetic and chromosomal diseases); *see also* Pet. 32–33. Indeed, Fan expressly states that "measuring aneuploidy remains challenging because of the high background of maternal DNA; fetal DNA often constitutes <10% of total DNA in maternal cell-free plasma." Ex. 1048, 16266.

We agree with Petitioner that an ordinarily skilled artisan, wishing to detect cfDNA genetic mutations as discussed in Fan or Forshew with high accuracy and sensitivity, would have been motivated to use Schmitt's improved DCS method, because the DCS method "reduces or eliminates artifactual mutations arising from DNA damage, PCR errors, and sequencing errors," and "allows rare variants in heterogeneous populations to be detected with unprecedented sensitivity." Ex. 1011, 2:56–60; *see also KSR*, 550 at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

We have carefully considered Patent Owner's arguments and evidence to the contrary, but remain persuaded that Petitioner has provided a

sufficient reason with rational underpinning for combining Schmitt with Fan or Forshew. *See* PO Resp. 35–38. Citing to the testimonies of Dr. Shendure and Dr. Quackenbush, Patent Owner argues that an ordinarily skilled artisan would not have understood "the background section [of Schmitt] to be contemplating application of DCS to fetal aneuploidy detection." PO Resp. 35 (citing Ex. 2025 ¶¶ 102–110; Ex. 2023 ¶ 20). We disagree. As explained above, Schmitt states that deep-sequencing techniques have been implemented in a variety of fields, including prenatal screening for fetal aneuploidy and for early detection and monitoring of cancer. Ex. 1011, 1:28–55. Schmitt then discusses the limitations of the prior-art techniques, such as limits on sensitivity and accuracy, and states that the method disclosed is an improvement over the prior art because it "reduces or eliminates artifactual mutations arising from DNA damage, PCR errors, and sequencing errors," and "allows rare variants in heterogeneous populations to be detected with unprecedented sensitivity." *Id.* at 1:56–2:62. Taken together, we find that an ordinarily skilled artisan would have viewed these teachings as an express suggestion to use the DCS method for the prior-art applications described (e.g., prenatal and cancer-mutation screening). Ex. 1104 ¶¶ 33–34.[15]

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[15] We are not persuaded otherwise by the testimonies of Dr. Shendure and Dr. Quackenbush. Dr. Quackenbush states that "Schmitt is merely disclosing that next-generation sequencing ('NGS') has been used by others to detect fetal aneuploidy." Ex. 2025 ¶ 103. Similarly, Dr. Shendure states that "Schmitt is merely mentioning in some introductory remarks that different techniques employing DNA sequencing have been used by others to detect fetal aneuploidy." Ex. 2023 ¶ 20. These statements fail to read the entire background section of Schmitt as a whole, and thus lack specificity and credibility. *See Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089,

Relying on Dr. Quackenbush's testimony, Patent Owner also argues that "there would be no good reason to apply Schmitt's DCS method to detecting fetal aneuploidy," because fetal aneuploidy is not a "rare mutation" and using DCS to detect mutations that are not rare "increase[s] the expense and complexity of the method." PO Resp. 35–37 (citing Ex. 2025 ¶¶ 106–107); PO Sur-Reply 10–11. As an initial matter, we note that, as of the earliest priority date of the '822 patent, ordinarily skilled artisans knew that barcode-based deep-sequencing techniques had been used to screen cfDNA for genetic defects such as aneuploidy successfully. Ex. 1002 ¶ 113; Ex. 1058, 72–74 (describing the use of unique molecular identifiers to detect trisomy 21); Ex. 1059, 1 (describing the use of barcode-based massively parallel sequencing for the detection of aneuploidy). But even if Patent Owner is correct that fetal aneuploidy does not qualify as a "rare mutation," the lack of economic feasibility due to increased complexity is not a teaching away from using Schmitt's DCS method for that purpose. *See In re Farrenkopf*, 713 F.2d 714, 718 (Fed. Cir. 1983) ("That a given combination would not be made by business[wo]men for economic reasons does not mean that persons skilled in the art would not make the combination because of some technological incompatibility. Only the latter fact would be relevant.").

Finally, Patent Owner argues that Schmitt, Fan, and Forshew are, at most, analogous art and that their use of next-generation sequencing "is not evidence that [an ordinarily skilled artisan] would have wanted to—or could have—combined these methods." PO Resp. 37–38 (citing Ex. 2025 ¶¶ 108–

1092 (Fed. Cir. 1997) ("Nothing in the rules or in our jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness.").

110). We note that analogous art can, in some instances, demonstrate a reason to combine references, such as where "[o]ne skilled in the art would naturally look to prior art addressing the same problem as the invention at hand, and . . . would find an appropriate solution." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1380 (Fed. Cir. 2007). Here, Schmitt teaches that deep-sequencing techniques have been used "in a variety of fields," including in "prenatal screening for fetal aneuploidy" and in "early detection of cancer." Ex. 1011, 1:38–45. Schmitt teaches, however, that deep sequencing "has limitations" in that it produces artifactual mutations resulting from DNA damage, PCR errors, and sequencing errors. *Id.* at 1:56–2:62. Schmitt teaches that the disclosed DCS method (which includes the "hybrid" embodiment discussed above) "reduces or eliminates artifactual mutations" associated with the prior art. *Id.* An ordinarily skilled artisan looking to screen cfDNA for prenatal or cancerous mutations with high accuracy and sensitivity would have naturally looked to improvements in the field of next-generation sequencing, such as Schmitt's DCS method. Ex. 1001 ¶¶ 99–111; Ex. 1104 ¶¶ 32–39. Thus, although the fact that the prior-art references are analogous is not dispositive on the issue of motivation to combine, we maintain that an ordinarily skilled artisan reading Schmitt would have understood that Schmitt's DCS method was a reasonable substitute for the deep-sequencing and error-correction techniques used in the prior art—such as the next-generation sequencing techniques Fan and Forshew used for prenatal cfDNA screening and for tumor cfDNA screening, respectively. *Id.*

In sum, we find that the facts here constitute a case of "the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*,

550 U.S. at 417. Thus, for all the above reasons, we find that a preponderance of the evidence supports Petitioner's contention that an ordinary artisan would have been motivated to combine the teachings of the Schmitt references with those of Fan or Forshew.

b. *Reasonable Expectation of Success*

We next consider whether Petitioner has shown by a preponderance of the evidence that an ordinarily skilled artisan would have had a reasonable expectation of success. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

In this case, the question before us is whether the ordinarily skilled artisan would have had a reasonable expectation that Schmitt's DCS method could be used successfully with a population of cfDNA molecules. Ex. 1001, 62:18–48 (claim 1). In making our findings as to "reasonable expectation of success," we keep in mind that we cannot demand absolute certainty. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success."); *see also Pfizer*, 480 F.3d at 1364 ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

Upon consideration of the entire record, we are persuaded by and adopt Petitioner's contentions (and Dr. Gabriel's testimony) that an ordinarily skilled artisan would have had a reasonable expectation of success in using Schmitt's DCS method to detect genetic mutations in cfDNA. *See*

Pet. 37–41; Ex. 1002 ¶¶ 112–120. In particular, we agree with Dr. Gabriel's testimony that all the necessary techniques for carrying out the claimed method steps of the '822 patent were known and required only ordinary skill to perform. *See* Ex. 1002 ¶¶ 116–117. In this regard, the '822 patent itself teaches that the techniques needed to implement the claimed method were well known and routine in the art. *See* Ex. 1001, 36:1–6 (stating that "cell free polynucleotides may be isolated and extracted using a variety of techniques known in the art" including by "commercially available kits"); *id.* at 38:20–25 (stating that "assignment of unique or non-unique identifiers, or molecular barcodes in reactions of this disclosure may follow methods and systems described by, for example," prior-art patents and patent applications); *id.* at 38:41–48 (stating that "PCR for sequencing may be performed using any means, including but not limited to use of commercial kits provided by Nugen (WGA kit), Life Technologies, Affymetrix, Promega, Qiagen and the like"); *id.* at 30:8–12 (stating that "subsequent sequencing of cell free polynucleotides" may be done "by techniques known in the art"); *id.* at 35:27–31 (as to mapping and aligning sequences, stating that "sequences can be interrogated using the genome brow[s]er available" online); *id.* at 45:64–46:5 (stating that "[c]onsensus sequences can be generated from families of sequence reads by any method known in the art").

We also agree with Dr. Gabriel's testimony that Schmitt itself reasonably suggests that the DCS method can be used successfully for several different types of applications by

> explain[ing] that the DCS method does not require substantive modification of existing sequencing workflows and can serve as a general technique for next generation sequencing:

> [T]he DCS approach can be generalized to nearly any
> sequencing platform because a double-stranded SMI tag
> can be incorporated into other existing adaptors, or for
> sequencing approaches that do not require adaptors, a
> double-stranded SMI tag can be ligated onto duplex DNA
> sample prior to sequencing [… and therefore the]
> compatibility of DCS with existing sequencing
> workflows, the potential for greatly reducing the error rate
> of DNA sequencing, and the multitude of applications for
> the double-stranded SMI sequences validate DCS as a
> technique that may play a general role in next generation
> DNA sequencing.

Ex. 1002 ¶ 114 (quoting Ex. 1011, 18:44–61) (alteration in original).

In sum, "[t]his is not a situation where the prior art gave no direction on how to reach a successful result." *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1026 (Fed. Cir. 2018). Instead, Schmitt suggests to the skilled artisan to use the DCS method as a general technique for next generation sequencing and error correction, and the '822 patent evinces that the technical details for isolating, barcoding, amplifying, sequencing, and analyzing cfDNA molecules were known to be routine in the art. These factors persuade us that an ordinarily skilled artisan would have had a reasonable expectation of success.

We are not persuaded by Patent Owner's arguments and evidence to the contrary. *See* PO Resp. 38–53. We observe that many of Patent Owner's arguments are, in essence, that the prior art fails to provide proof that using the DCS method to analyze cfDNA would have been successful. *See, e.g.*, PO Resp. 38–41 (characterizing Petitioner's evidence of the successful prior-art use of barcode-based sequencing and error correction for cfDNA irrelevant because none "use[d] the Schmitt method," and arguing that "[e]ven if other methods using [next-generation sequencing] had been

applied to cfDNA, it does not establish that the different Schmitt method is applicable to cfDNA"); *id.* at 41–42 (arguing that "Schmitt does not tag, much less analyze fragments, similar to the naturally fragmented size of cfDNA"); *id.* at 45 (arguing that "Schmitt applies the DCS method exclusively to samples of cellular DNA" and "does not even mention applying DCS to cfDNA, let alone provide any corresponding analysis").

But the test for obviousness does not require "actual success" in the prior art. *See Endo Pharm. Inc. v. Actavis LLC,* 922 F.3d 1365, 1379 (Fed. Cir. 2019) ("As we have repeatedly held, obviousness requires only a reasonable expectation of success, not proof of actual success."). "[O]nly a reasonable expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d 1364; *see also Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success."). And here, we find that a preponderance of the evidence supports Petitioner's contention that an ordinarily skilled artisan would have had a *reasonable*, even if not absolute, expectation that the DCS method could have been used to analyze cfDNA successfully for the reasons discussed above.

Patent Owner also argues an ordinarily skilled artisan would not have had a reasonable expectation of success in substituting genomic DNA with cfDNA because the skilled artisan would have considered Schmitt's DCS method to be incompatible with cfDNA. *See* PO Resp. 41–53. In this regard, Patent Owner argues that "there are several critical aspects of the Schmitt method (e.g., random shearing, optimal fragment size, randomly generated tags, numerous processing steps) that would be recognized as being incompatible with cfDNA sample analysis." *Id.* at 46 (citing Ex. 2023 ¶¶ 21–22). We address these alleged incompatibilities individually below.

First, Patent Owner argues that DCS is incompatible with cfDNA because "Schmitt describes the optimal range of fragment sizes for DCS is 200–500 bp"—a size that is greater than that of naturally occurring cfDNA (i.e., about 140–170 bp). *Id.* at 41–42, 46–47. This argument is not persuasive because nothing in Schmitt limits the applicability of DCS to DNA fragments of approximately 200–500 bp in size. Instead, Schmitt clearly teaches as part of the DCS method "size-selecting for *appropriate length* fragments." Ex. 1011, 3:53–56 (emphasis added). That the appropriate length for fragments analyzed in Example 1 of Schmitt was 200–500 bp does not teach an ordinarily skilled artisan away from the use of other, differently sized, fragments for different needs. *See* Ex. 1011, 19:57–20:15 (describing sequencing library preparation for Example 1); *see also* Ex. 1104 ¶¶ 48–50.

Second, Patent Owner argues that Schmitt's hybrid DCS method is incompatible with cfDNA because that method relies on a random shearing step to label the DNA. PO Resp. 42 (citing Ex. 1011, 9:9–13, 25:64–65, 17:41–45). Patent Owner also argues that Dr. Gabriel conceded that shearing is incompatible with cfDNA. *Id.* at 50 (citing Ex. 2021, 158:4–12; Ex. 2022, 105:11–20; Ex. 2023 ¶¶ 33–34). As discussed above, however, Patent Owner's arguments about shearing are not persuasive. *Supra* § IV.E.1.b. The record evidence amply supports Petitioner's contention that an ordinarily skilled artisan would have understood that cfDNA is already fragmented by nature and, thus, would have simply omitted the shearing step when tagging cfDNA with Schmitt's short 4-mer tags. Ex 1002 ¶¶ 118, 143; Ex. 1052, 94 (describing plasma DNA library preparation and stating that "plasma DNA molecules [are] already fragmented in nature, so no additional fragmentation step [is] required"); Ex. 1104 ¶ 46. Again, "[a] person of

ordinary skill is also a person of ordinary creativity, not an automaton."
KSR, 550 U.S. at 421.[16]

Third, Patent Owner argues that Schmitt's DCS method "requires large quantities of input DNA that are simply not available when working with cfDNA due to minute quantities that are reasonably obtained from patients." PO Resp. 46, 49 (citing Ex. 2023 ¶ 32). These large amounts of DNA are necessary, Patent Owner argues, "[i]n view of inefficiencies in the method and steps requiring discarding significant amounts of sample and data." *Id.* at 49. In particular, Patent Owner argues that "Schmitt instructs additional steps that discard sample and data during processing and analysis." PO Resp. 47 (citing Ex. 1011, 20:42–43, 20:47–50, 20:53–55, 20:65, 21:4–18); *see also id.* at 47–49 (discussing SMI tags as "an additional source of data loss). Patent Owner argues that "[t]he difference in the amount of DNA between what is used in the Schmitt method and what is practicable to obtain from a patient is not trivial" and "would require fundamental modification and redesign of the DCS method." *Id.* at 49–50.

Although we have carefully considered Patent Owner's arguments and evidence on this topic, we remain persuaded that an ordinarily skilled artisan

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[16] Moreover, although a subtle point, we disagree with Patent Owner that an ordinarily skilled artisan would have understood *the process of shearing* to be a critical aspect of the hybrid method. It is true that the hybrid method uses a combination of sheared ends and a shorter n-mer tag to create a "unique" molecular identifier. Ex. 1011, 9:9–13. But the lesson the skilled artisan would have drawn from Schmitt is that the *sequences* at the ends of the DNA molecule plus the non-unique *sequences* of the 4-mer create a unique identifier. *Id.*; *see also* Ex. 1104 ¶ 47. Again, ligation of adaptors and tags to DNA sequences (whether the DNA is blunt-ended or contains overhanging molecules) was a routine, conventional activity in the art as of the earliest priority date of the '822 patent. *See, e.g.*, Ex. 1011, 19:5–20:15; Ex. 1004, 16–34; Ex. 1048, 16270–271.

would have had a reasonable expectation of success. In this regard, the "sample" or "data" to which Patent Owner refers relates to digital information, not physical molecules of DNA. Ex. 1002 ¶¶ 174–176, 191–192 (describing the process of filtering out sequence reads that do not meet certain quality thresholds). Dr. Shendure conceded during cross-examination that "the actual manipulations are related to the removal of data rather than molecules." Ex. 1102, 75:22–79:17. In addition, as discussed above, Schmitt teaches that "the DCS approach can be generalized to nearly any sequencing platform" and emphasizes the "compatibility of DCS with existing sequencing workflows." Ex. 1011, 18:44–61. Schmitt states that the compatible sequencing platforms are, for example, "the Illumina sequencing platform, ABI SOLiD sequencing platform, Pacific Biosciences sequencing platform, 454 Life Sciences sequencing platform, Ion Torrent sequencing platform, Helicos sequencing platform, and nanopore sequencing technology." *Id.* at 15:32–38. Petitioner points out that Fan used approximately 1–8 ng of cfDNA in the Solexa/Illumina sequencing platform with success, Pet. Reply 24 (citing Ex. 1048, 16270–71), thus suggesting that any necessary modifications of these well-known sequencing platforms would have been a routine activity for an ordinarily skilled artisan.

Finally, Patent Owner argues that several articles published after Schmitt, including one written by the DCS inventors, show that the DCS method "is inefficient and poorly suited for cfDNA samples." PO Resp. 43–45 (citing Ex. 2002; Ex. 2039; Ex. 2040; Ex. 2041; Ex. 1057). But as we pointed out in the Institution Decision, Inst. Dec. 26, a certain tagging efficacy is not recited in claim 1 of the '822 patent, *see* Ex. 1001, 62:17–48

(claim 1).[17] Patent Owner's argument about efficacy, therefore, is not persuasive. *See Sound View Innovations, LLC v. Hulu, LLC*, 2020 WL 3583556, at *3 (Fed. Cir. July 2, 2020) (holding that "[s]ince the claims here did not require a certain level of practicality, the Board did not err in finding a reasonable expectation of success in meeting the limitations of the claimed invention" (quotation marks and alternations omitted)).

3. *Objective Indicia of Non-Obviousness*

We must consider any evidence of objective indicia of non-obviousness before reaching our conclusion on obviousness *vel non*. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Notwithstanding what the teachings of the prior art would have suggested to one of ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Patent Owner presents evidence of two of these considerations: (1) long-felt need and (2) commercial success. PO Resp. 57–62; PO Sur-Reply 20–23.

a. *Guardant360*

Patent Owner offers the Guardant360 product as evidence for long-felt need and commercial success of the claimed invention. PO Resp. 57. According to Patent Owner, "Guardant360 is a 'liquid biopsy' assay that provides clinically actionable sequence information from cfDNA molecules

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[17] In contrast, claim 1 of U.S. Patent 9,902,992 B2, which was at issue in related proceedings IPR2019-00636 and IPR2019-00637, expressly recites "tag[ging] at least 20% of the cfDNA molecules." Institution in those proceedings was denied. *See* IPR2019-00636, Paper 10; IPR2019-00637, Paper 10.

obtained from a routine blood draw from cancer patients." *Id.* at 58 (citing Ex. 2034, 4). Patent Owner argues that Guardant360 embodies "at least claim 1 of the '822 patent," including "convert[ing] cfDNA obtained from a patient into non-uniquely tagged parent polynucleotides which are then amplified and sequenced," *id.* (citing Ex. 2029, 5, 17–18; Ex. 2030, 3539, 3540, 3542, 3544); mapping the resulting reads to a reference genome and grouping into families "based on start and stop position and identifier sequence," *id.* (citing Ex. 2029, 19; Ex. 2030, 3540–3541); and collapsing sequence reads at each genetic locus "to generate a base call" and determining "the frequency of one or more bases at each locus," *id.* (citing Ex. 2029, 19; Ex. 2030, 3544).

b. *Nexus*

At the outset, we determine that we can give Patent Owner's arguments about long-felt need and commercial success no weight in our obviousness analysis. "For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quotation marks and emphasis omitted); *see also Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) ("In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a nexus to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention." (quotation omitted)).

Patent Owner argues that we must presume a nexus. PO Resp. 57–58. But a nexus is presumed only when "the patentee shows that the asserted objective evidence is tied to a specific product and that product 'embodies

the claimed features, and is coextensive with them.'" *Fox Factory*, 994 F.3d at 1373 (quoting *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018)); *see also WBIP*, 829 F.3d at 1329 (setting forth circumstances in which the presumption of nexus applies). And here, Patent Owner has failed to show with specific and credible evidence that claim 1 and Guardant360 are "coextensive."

For example, Patent Owner states that "Dr. Quackenbush explains [that] the Guardant360 test embodies at least claim 1 of the '822 patent," but provides no actual citations to, or discussion of, Dr. Quackenbush's testimony. PO Resp. 58. We decline to search through Dr. Quackenbush's Declarations for this evidence. *See DeSilva v. DiLeonardi*, 181 F.3d 865, 866–67 (7th Cir. 1999) ("A brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record."). Patent Owner provides citations to Exhibit 2029[18] and Exhibit 2030[19], but these documents appear to be research articles and do not provide any legal or factual analysis of claim 1 in relationship to Guardant360. Thus, we determine that Patent Owner's arguments fall well short of a persuasive showing of nexus.

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[18] Richard B. Lanman et al., *Analytical and Clinical Validation of a Digital Sequencing Panel for Quantitative, Highly Accurate Evaluation of Cell-Free Circulating Tumor DNA*, PLOS ONE. 1–27 (Oct. 16, 2015) (Ex. 2029).

[19] Justin I. Odegaard et al., *Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies*, 24(15) CLIN. CAN. RES. 1–27 (Aug. 1, 2018) (Ex. 2030).

4. Conclusion as to Obviousness

In sum, we find that the combination of Schmitt, Schmitt 2012, and Fan or Forshew teaches or suggests each and every element of claims 1–11, 13, and 17–20. We find that an ordinarily skilled artisan would have been motivated to combine Schmitt, Schmitt 2012, and Fan or Forshew and would have had a reasonable expectation of success in achieving the claimed invention. We also find that Patent Owner has failed to persuasively show secondary considerations of non-obviousness for failure to show persuasively that the Guardant360 product is coextensive with claim 1. We are therefore unable to accord Petitioner's evidence any weight. *Fox Factory*, 944 F.3d at 1373.

Thus, after carefully considering the arguments and evidence, we determine that the record as a whole weighs in favor of a conclusion of obviousness of claims 1–11, 13, and 17–20, especially given the disclosures of the art of record in this case and strength of the obviousness case based on the first three *Graham* factors. We find that Petitioner fails to prove by a preponderance of the evidence that claim 12 would have been obvious.

V. CONCLUSION[20]

Petitioner establishes by a preponderance of the evidence that claims 1–11, 13, and 17–20 of the '822 patent are unpatentable. Petitioner fails to establish by a preponderance of the evidence that claim 12 of the '822 patent is unpatentable.

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–13, 17–20	103(a)	Schmitt, Schmitt 2012, and Fan or Forshew	1–11, 13, 17–20	12
Overall Outcome			1–11, 13, 17–20	12

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–11, 13, and 17–20 of the '822 patent have been proven to be unpatentable;

ORDERED that claim 12 of the '822 patent has not been proven to be unpatentable; and

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

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

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