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Paper 54
Date: December 11, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

NATERA, INC.,
Patent Owner.

IPR2019-01201
Patent 8,682,592 B2

Before GRACE KARAFFA OBERMANN, SUSAN L. C. MITCHELL, and CYNTHIA M. HARDMAN, *Administrative Patent Judges*.

HARDMAN, Administrative Patent Judge.

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

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–27 of U.S. Patent No. 8,682,592 B2 ("the '592 Patent," Ex. 1001). We have jurisdiction under 35 U.S.C. § 6.

Petitioner has the burden of proving unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 316(e) (2018). Having reviewed the parties' arguments and supporting evidence, for the reasons discussed below, we find that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–27 are unpatentable. Additionally, for the reasons discussed below, we deny Petitioner's Motion to Exclude (Paper 48).

A. *Procedural History*

Illumina, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–27 of the '592 Patent. Paper 1 ("Pet."). Natera, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-reply to the Preliminary Response. Papers 13, 18.

In view of the then-available preliminary record, we concluded that Petitioner satisfied the burden, under 35 U.S.C. § 314(a), to show that there was a reasonable likelihood that Petitioner would prevail with respect to at least one of the challenged claims. Accordingly, we instituted an *inter partes* review of all the challenged claims, on all of the asserted grounds. Paper 19 ("Inst. Dec.").

After institution, Patent Owner filed a Response. Paper 27 ("PO Resp."). Petitioner filed a Reply. Paper 35 ("Reply"). Patent Owner filed a Sur-reply. Paper 43 ("Sur-reply").

Petitioner filed a Motion to Exclude Evidence. Paper 48. Patent Owner opposed that motion. Paper 49. Petitioner filed a Reply. Paper 50.

On September 16, 2020, we held an oral hearing, the transcript of which is of record. Paper 53 ("Tr.").

B. *Real Parties-in-Interest*

Petitioner and Patent Owner each identify themselves as the real parties-in-interest. Pet. 69; Paper 6 (Patent Owner's Updated Mandatory Notices), 1.

C. *Related Matters*

The parties identify *Illumina, Inc. v. Natera, Inc.*, United States District Court for the Northern District of California, Case No. 18-cv-01662, as a related matter. Pet. 69; Paper 6, 1.

D. *The '592 Patent and Relevant Background*

The '592 Patent, entitled "System and Method for Cleaning Noisy Genetic Data from Target Individuals Using Genetic Data from Genetically Related Individuals," generally relates to

> acquiring, manipulating and using genetic data for medically predictive purposes, and specifically to a system in which imperfectly measured genetic data is made more precise by using known genetic data of genetically related individuals, thereby allowing more effective identification of genetic irregularities that could result in various phenotypic outcomes.

Ex. 1001, 1:23–29, code (54). According to the Specification, "to make accurate phenotypic predictions[,] high quality genetic data is critical." *Id.* at 8:15–17. Yet, in the case of prenatal or pre-implantation genetic diagnoses, "a complicating factor is the relative paucity of genetic material available." *Id.* at 8:17–19. The '592 Patent discloses methods that

> make use of imperfect knowledge of the genetic data of the mother and the father, together with the knowledge of the mechanism of meiosis and the imperfect measurement of the embryonic DNA, in order to reconstruct, in silico, the embryonic DNA at the location of key SNPs [single nucleotide polymorphisms] with a high degree of confidence.

Id. at 8:45–50.

In one embodiment, after fetal or embryonic genetic data has been measured, it "can be used to detect if the cell is aneuploid, that is, if fewer or more than two of a particular chromosome is present in a cell." *Id.* at 8:67–9:2. "A common example of this condition is trisomy-21, which gives rise to Down syndrome." *Id.* at 9:2–4. The Specification states that aneuploidy is detected "by creating a set of hypotheses about the potential states of the DNA, and testing to see which one has the highest probability of being true given the measured data." *Id.* at 9:7–10.

E. *Illustrative Claim*

Claim 1, the only independent claim of the '592 Patent, is illustrative and is reproduced below:

> 1. An ex vivo method for determining a number of copies of a chromosome or chromosome segment of interest in the genome of an individual, the method comprising:

using a single nucleotide polymorphism (SNP) genotyping array or high throughput DNA sequencing to measure genetic material and produce genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment of interest in the individual, wherein the genetic data is noisy due to a small amount of genetic material from the individual; and wherein the small amount of genetic material from the individual is from fifty or fewer of the individual's cells, 0.3 ng or less of the individual's DNA, extracellular DNA from the individual found in maternal blood, or combinations thereof;

creating a set of one or more hypotheses specifying the number of copies of the chromosome or chromosome segment of interest in the genome of the individual;

determining, on a computer, the probability of each of the hypotheses given the produced genetic data; and

using the probabilities associated with each hypothesis to determine the most likely number of copies of the chromosome or chromosome segment of interest in the genome of the individual.

Ex. 1001, 62:39–62.

F. *Prior Art and Instituted Grounds of Unpatentability*

We instituted trial based on the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–12, 15–17, 19–23, 27	103(a)[1]	Dhallan[2]
18	103(a)	Dhallan, Bianchi[3]
24–26	103(a)	Dhallan, Sham[4]
1–27	103(a)	Rabinowitz[5]

Inst. Dec. 52; Pet. 9.

In support of its patentability challenges, Petitioner relies on two declarations from David Peters, Ph.D., among other evidence. *See* Ex. 1004 ("Peters Decl."); Ex. 1059 ("Peters Second Decl."). Patent Owner relies on

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[1] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. § 103 that became effective after the filing of the application that led to the '592 Patent. Therefore, we apply the pre-AIA version of 35 U.S.C. § 103.

[2] Dhallan, US 2004/0137470 A1, published July 15, 2004 (Ex. 1002).

[3] Bianchi, *Fetal Cells in the Maternal Circulation: Feasibility for Prenatal Diagnosis*, 105(3) Br. J. Haematol. 574–83 (1999) (Ex. 1034).

[4] Sham et al., *DNA Pooling: A Tool for Large-Scale Association Studies*, 3(11) Nat. Rev. Genet. 862–71 (2002) (Ex. 1021).

[5] Rabinowitz et al., US 2007/0184467 A1, published Aug. 9, 2007 (Ex. 1003).

a declaration from John Quackenbush, Ph.D., among other evidence. Ex. 2012 ("Quackenbush Decl.").

II. ANALYSIS

Under 35 U.S.C. § 103(a), a patent claim is unpatentable if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An obviousness determination requires finding "a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

A. *Level of Ordinary Skill in the Art*

Petitioner contends that a person of ordinary skill in the art as of the relevant date would have

> been a member of a team of scientists developing genetic techniques to collect and analyze genetic data. The POSA [person of ordinary skill in the art] would have had an M.D. or master's or Ph.D. in molecular biology, genetics, bioinformatics, or a related field, and, through either education or work experience, 2-3 years of experience with nucleic acid sequencing, sample preparation, and prenatal diagnostics.

Pet. 6; *see also* Ex. 1004 (Peters Decl.) ¶ 23 (addressing level of ordinary skill in the art). In its Patent Owner Response, Patent Owner neither comments on this proposal, nor proposes an alternative level of ordinary skill in the art.[6]

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[6] For completeness, we note that Dr. Quackenbush's declaration includes the opinion that

> a person of ordinary skill in the art would have been a member of a team of scientists developing techniques to obtain and analyze genetic data. Such a person would have (1) a masters and/or PhD degree in Molecular Biology, or Genetics, or a related discipline, with a working knowledge on the use of Bioinformatics; or (2) a masters and/or PhD degree in Bioinformatics, Computational Biology, or Biostatistics, or a related discipline, with a working knowledge of Molecular Biology/Genetics. At least one member of that team, but not necessarily every member of that team, would have had, through either education or work experience, 2-3 years of experience with molecular biology techniques relevant in the field of prenatal diagnostics.

Ex. 2012 (Quackenbush Decl.) ¶ 45. Dr. Quackenbush states, however, that his opinions would not change if he were to apply Dr. Peters' proposed level of ordinary skill in the art. *Id.* ¶ 47.

Because Petitioner's proposed definition is consistent with the cited prior art, we apply it for purposes of this Decision.[7] In our view, moreover, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. *Claim Construction*

The Board interprets a claim using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe a 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.*

Petitioner argues that "[n]o term requires express construction in this proceeding." Pet. 5. Petitioner notes, however, that the district court construed two claim terms, and states that "[t]he Court's constructions are

[7] We would reach the same ultimate conclusions under Dr. Quackenbush's proposal. *See* Ex. 2012 ¶¶ 45, 47 (Dr. Quackenbush, proposing a somewhat different definition, but indicating that the selection of one definition over the other would not change the ultimate result).

applied in this Petition."[8] *Id.* at 6; *see also* Ex. 1004 (Peters Decl.) ¶ 27 (Dr. Peters, indicating that he used the District Court's claim constructions in his analysis). Although Patent Owner does not address claim construction in its briefing, we note that Dr. Quackenbush indicated that he "applied the district court's constructions in [his] analysis." Ex. 2012 (Quackenbush Decl.) ¶ 69.

Only claim terms in controversy need be construed. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). On this record, neither party requests claim construction, and we determine that, for purposes of our decision, no claim term requires express construction.

C. *Obviousness of Claims 1–12, 15–17, 19–23, and 27 Over Dhallan*

Petitioner argues that claims 1–12, 15–17, 19–23, and 27 are unpatentable as obvious over Dhallan. Pet. 11. Below, we provide an overview of Dhallan. We then address claim 1, followed by dependent claim 5, and finally, the remainder of the dependent claims Petitioner challenges as obvious over Dhallan (claims 2–4, 6–12, 15–17, 19–23, and 27).

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[8] The District Court construed (i) the term "genetic data for some or all possible alleles" as meaning "genetic data for some or all possible base pairs at a given locus;" and (ii) the term "at least 100 loci on the chromosome or chromosome segment of interest in the individual" as meaning "at least 100 loci on the chromosome or chromosome segment of interest from only the individual." Ex. 1008, 12, 15; Pet. 5.

1. Overview of Dhallan (Exhibit 1002)

Dhallan, entitled "Methods for Detection of Genetic Disorders," discloses "a rapid, non-invasive method" that is "useful for detection of chromosomal abnormalities," including "monosomies, trisomies, and other aneuploidies." Ex. 1002, code (54), ¶ 3. Dhallan discloses that in one embodiment, the method comprises "quantitating the relative amount of the alleles at a heterozygous locus of interest, . . . wherein said relative amount is expressed as a ratio, and wherein said ratio indicates the presence or absence of a chromosomal abnormality." *Id.* ¶ 42. Specifically, Dhallan explains that

> [t]he ratio of alleles at a heterozygous site is expected to be about 1:1 (one A allele and one G allele). However, if an extra chromosome is present the ratio is expected to be about 1:2 (one A allele and 2 G alleles or 2 A alleles and 1 G allele).

Id. ¶ 826.

Dhallan's Example 14 reports an experiment that was designed to "recapitulate the in vivo scenario of blood from a pregnant female." *Id.* ¶ 2157. Dhallan teaches that maternal DNA was mixed with DNA isolated from her child, who previously had been diagnosed with trisomy 21, in various ratios to represent varying percentages of fetal DNA. *Id.* In particular, samples containing 100% Down syndrome DNA and mixtures of maternal blood and 75% Down syndrome DNA, 50% Down syndrome DNA, and 40% Down syndrome DNA were created and tested. *Id.* ¶ 2200.

In each of the samples, a total of 768 SNPs on chromosome 13 and 768 SNPs on chromosome 21 were genotyped. *Id.* ¶¶ 2166–83, 2196–97.

SNPs homozygous for the maternal DNA and heterozygous for the child DNA were further analyzed to create the allele ratios. *Id.* ¶¶ 2198–200. The allele ratio at each heterozygous SNP was calculated by dividing the value obtained for allele 1 by the value obtained for allele 2, e.g., "if SNP X can either be adenine (A) or guanine (G), the ratio at SNP X was calculated by dividing the value obtained for adenine by the value obtained for guanine." *Id.* ¶ 2201.

Dhallan notes that for the sample containing 100% Down syndrome DNA, 62 SNPs on chromosome 13 and 49 SNPs on chromosome 21 were analyzed. *Id.* ¶¶ 2202–06. The average ratio of allele 1 to allele 2 on chromosome 13 was approximately 1.0, whereas the average ratio for chromosome 21 was 0.531, in line with expectations. *Id.* Dhallan concluded that "[s]tatistical analysis revealed a confidence value of 99.9% that the ratios obtained on chromosome 13 and on chromosome 21 represented true differences, rather than random numerical fluctuations in value." *Id.* ¶ 2206. Dhallan notes that the ratios obtained upon analysis of the 75% Down syndrome DNA, 50% Down syndrome DNA, and 40% Down syndrome DNA mixtures similarly matched the expected ratios. *Id.* ¶¶ 2207–23.

Dhallan discloses that template DNA for use in the disclosed methods can be obtained from various sources, including from a single cell of an embryo, or from fetal DNA obtained from maternal blood. *Id.* ¶¶ 167–69.

Dhallan also teaches use of commercially available SNP genotyping arrays for producing the genetic data for use in the method. *Id.* ¶ 43.

2. Analysis of Claim 1[9]

a) Overview of the Parties' Arguments

Petitioner argues that Dhallan is directed to a non-invasive method of detecting chromosomal abnormalities, which includes "determining alleles at a locus of interest and quantitating a ratio for the alleles at the locus, where the ratio indicates the presence or absence of a chromosomal abnormality." Pet. 11 (citing Ex. 1002, Abstract). According to Petitioner, Dhallan hypothesizes that an individual with a normal number of chromosomes will have a balanced ratio of alleles, indicating an equal number of copies of maternal and paternal chromosomes. *Id.* In the case of

[9] Claim 1 recites that the "small amount of genetic data" can be from "[i] fifty or fewer of the individual's cells, [ii] 0.3 ng or less of the individual's DNA, [iii] extracellular DNA from the individual found in maternal blood, or [iv] combinations thereof." Ex. 1001, 62:49–53 (bracketed numbers added for ease of reference). Petitioner's unpatentability arguments for claim 1 focus on option [i], with Petitioner arguing that it would have been obvious to use DNA from a single fetal cell in the claimed method. *See generally* Pet. 14–33; Tr. 15:8–10 (Petitioner's counsel stating: "I don't think there's any dispute between Illumina and Natera that for claim 1, we were talking about a single cell from an embryo or a single cell from maternal blood."). To the extent Petitioner also argued unpatentability under options [ii] and [iii] in connection with claim 1, it did so by cross-referencing its arguments for claims 4, 5, and 17. *See, e.g.*, Pet. 20, 29, 33. As such, we address Petitioner's arguments under options [ii] and [iii] in connection with our analysis of claims 4, 5, and 17.

trisomy 21, however, Dhallan hypothesizes that the individual will have an imbalanced ratio of alleles, reflecting an extra copy of the chromosome. *Id.* at 11–13.

According to Petitioner, Dhallan's Example 14 is a "proof-of-principle experiment for detecting chromosome 21 trisomy in different samples." *Id.* at 12. Following "[t]esting the DNA of a Down syndrome individual, Dhallan determined the average ratio for heterozygous SNPs measured on chromosome 21 as 0.531, consistent with the hypothesis that there is an extra copy of chromosome 21 in that individual." *Id.* at 13 (citing Ex. 1002 ¶ 2204). Petitioner further argues that "Dhallan determined the probability (confidence interval) that this hypothesis represents a true aneuploidy, as opposed to 'random numerical fluctuations in value,'" and "concluded that the method accurately identified trisomy 21." *Id.* (quoting Ex. 1002 ¶ 2206).

Against that backdrop, Petitioner argues that Dhallan teaches each limitation of independent claim 1. *Id.* at 14–27. For example, Petitioner argues that Dhallan teaches use of genetic data that is "noisy," i.e., "incomplete," because various experimental errors can occur (such as poor PCR amplification), and because "[t]he '592 patent concedes that analysis of a single cell would inherently result in noisy data." *Id.* at 20 (citing Ex. 1001, 62:25–26 (defining "noisy" data as "incomplete")), 21 (citing Ex. 1001, 8:19–23 (referencing "the inherently noisy nature of the measured genetic data in cases where limited genetic material is used for

genotyping")); Ex. 1004 (Peters Decl.) ¶ 105. Petitioner relies on Dhallan's calculation of confidence intervals[10] as satisfying the "determining . . . the probability" claim limitation, and argues that these confidence intervals were used to determine the probability that the calculated ratio accurately reports an actual difference in the number of chromosomes, thus satisfying the "using the probabilities . . . " limitation. *Id.* at 24, 26–27.

As to motivation to combine, Petitioner argues that the extent it would have been necessary to combine disparate teachings in Dhallan, a person of ordinary skill would have been motivated to do so. *See, e.g.*, *id.* at 28–29. For example, although Dhallan reports that Example 14 used a SNP genotyping technique with fluorescent labels rather than a SNP genotyping array as claimed, Petitioner argues that "it would have been obvious to a POSA to use the same method with genetic data generated by one of the SNP genotyping arrays disclosed in Dhallan." *Id.* at 12, 18; Ex. 1002 ¶ 97. According to Petitioner, this is because Dhallan genotypes a large number of SNPs, and teaches that commercially-available SNP genotyping arrays can efficiently and reliably produce genetic data for many thousands of SNPs. Pet. 16–17, 29. Additionally, although Dhallan's Example 14 used DNA from an already-born child, Petitioner argues that a person of ordinary skill

[10] Dhallan alternately refers to the "confidence interval" as a "confidence value." *Compare* Ex. 1002 ¶¶ 2206, 2211, 2215, and 2219 (disclosing certain "confidence value[s]") *with id.* ¶ 2221 (referring to the same confidence values as "confidence interval[s]").

would have been motivated to use the method with DNA from a single fetal cell, which qualifies as a "small amount of genetic material" as recited in claim 1. *Id.* at 9–20. This is because, Petitioner argues, Dhallan discloses use of a single cell as a preferred embodiment, and testing a single embryo cell was standard in connection with in vitro fertilization. *Id.* at 29.

Finally, Petitioner argues that a person of ordinary skill would have had a reasonable expectation of success in using a single cell in Dhallan's methodology because "[t]he preimplantation analysis of one embryo cell, including steps of amplification and hybridization, to screen for genetic conditions including aneuploidy was well-known." *Id.* at 31. Petitioner also argues that a person of ordinary skill "would have expected that the techniques disclosed in Dhallan would successfully generate sufficient DNA from a single cell to carry out genotyping with a SNP array." *Id.* at 32.

Patent Owner argues that "Dhallan does not teach at least two elements of claim 1, namely 'determining the probability of each of the hypotheses' . . . and using the 'noisy' genetic data 'to determine the probability of each hypothesis.'" PO Resp. 18. Patent Owner additionally argues that Petitioner "has failed to show motivation to use a single fetal cell in Dhallan's Example 14," because Example 14 is designed to "distinguish between maternal and child DNA *when both exist in maternal blood*," not to test "pre-isolated fetal DNA." *Id.* at 33.

Patent Owner also argues that when using DNA from a single cell, a person of ordinary skill would not have would not have had a reasonable

expectation of success in arriving at the claimed subject matter by carrying out Dhallan's method because: (1) amplification bias "would have changed the ratio of one DNA sequence to another" (*id.* at 38); (2) "very low amounts of DNA could not be reliably used for SNP genotyping arrays (even with intervening amplification)" (*id.* at 47); and (3) a person of ordinary skill "would not have expected to be reasonably successful in isolating a single fetal cell from maternal blood" (*id.* at 50).

b) Analysis of Claim 1

We find, on the full trial record, that Petitioner has not carried its burden of demonstrating the unpatentability of claim 1 over Dhallan, because it has not demonstrated a reasonable expectation of success in arriving at the claimed method using Dhallan's methodology with a SNP genotyping array and DNA from a single fetal cell. In particular, we agree with Patent Owner that Petitioner has not established that at the relevant time, very low amounts of DNA could be reliably used, even after intervening amplification, with a SNP genotyping array to determine the number of copies of a chromosome according to Dhallan's methodology. As will be discussed, Patent Owner cites evidence demonstrating that at the relevant time, "various researchers had determined that very low amounts of DNA could not be reliably used for SNP genotyping arrays (even with intervening amplification)" (PO Resp. 47), which is particularly important because Petitioner argues that in Dhallan's method, a person of ordinary skill would have genotyped hundreds or thousands of SNPs to determine the most likely number of chromosome copies in the individual's genome. *See,*

e.g., Pet. 25 ("In practice, Dhallan's analysis genotypes hundreds of SNP loci."); *see also* Ex. 1004 (Peters Decl.) ¶ 87 (noting that in Dhallan's method, "The alleles of hundreds or thousands of SNPs . . . are determined.").

We begin by analyzing the arguments and evidence in the Petition. Petitioner argues a reasonable expectation of success in using one embryonic cell in Dhallan's method because "[t]he preimplantation analysis of one embryo cell, including steps of amplification and hybridization, to screen for genetic conditions including aneuploidy was well-known." Pet. 31. In support, Petitioner cites three articles: Hartwell (Ex. 1010), Hellani (Ex. 1023), and Munné (Ex. 1038). *Id.*; *see also* Ex. 1004 (Peters Decl.) ¶ 131 (addressing Hartwell, Hellani, and Munné).

Petitioner's cited articles persuasively demonstrate that DNA from single cells was routinely used to screen for genetic conditions, including aneuploidy. *See, e.g.*, Ex. 1004 (Peters Decl.) ¶ 131 (opining that "by 2004 it was routine to carry out genetic testing on one cell from an embryo"). This evidence does not, however, persuade us of a reasonable expectation of success, because as Dr. Quackenbush persuasively establishes (and Petitioner does not dispute), the genetic screening methods employed in these articles did not involve using a SNP genotyping array as recited in claim 1. Ex. 2012 (Quackenbush Decl.) ¶¶ 177, 179; PO Resp. 44–45. Rather, Hartwell uses hybridization probes to detect the presence or absence of a specific allele related to cystic fibrosis. Ex. 1010, 371–73; Ex. 2012

(Quackenbush Decl.) ¶ 179. As Dr. Quackenbush persuasively establishes, techniques testing for the presence or absence of particular mutations use "comparatively small amounts of starting materials," because "one is simply testing for the presence or absence of a particular mutation." Ex. 2012 (Quackenbush Decl.) ¶ 188. Techniques that test for the presence or absence of a mutation "stand in stark contrast to aneuploidy detection such as that described by Dhallan where the absolute amount of each allele (or the relative amount as a ratio) must be accurately determined." *Id.* ¶ 189.

Both Hellani and Munné use high-level techniques that permit detecting chromosomal aberrations, but do not involve producing genetic data for alleles at "at least 100 loci" using a SNP genotyping array, as recited in claim 1. Ex. 2012 (Quackenbush Decl.) ¶¶ 175–79; Sur-reply 16. Hellani discloses amplifying DNA from a single cell by multiple displacement amplification ("MDA"), then analyzing the amplification product via a comparative genomic hybridization ("CGH") microarray to detect trisomy 21. Ex. 1023, 850–51; Ex. 2012 (Quackenbush Decl.) ¶ 177. Munné uses fluorescent in situ hybridization ("FISH") to perform preimplantation genetic diagnoses using DNA from a single cell. Ex. 1038, 93; Ex. 2012 (Quackenbush Decl.) ¶ 179. Petitioner has not adequately demonstrated that the amount of DNA needed to perform the FISH and CGH analyses reported in Hellani and Munné is comparable to that needed to carry out the claimed method using Dhallan's aneuploidy analysis.

Petitioner additionally argues that a person of ordinary skill "would have expected that the techniques disclosed in Dhallan would successfully generate sufficient DNA from a single cell to carry out genotyping with a SNP array." Pet. 32. Petitioner points to Dhallan's teaching that "a minimal amount of template DNA is not limiting for the number of loci that can be detected," because DNA can be amplified. *Id.* at 31 (quoting Ex. 1002 ¶ 270 and citing *id.* ¶¶ 2334, 2380); *see also* Ex. 1004 (Peters Decl.) ¶¶ 132–33 (addressing Dhallan's teaching). Petitioner also points to Dhallan's disclosure of SNP genotyping array protocols. *Id.* at 32 (citing Ex. 1002 ¶¶ 2237–334 (HuSNP), 2346–90 (BeadArray)). But despite Dhallan's teachings, Dr. Quackenbush persuasively establishes (and Petitioner does not dispute) that "Dhallan provides no actual examples in which a 'minimal amount of template DNA' is used to generate genetic data for chromosomal analysis," and "never uses data from a SNP array to make any chromosomal determinations based upon a small amount of genetic material." Ex. 2012 (Quackenbush Decl.) ¶¶ 183, 197. While a lack of a working example is not dispositive, it is important here, in view of Patent Owner's affirmative evidence (discussed below) that very low amounts of DNA could not be reliably used for SNP genotyping arrays, even with intervening amplification.

Petitioner also relies on articles that elaborate on the DNA amplification techniques taught in Dhallan. *See* Ex. 1004 (Peters Decl.) ¶ 133 (discussing Hellani (Ex. 1023), Zhang (Ex. 1030), Dietmaier

(Ex. 1035), and Hu (Ex. 1036)). While these references demonstrate that techniques were known to amplify DNA from a single cell, we are not persuaded that they support a reasonable expectation of success, because the record does not speak to whether such amplification produces enough DNA to achieve the claimed subject matter using Dhallan's method with a SNP genotyping array. Both Hellani and Hu use the amplification product in a CGH analysis. Ex. 2012 (Quackenbush Decl.) ¶¶ 177, 179. Zhang discusses amplification of DNA from sperm cells, and Dietmaier addresses amplification of DNA from tumor cells. *Id.* at ¶¶ 180, 181. These references neither use the amplification product in a SNP array, nor "measure genetic material and produce genetic data for some or all possible alleles at a plurality of at least 100 loci on the chromosome or chromosome segment," as recited in claim 1. *Id.* at ¶¶ 177 (Hellani), 179 (Hu), 182 (Zhang, Dietmaier); PO Resp. 44–45.

Petitioner next argues that commercial SNP genotyping arrays were used with amplified DNA to detect DNA copy number changes and chromosomal copy number abnormalities. Pet. 32 (citing Ex. 1032 (Zhao) and Ex. 1037 (Wong)). We agree with Petitioner that Zhao and Wong amplified DNA and used SNP genotyping arrays to detect DNA copy number changes. Ex. 1004 (Peters Decl.) ¶ 135 (citing Ex. 1032, 3060; Ex. 1037, 1). However, as Dr. Quackenbush persuasively establishes (and Petitioner does not dispute), Zhao and Wong "do not use DNA generated from a single cell (or generally, from a small amount of genetic material)."

Ex. 2012 (Quackenbush Decl.) ¶ 195; PO Resp. 48. Indeed, Zhao amplified 250 ng of template DNA, and Wong amplified 10 ng of template DNA. Ex. 1032, 3061; Ex. 1037, 2. Both amounts are far more than the "minute amounts" of DNA found in a single human diploid cell, which is about 7 picograms. Ex. 2012 (Quackenbush Decl.) ¶ 57; Ex. 1004 (Peters Decl.) ¶ 143.

Petitioner also relies on Jenkins (Ex. 1011), which teaches that commercial SNP genotyping platforms can deliver over 100,000 genotypes per day with an accuracy of >99%. Pet. 32; Ex. 1011, Abstract; Ex. 1004 (Peters Decl.) ¶ 135. Jenkins, however, does not address accuracy of the platforms when using DNA from a small amount of genetic material, and as Dr. Quackenbush persuasively establishes, "a person of ordinary skill in the art would have expected genotyping performance to be significantly reduced when using DNA amplified from a single cell." Ex. 2012 (Quackenbush Decl.) ¶ 196; PO Resp. 48–49. Accordingly, we are not persuaded that Jenkins establishes a reasonable expectation of success, particularly in view of additional evidence raised by Patent Owner and discussed below.

In sum, Petitioner's evidence in the Petition establishes that single cells were used for genetic analysis, amplification techniques were known, and SNP arrays could be used to analyze chromosome imbalances. Petitioner's evidence, however, does not persuasively address the interplay between the amount of DNA in a single cell and the amount of DNA or amplified DNA needed to carry out the claimed method using a SNP

genotyping array and Dhallan's aneuploidy analysis. This is important because Patent Owner cites evidence demonstrating that at the relevant time, "various researchers had determined that very low amounts of DNA could not be reliably used for SNP genotyping arrays (even with intervening amplification)." PO Resp. 47.

For example, Patent Owner cites Lovmar (Ex. 2017), which teaches that following amplification (MDA), genotyping even tens of SNPs was not possible when using more DNA than is found in a single cell. Ex. 2012 (Quackenbush Decl.) ¶ 190. Lovmar amplified "3, 0.3, 0.03 or 0.003 ng genomic DNA to select the optimal amount for further use." Ex. 2017, 2. Lovmar found that with "0.03 ng of genomic DNA (~10 genome equivalents), measurable signals were obtained for 22 out of 32 SNP genotyping reactions, but the signal intensity ratios varied so much between the parallel assays that assignment of the SNP genotypes would have been difficult." *Id.* at 8. Lovmar concluded that "[t]he major determinant for successful genotyping is the amount of DNA subjected to MDA," and that "about 1000 genome equivalents (3 ng) of DNA should be used." *Id.* at 9; *see also* Ex. 2012 (Quackenbush Decl.) ¶ 190 (addressing Lovmar). Thus, according to Lovmar, the minimum amount of template (input) DNA needed to be amplified for successful SNP genotyping is 3 ng, which is far more than the "minute amounts" of DNA found in a single human diploid cell, i.e., about 7 pg (i.e., about 0.007 ng). Ex. 2012 (Quackenbush Decl.) ¶ 57 ("[A] single human diploid cell contains minute amounts of DNA,

recognized to be about 7 pg."); Ex. 1004 (Peters Decl.) ¶ 143 (noting that the amount of DNA in a single cell is "approximately 7 pg").

Patent Owner cites other references that likewise demonstrate the interplay between input DNA amount and reliable SNP genotyping array performance. PO Resp. 47. For example, Bergen (Ex. 2033) teaches that compared to using higher input DNA amounts, "we observed significantly reduced SNP genotyping performance when using 1 ng of gDNA or wgaDNA in TaqMan® SNP genotyping assays with respect to completion rate, due to a significant increase in the undetermined genotype rate (Table 4)." Ex. 2033, 4; *see also* Ex. 2012 (Quackenbush Decl.) ¶ 191 (discussing Bergen). Park (Ex. 2035) teaches that, for sources other than whole blood, minimum input DNA to obtain "sufficient and reliable amplified product for a run of BeadArray genotyping" was 0.5 ng (i.e., 500 pg), and that genotyping performance decreased with amplification.[11] Ex. 2035, 1521; *see also* PO Resp. 47–48; Ex. 2012 (Quackenbush Decl.) ¶ 192 (discussing Park). This amount of DNA (0.5 ng) is significantly more than the approximately 7 pg (0.007 ng) of DNA found in a single human diploid cell. Ex. 2012 (Quackenbush Decl.) ¶ 57; Ex. 1004 (Peters Decl.) ¶ 143; *see also* Ex. 1001, 29:53–55 (noting that 0.3 ng of DNA is the amount found in approximately 50 human diploid cells).

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[11] BeadArray is the same commercial genotyping array taught in Dhallan's Example 18. Ex. 2012 (Quackenbush Decl.) ¶ 192 n.7; Ex. 1002 ¶ 2346.

Thus, we are persuaded by Dr. Quackenbush's opinion that, "in view of reports such as these, a person of ordinary skill in the art would not have reasonably expected to obtain reliable [quantitative] genotyping results from DNA amplified from a single cell," but instead would have expected "that significantly more DNA than a single cell would be needed to reliably determine embryonic or fetal genotype, even when using MDA to amplify the DNA." Ex. 2012 (Quackenbush Decl.) ¶ 193. This issue is particularly critical given Petitioner's argument that to produce an accurate aneuploidy determination using Dhallan's methodology, many hundreds or thousands of SNPs need to be genotyped. *See, e.g.*, Pet. 17 ("Dhallan measures genetic material (DNA) to produce genetic data for the alleles at 768 SNP loci on chromosome 21."); *id.* at 25 ("In practice, Dhallan's analysis genotypes hundreds of SNP loci."); *see also* Ex. 1004 (Peters Decl.) ¶ 87 ("The alleles of hundreds or thousands of SNPs . . . are determined."); *id.* ¶ 92 (arguing that a person of ordinary skill would have been motivated to apply Dhallan's teachings to many thousands of SNPs in order to increase accuracy of the method); *id.* ¶ 134 ("[A]s taught by Dhallan, commercial genotyping arrays are able to genotype the number of SNPs needed to produce an accurate aneuploidy determination (more than 700 SNP loci or more, if needed, as taught by Example 14)."); *see also* Ex. 1059 (Peters Second Decl.) ¶ 19 ("As Dhallan teaches, many hundreds or thousands of SNP should be analyzed, particularly when the amount of DNA is lower.").

Petitioner's Reply does not persuasively respond to this issue. Petitioner does not specifically comment on Bergen (Ex. 2033) or Park (Ex. 2035) in the Reply.[12] *See generally* Reply. Petitioner mentions Lovmar, but only to argue that "subsequent prior art articles demonstrate that—notwithstanding Lovmar's disclosure—artisans successfully used DNA amplified from a single cell for aneuploidy analysis, including in conjunction with microarrays." Reply 18–19. As support, Petitioner cites Hellani, arguing that Hellani acknowledges Lovmar and concludes that "MDA of single cells was suitable for use with 'microarrays' due to its 'very high amplification efficiency and a constant ADO [allele drop out].'" *Id.* at 19 (citing Ex. 1023, 851, 852; Ex. 1059 (Peters Second Decl.) ¶ 36).

Petitioner, however, does not elaborate on how Hellani purportedly overcame the issues raised in Lovmar. Like Lovmar, Hellani discloses amplifying DNA from a single cell using MDA. Ex. 2017, 8 (discussing MDA reactions); Ex. 1023, 847. Hellani then analyzes the MDA amplification product via a CGH microarray to detect trisomy 21. Ex. 1023, 850–51; Ex. 2012 (Quackenbush Decl.) ¶ 177. But as discussed above,

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[12] Dr. Peters does address Park (Ex. 2035), but only to argue that it teaches using "roughly five human cells worth of DNA" to "yield a reliable amplified product for use in microarray genotyping experiments." Ex. 1059 (Peters Second Decl.) ¶ 37. As will be discussed below, however, we do not consider this argument, because it represents an impermissible shift in theory from that presented in the Petition. The Petition exclusively focused on a reasonable expectation of success in carrying out claim 1 using DNA from a single cell.

Petitioner has not persuasively rebutted Dr. Quackenbush's testimony that CGH does not involve "generating genetic data for some or all possible alleles at specific loci." Ex. 2012 (Quackenbush Decl.) ¶ 176; Sur-reply 16. Petitioner also has not addressed the relative amounts of input DNA needed for CGH microarrays versus SNP genotyping microarrays, let alone persuasively established that the successful use of an MDA amplification product in a CGH array as reported in Hellani would have translated to a reasonable expectation of success in using an MDA amplification product in a SNP genotyping array to carry out claim 1 using Dhallan's methodology.[13]

Petitioner also cites Wang (Ex. 1070) and Wilton (Ex. 1071), but does not substantively discuss these references in the Reply brief. Reply 19. Instead, the Reply merely cites Dr. Peters' discussion of these references. *Id.* (citing Ex. 1059 (Peters Second Decl.) ¶ 36). Our rules, however, prohibit incorporating arguments by reference from one document into another document. 37 C.F.R. § 42.6(a)(3). Thus, we do not consider Wang and Wilton. *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12, at 10 (PTAB Aug. 29, 2014) (informative) ("[W]e will not consider arguments that are not made in the Petition, but are instead incorporated by reference to the cited paragraphs" of an expert declaration.).

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[13] Dr. Peters states that the MDA (amplification) process in Hellani generated 35 µg of DNA. Ex. 1004 (Peters Decl.) ¶ 133. Petitioner, however, has neither specifically addressed whether this amount of DNA is sufficient to practice the method of claim 1 using Dhallan's methodology, nor quantified the amount of DNA needed to do so.

However, even if we were to consider these references, we agree with Patent Owner that neither "is focused on producing the *quantitively* [sic] accurate data that would be necessary for Dhallan's method." Sur-reply 16; *see also* Ex. 2012 (Quackenbush Decl.) ¶¶ 188–89 (distinguishing prior art that uses comparatively small amounts of input DNA for genetic analysis from Dhallan's analysis, where the relative amount of each allele must be accurately quantitated).

In the Reply, Petitioner also argues that the claims are obvious because the '592 Patent "relies on well-known PCR-based amplification techniques and commercial arrays to perform the claimed method," and thus "the claimed invention adds nothing beyond the teachings of [the prior art]." Reply 19 (quoting *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005)) (alteration in original); *see also id.* (arguing that Patent Owner's witnesses testified (in other proceedings) that genotyping arrays were known). Petitioner, however, has not established that the claimed embodiments disclosed in the '592 Patent necessarily require quantifying the ratio of hundreds or thousands of alleles in the same manner required by Dhallan's methodology.[14] *See, e.g.*, Tr. 12:15–24

[14] To the extent Petitioner is suggesting that the challenged claims suffer a defect under 35 U.S.C. § 112, Petitioner is not permitted to request cancellation of claims under 35 U.S.C. § 112 in a petition for *inter partes* review. *See* 35 U.S.C § 311(b); 37 C.F.R. § 42.104(b)(2); *see also* Reply 14 (arguing that "If a specialized amplification process was necessary to

(conceding that the methods in the '592 Patent are not quantitated methods like those in Dhallan).

Petitioner also argues that Dhallan, which encourages use of its methodology with a single cell, is "presumed enabled." Reply 12 (citing *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354–55 (Fed. Cir. 2003)). This argument is beside the point, because Patent Owner is not arguing that Dhallan lacks enablement, but rather, that Petitioner has failed to establish a reasonable expectation of success. PO Resp. 46–50. Enablement and reasonable expectation of success are different legal requirements governed by different legal standards, and a presumption of enablement does not compel a finding of reasonable expectation of success. *See UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1327 (Fed. Cir. 2018) (disagreeing that a "presumption [of enablement] establishes a reasonable expectation of success as a matter of law" and noting appellants' lack of identification of authority for the proposition that the presumption of enablement precluded a finding of lack of reasonable expectation of success). Moreover, as discussed above, Patent Owner has presented rebuttal evidence and argument that persuasively shows that those of ordinary skill would not have expected to practice claim 1 using Dhallan's method and DNA from a single cell in a SNP genotyping array, as Petitioner proposed.

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perform the claims, Natera would have been obligated to disclose it in its specification. 35 U.S.C. §112(1) (pre-AIA).").

Petitioner additionally argues that Patent Owner's expectation of success arguments focus solely on Dhallan's single cell disclosure, while "ignor[ing] Dhallan's disclosure that its methodology can be performed using 2–32 cells, which also falls within the claims." Reply 18 (citing, e.g., Pet. 13–14). Patent Owner responds that this is an improper attempt to change the thrust of the obviousness theory presented in the Petition. Sur-reply 16–17. We agree with Patent Owner.

Although the Petition references portions of Dhallan that address using sources of DNA other than a single cell (*see, e.g.*, Pet. 13–14, citing Ex. 1002 ¶¶ 44, 74), this is by way of background only, falling within a section titled "Introduction to Dhallan." *See* Pet. 11. Petitioner's detailed obviousness arguments for claim 1 are limited to use of DNA from a single cell, and do not extend to DNA from multiple cells.[15] *See, e.g.*, *id.* at 19–20 (arguing that, because Dhallan's preferred embodiment is one embryo cell, Dhallan teaches the claimed limitation reciting "wherein the small amount of genetic material from the individual is from fifty or fewer of the individual's

[15] As noted above, claim 1 recites several possible sources for the claimed "small amount of genetic data." *See supra* n.9. Here we focus on Petitioner's unpatentability arguments based on option [i], but note that Petitioner's unpatentability arguments under options [ii] and [iii] also did not extend to use of DNA from multiple cells. *See, e.g.*, Pet. 20 (cross-referencing arguments for claims 4, 5, and 17); *id.* at 34 (for claim 4, arguing option [ii] based on "a single human cell"); *id.* at 35 (for claim 5, arguing option [iii] based on "extracellular fetal DNA from maternal blood"); *id.* at 42 (for claim 17, arguing option [iii] based on a "single fetal cell").

cells"); *id.* at 29 ("A POSA would have been motivated to use a single cell as the source of genetic material . . . ."); *id.* at 31 ("A POSA would have reasonably expected success in using Dhallan's methodology, for example as described in Example 14, on one embryonic cell."). Accordingly, we agree with Patent Owner that Petitioner is impermissibly attempting to change the thrust of its obviousness theory on reply. Sur-reply 16–17. We will not consider Petitioner's belated attempt to argue a reasonable expectation of success in using more than a single cell in the claimed method. 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the . . . patent owner response.").

In short, Patent Owner has persuasively established that a minimal amount of DNA can limit the number of loci that can be detected by a SNP genotyping array. *See, e.g.*, Sur-reply 13 ("[S]killed artisans had difficulty even *assigning genotypes* (let alone quantitating alleles) when performing even 32 genotyping reactions using more DNA than that available from a single cell.") (citing Ex. 2017, 8). Petitioner has not persuasively established that a single cell would provide sufficient DNA, even after amplification, to carry out the method of claim 1 when using Dhallan's methodology and a SNP genotyping array.

Accordingly, based on our consideration of the arguments and evidence advanced by Petitioner and Patent Owner on this full trial record, we determine that Petitioner has not shown, by a preponderance of the evidence, that claim 1 of the '592 Patent would have been unpatentable over

Dhallan. Because this issue is dispositive of whether Petitioner has met its burden of proving unpatentability, we do not reach the parties' other arguments regarding claim 1. *Cf. Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (finding that an administrative agency is at liberty to reach a decision based on a single dispositive issue because doing so "can not only save the parties, the [agency], and [the reviewing] court unnecessary cost and effort," but can "greatly ease the burden on [an agency] faced with a . . . proceeding involving numerous complex issues and required by statute to reach its conclusion within rigid time limits").

3. Analysis of Dependent Claim 5

Claim 5 depends from claim 1 and recites "wherein the small amount of genetic material is from extracellular DNA from the individual found in maternal blood."[16] Ex. 1001, 63:4–6. Petitioner argues that Dhallan motivates use of extracellular fetal DNA from maternal blood in the disclosed methodology with a reasonable expectation of success. Pet. 35–36. We note that Petitioner's argument as presented in the Petition requires isolation of a sample of 100% extracellular fetal DNA from maternal blood as a prerequisite to using the extracellular fetal DNA in Dhallan's methodology. For example, Petitioner argues that a person of ordinary skill "would have been motivated to use extracellular fetal DNA ***from*** maternal

[16] Fetal extracellular DNA is also called cell-free fetal DNA, and "consists of fragments of fetal DNA that circulate freely in the maternal blood." Ex. 2012 (Quackenbush Decl.) ¶ 59.

blood in Dhallan's analysis," and Dr. Peters' supporting testimony opines on a motivation to apply Dhallan's methodology "to extracellular fetal template DNA ***purified from*** maternal blood." *Id.* at 36 (emphasis added); Ex. 1004 (Peters Decl.) ¶ 147 (emphasis added). Indeed, at the oral hearing, Petitioner's counsel affirmed that "Illumina's entire petition was based for claim 5 on an isolated amplified sample of cell-free fetal DNA." Tr. 15:16–18.

Based on the complete record, we find that Petitioner has failed to demonstrate a credible motivation and reasonable expectation of success in carrying out the method of claim 1 when using Dhallan's methodology and an isolated sample of extracellular fetal DNA from maternal blood. As such, Petitioner has not carried its burden of proving, by a preponderance of the evidence, that Dhallan renders claim 5 unpatentable as obvious.

We begin by assessing the arguments and evidence in the Petition regarding motivation. We find that none of Petitioner's cited evidence supports a motivation to purify fetal template DNA from maternal blood. First, Petitioner and Dr. Peters rely on portions of Dhallan. Pet. 35 (citing Ex. 1002 ¶¶ 169, 176, 2223, 40, 2152, 2157, 2273, 2346); Ex. 1004 (Peters Decl.) ¶ 145.[17] Dhallan paragraph 176 teaches that fetal and maternal DNA

[17] Petitioner also cross-references Section VI.A of the Petition, which is entitled "Introduction to Dhallan," but contrary to our rules, it is not clear precisely what evidence, if any, Petitioner intends to rely upon from this section in connection with the alleged unpatentability of claim 5. Pet. 35;

can be isolated from the plasma fraction of a maternal blood sample, but does not address isolating fetal and maternal DNA from each other. Ex. 1002 ¶ 176. Dhallan paragraph 40 teaches that extracellular fetal DNA has been used to determine sex of the fetus and fetal rhesus D genotype. *Id.* ¶ 40. This paragraph, however, does not expressly indicate that these tests necessarily involved the physical isolation of extracellular fetal DNA from maternal blood to perform the analyses.

The remainder of the cited paragraphs of Dhallan generically teach use of extracellular fetal DNA in Dhallan's method, but do not address isolating extracellular fetal DNA from maternal blood. *See id.* ¶¶ 169, 2152, 2157, 2223, 2273, 2346. Dr. Peters opines that Dhallan paragraphs 2273 and 2346, which respectively relate to Examples 16 and 18, teach that "fetal DNA from isolated maternal plasma can be analyzed using SNP genotyping arrays." Ex. 1004 (Peters Decl.) ¶ 145. These paragraphs, however, state that isolated maternal plasma "contains ***both*** maternal template DNA and fetal template DNA." Ex. 1002 ¶¶ 2273, 2346 (emphasis added). Petitioner does not point us to further statements indicating that the fetal template DNA is isolated from the maternal template DNA prior to analysis, which suggests that the experiments in Examples 16 and 18 are carried out on a mixed sample of maternal and fetal DNA.

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see 37 C.F.R. § 42.104(b)(5) (A petitioner must identify with particularity in the petition "the supporting evidence relied upon to support the challenge.").

Petitioner additionally relies on two articles, Bianchi (Ex. 1034) and Lo 1997 (Ex. 1049), to support the proposition that "[m]aternal blood as a source of fetal DNA was known in the art to be a safer and more desirable sample source relative to in utero sources such as amniocentesis." Pet. 35. This argument does not address the relevant issue, namely, whether the articles support a motivation to isolate or purify the fetal DNA from the maternal blood.

In short, we find that Petitioner has demonstrated that Dhallan motivates use of fetal DNA found in maternal blood in the disclosed method (*see, e.g.*, Ex. 1002 ¶ 169), but has not persuasively shown that a person of ordinary skill would have been led to first isolate the extracellular fetal DNA from maternal blood before using it in Dhallan's method.

Turning to Petitioner's argument that a person of ordinary skill in the art would have had a reasonable expectation of success in isolating extracellular fetal DNA from maternal blood for use in the claimed method, Petitioner relies on Dr. Peters' testimony and two additional pieces of evidence—Dhallan, and the '592 Patent itself. *See* Pet. 36. We address each piece of evidence in turn.

First, Petitioner argues that "Dhallan cites prior art references that successfully used such extracellular fetal DNA from maternal blood in genomic analyses." *Id.* (citing Ex. 1002 ¶¶ 39–40). The cited portion of Dhallan (paragraphs 39 and 40), in turn, cites three prior art references: Lo

1997 (Ex. 1049), Lo 1998 (Ex. 2027), and Pertl.[18] Ex. 1002 ¶¶ 39–40. The Petition, however, does not expressly address the teachings of these references in connection with a reasonable expectation of success.[19] *See generally* Pet. 31–33. Although the Petition focuses on the prior art references cited in Dhallan paragraphs 39 and 40 rather than the content of these paragraphs themselves, for completeness we note that these paragraphs also do not expressly address physical isolation of fetal DNA from maternal blood. Rather, paragraph 39 indicates that "[f]etal DNA has been *detected* and quantitated in maternal plasma and serum." Ex. 1002 ¶ 39 (emphasis added). Nothing in this statement indicates that the extracellular fetal DNA detected in the maternal sample was physically isolated from that sample. Paragraph 40 indicates that extracellular fetal DNA has been used to determine sex of the fetus and fetal rhesus D genotype. *Id.* ¶ 40. As noted above, this paragraph does not expressly indicate that these tests involved the physical isolation of extracellular fetal DNA from maternal blood.

Petitioner's second piece of evidence cited to support a reasonable expectation of success is the '592 Patent itself. Pet. 36. Petitioner argues

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[18] Pertl and Bianchi, 98 Obstetrics and Gynecology 483–90 (2001).

[19] Lo 1998 (Ex. 2027) was first made of record as part of Patent Owner's Response—after filing of the Petition. Pertl is not of record. The Petition and Dr. Peters address Lo 1997, but only in connection with arguing motivation. Pet. 35; Ex. 1004 (Peters Decl.) ¶¶ 61, 146. Neither the Petition nor Dr. Peters identifies any teachings in Lo 1997 relating to physical isolation of fetal extracellular DNA from maternal blood.

that "[t]he '592 patent admits that prior art techniques had been demonstrated to isolate and amplify extracellular fetal DNA from maternal blood." *Id.* (citing Ex. 1001, 1:66–2:1). The cited portion of the '592 Patent in turn states: "Fetal DNA isolation has been demonstrated using PCR amplification using primers with fetal-specific DNA sequences." Ex. 1001, 1:66–2:1.

We determine that Petitioner's reliance on the cited sentence of the '592 Patent is not sufficient to carry Petitioner's burden on reasonable expectation of success. Contrary to Petitioner's contention, the sentence itself does not refer to "prior art" techniques. Pet. 36. To be sure, the sentence uses the past tense ("has been demonstrated"), but it does not indicate who performed the work. *Cf. Riverwood Int'l Corp. v. R.A. Jones & Co., Inc.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003) (indicating that while a reference can become prior art by admission, that doctrine is inapplicable when the subject matter at issue is the inventor's own work). Nor does this brief statement cite any contemporaneous or supporting evidence relating to isolating extracellular fetal DNA from maternal blood.

Even if we were to take the cited sentence of the '592 Patent as an admission that physically isolating extracellular fetal DNA from maternal blood was known in the prior art, we find that the next sentence of the '592 Patent undercuts any reasonable expectation of success in creating a sample of isolated fetal DNA for use in the claimed method using Dhallan's methodology and a SNP genotyping array. The next sentence states: "Since

only tens of molecules of each embryonic SNP are available through these techniques, the genotyping of the fetal tissue with high fidelity is not currently possible." Ex. 1001, 2:1–4. This calls into question whether a person of ordinary skill in the art would have been able to isolate enough extracellular fetal DNA (even with subsequent amplification) to carry out claim 1 using Dhallan's method, because, as discussed above, Petitioner argues that the artisan would have genotyped many hundreds or thousands of SNPs in carrying out Dhallan's method.[20]

Petitioner also cites various paragraphs of Dr. Peters' declaration in support of arguing a reasonable expectation of success for claim 5. Pet. 36 (citing Ex. 1004 (Peters Decl.) ¶¶ 125–28, 134–35, 146–47). In paragraphs 125–28 and 134–35, Dr. Peters discusses using SNP genotyping arrays, but does not specifically address isolating extracellular fetal DNA from maternal blood. Ex. 1004 (Peters Decl.) ¶¶ 125–28, 134–35. In paragraph 146, Dr. Peters discusses maternal blood as a source of fetal DNA, and indicates that a person of ordinary skill would have been motivated to apply Dhallan's methodology to "extracellular fetal template DNA purified from maternal blood," but does not cite any reference

[20] At the oral hearing, Petitioner argued that if a person of ordinary skill "can't get a sample of extracellular fetal DNA, then this claim has an enablement problem." Tr. 40:7–9. We reiterate that Petitioner may not request (nor may we decide) the cancellation of claims under 35 U.S.C. § 112 in a petition for *inter partes* review. *See supra* n.14.

addressing purification of extracellular fetal template DNA from maternal blood. *Id.* ¶ 146.

In paragraph 147, Dr. Peters cites paragraphs 39 and 40 of Dhallan, and the same portion of the '592 Patent cited in the Petition (Ex. 1001, 1:66–2:1), but does not add any analysis beyond that presented in the Petition. Ex. 1004 (Peters Decl.) ¶ 147. Dr. Peters also cites additional paragraphs of Dhallan, which we already addressed above in connection with motivation. *Id.* (citing Ex. 1002 ¶¶ 169, 176, 2152, 2157, 2223, 2273, 2346). Finally, Dr. Peters cross-references paragraphs 87–97, 125–28, and 134–37 of his declaration, but these paragraphs also do not address isolating extracellular fetal DNA from maternal blood. *Id.*

We acknowledge Petitioner's position, articulated at the oral hearing, that Patent Owner raised "a completely new argument" in its demonstratives that "there's no way to get 100 percent sample of isolated cell-free fetal DNA," which argument should be stricken for being raised too late. Tr. 16:8–17:8. This argument was actually first raised in Patent Owner's Sur-reply (*see* Sur-reply 22–23), but even then, it comes too late, given that Petitioner argued (in the Petition) that a person of ordinary skill would have been motivated to use "extracellular fetal DNA ***from*** maternal blood," or, as Dr. Peters phrases it in the supporting citation, "extracellular fetal template DNA ***purified from*** maternal blood."[21] Pet. 35 (emphasis added); Ex. 1004

[21] During the oral hearing, Petitioner asserted that the argument it presented

(Peters Decl.) ¶ 146 (emphasis added). Thus, although we do not credit Patent Owner's belated argument, it is Petitioner's "burden to demonstrate both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Intelligent Bio-Sys., Inc.*, 821 F.3d at 1367–68 (quoting *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012)); *see also* 35 U.S.C. § 316(e) ("[T]he petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence."). "To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead

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in the Petition for claim 5 was necessarily based on an isolated sample of cell-free fetal DNA, because Petitioner employed the District Court's claim construction, which Petitioner characterizes as requiring an isolated sample of cell-free fetal DNA. *See, e.g.*, Tr. 14:24–16:7. Patent Owner disputes both whether the District Court's claim construction applies here, and whether the construction is limited to an isolated sample of cell-free fetal DNA. *See, e.g.*, *id.* at 32:6–33:10; *but see* Ex. 2012 (Quackenbush Decl.) ¶ 69 (Patent Owner's expert indicating that he applied the District Court's constructions). As discussed above, neither party requested claim construction in this case, and we reiterate that no claim term requires express construction. Instead, we find that the Petition and evidence cited therein clearly signal that Petitioner is arguing use of a 100% sample of cell-free fetal DNA isolated or purified from maternal blood in Dhallan's method. *See, e.g.*, Pet. 35; Ex. 1004 (Peters Decl.) ¶ 146 (opining on extracellular fetal DNA "purified from a maternal blood sample").

articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Here, we find that Petitioner fails to articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.[22]

For the above reasons, we are not persuaded that Petitioner has carried its burden of establishing that claim 5 is unpatentable as obvious over Dhallan. Because this issue is dispositive of whether Petitioner has met its burden of proving unpatentability of claim 5, we do not reach the parties' other arguments regarding claim 5. *Cf. Beloit Corp.*, 742 F.2d at 1423.

4. Analysis of Remaining Dependent Claims Challenged as Obvious Over Dhallan

a) Claims 2–4, 17, and 20

Dependent claims 2–4, 17, and 20 each recite limitations related to the amount of genetic material used in the claimed method.

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[22] We note that "institution of an IPR does not by itself translate to a conclusion of unpatentability." *Magnum Oil*, 829 F.3d at 1376 n.1. Although we found Petitioner's arguments for claim 5 sufficient for institution (*see* Inst. Dec. 27–28), "the Board is not bound by any findings made in its Institution Decision," and "there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial." *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (quoting 35 U.S.C. § 314(a) (2012)).

Claims 2 and 4 each depend from claim 1, and recite that "the small amount of genetic material" is "from twenty or fewer of the individual's cells," and "from 0.3 ng or less of the individual's DNA," respectively. Ex. 1001, 62:63–65, 63:1–3. Although these claims permit use of DNA from more than one cell, Petitioner limited its unpatentability arguments for these claims to the use of DNA from a single cell. *See* Pet. 34 (for claim 2, arguing that a person of ordinary skill "would have been motivated to use Dhallan's method to analyze genetic material ***from one cell*** from an individual with a reasonable expectation of success," and for claim 4, arguing that "it would have been obvious to apply Dhallan's method to analyze ***a single cell***") (emphases added).

Claim 3 depends from claim 2, and recites that "the small amount of genetic material is from one of the individual's cells." Ex. 1001, 62:66–67. Petitioner's arguments with respect to unpatentability of claim 3 are also limited to use of genetic material from a single cell. *See* Pet. 34.

Claim 17 depends from claim 1 and recites in relevant part: "wherein the sample is a maternal blood sample comprising DNA from the fetus and DNA from the mother of the fetus." Ex. 1001, 63:40–43. Claim 20 depends from claim 1 and recites in relevant part that the genetic material is found in "cells from the individual found in maternal blood, [and] genetic material known to have originated from the individual." *Id.* at 64:9–25. Petitioner's unpatentability arguments for claims 17 and 20 are also limited to arguing use of genetic material from a single cell. *See* Pet. 42 (with respect to claim

17, arguing that "A POSA would have been motivated to apply Dhallan's method, as exemplified in Example 14, to analyze DNA isolated ***from a single fetal cell*** . . . ."), 44 (with respect to claim 20, arguing that "Dhallan . . . discloses that the genetic material is preferably taken from ***one embryonic cell*** (i.e., DNA known to have originated from the individual), ***or fetal cell*** from maternal blood.") (emphases added).

For the same reasons discussed above with respect to claim 1, we determine that Petitioner has not shown, by a preponderance of the evidence, that claims 2–4, 17, or 20 of the '592 Patent are unpatentable as obvious over Dhallan. In particular, on this record, Petitioner has not persuasively established that a single cell would provide sufficient DNA, even after amplification, to carry out the method of these claims to accurately determine a number of copies of a chromosome of interest when using Dhallan's methodology and a SNP genotyping array.

b) Claims 6–12, 15, 16, 19, 21–23, and 27

Claims 6–12, 15, 16, 19, 21–23, and 27 depend directly or indirectly from claim 1. Petitioner's arguments for these claims do not address the deficiency discussed above regarding Petitioner's arguments for claim 1. *See* Pet. 36–40 (claims 6–12), 40–42 (claims 16, 17), 43–44 (claim 19), 45–46 (claims 21–23 and 27). Accordingly, for the same reasons discussed above with respect to claim 1, we determine that Petitioner has not shown, by a preponderance of the evidence, that claims 6–12, 15, 16, 19, 21–23, and 27 are unpatentable as obvious over Dhallan.

D. *Obviousness of Claim 18 Over Dhallan and Bianchi*

Claim 18 depends from claim 1 and recites in relevant part that "the method further comprises performing amniocentesis or chorion villus biopsy." Ex. 1001, 63:44–46. Petitioner argues that claim 18 is unpatentable as obvious over the combination of Dhallan and Bianchi (Ex. 1034). Pet. 46–47.

Bianchi is a review article that discusses prenatal screening for chromosome abnormalities such as trisomy 21. Ex. 1034, 574. Bianchi explains that pregnant women are routinely screened for Down syndrome risk via serum screening, and women found to have a fetus at high risk are offered amniocentesis. *Id.* Petitioner argues that, per Bianchi, it was well known to use amniocentesis or chorion villus biopsy to confirm a Down syndrome diagnosis following a suspect result from a non-invasive screening. Pet. 46–47.

Petitioner's arguments for claim 18 do not address the deficiencies discussed above for claim 1. *See id.* Accordingly, for the same reasons discussed above for claim 1, we find that Petitioner has not shown, by a preponderance of the evidence, that claim 18 is unpatentable over Dhallan and Bianchi.

E. *Obviousness of Claims 24–26 Over Dhallan and Sham*

Petitioner argues that claims 24–26 are unpatentable as obvious over Dhallan and Sham (Ex. 1021). Pet. 47–51. Claim 24 depends from claim 1 and recites "normalizing the genetic data for differences in measurement efficiency between the loci." Ex. 1001, 64:38–40. Claim 25 depends from

claim 1 and recites "amplifying the genetic material of the target individual; and normalizing the genetic data for differences in amplification and/or measurement efficiency between the loci." *Id.* at 64:41–45. Claim 26 depends from claim 1 and recites "amplifying the genetic material of the target individual; and normalizing the genetic data for differences in amplification and/or measurement efficiency between the loci, chromosome segments, or chromosomes." *Id.* at 64:46–51.

Sham is a review article that addresses "developments in quantitative genotyping assays and in the design and analysis of pooling studies." Ex. 1021, Abstract. Sham indicates that, in genotyping data, "many SNPs show differential amplification during PCR," which "causes the signal that represents the more efficiently amplified allele to be higher than expected from its true frequency in a pooled sample." *Id.* at 865. Sham teaches that "[t]o obtain unbiased estimates of allele frequencies, the strength of allele-specific signals should be corrected by a factor that is obtained from reference samples of known allele frequencies." *Id.* Petitioner argues that, per Sham, "it was common practice to normalize genetic data from a[] SNP genotyping array" to improve the quality of the data. Pet. 48–50 (citing, e.g., Ex. 1021, 865; Ex. 1002 ¶¶ 699, 812, 826, 1054, 1062–63, 2316).

Petitioner's arguments for claims 24–26 do not address do not address the deficiencies discussed above for claim 1. *See id.* at 48–50. Accordingly, for the same reasons discussed above for claim 1, we find that Petitioner has

not shown, by a preponderance of the evidence, that claims 24–26 are unpatentable over Dhallan and Sham.

F. *Obviousness of Claims 1–27 Over Rabinowitz*

Petitioner challenges claims 1–27 under 35 U.S.C. § 103 as obvious over Rabinowitz (Ex. 1003). Pet. 51. A threshold question is whether Rabinowitz qualifies as prior art to the challenged claims. As such, we begin by setting forth the priority chain for the '592 Patent.

The '592 Patent issued from Application Ser. No. 13/793,186 (the "'186 application"), filed on March 11, 2013, which is a continuation of Application Ser. No. 11/603,406 (the "'406 application"), filed on November 22, 2006. The '592 Patent claims priority to a number of provisional applications, with Provisional Application No. 60/817,741 (the "'741 provisional"), filed Jun. 30, 2006, being relevant here.

Petitioner argues that Rabinowitz qualifies as prior art because claim 1 of the '592 Patent (the only independent claim) lacks written description support for the limitation "high throughput DNA sequencing." Pet. 51–52. As such, Petitioner argues that the challenged claims are entitled to an effective filing date no earlier than March 11, 2013 (i.e., the filing date of the '186 application). *Id.* Given this alleged effective filing date, Petitioner argues that Rabinowitz, which was published on August 9, 2007, qualifies as prior art. *See* Ex. 1003, code (43); Pet. 51.

A patent application is entitled to claim priority to the filing date of a prior application only "for an invention disclosed [in the prior application] in the manner provided by [35 U.S.C. §] 112(a)." 35 U.S.C. § 120 (2018). In

other words, "[f]or claims to be entitled to a priority date of an earlier-filed application, the application must provide adequate written description support for the later-claimed limitations." *Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906 (Fed. Cir. 2018). The test for adequate written description is whether the disclosure "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). This "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

Petitioner argues that "[h]igh throughput DNA sequencing is not disclosed in the specification, nor is it described in any of the priority applications." Pet. 4. Rather, Petitioner argues, the sole disclosed sequencing technique is pyrosequencing, but the application expressly states that pyrosequencing "***is not currently conducive to high-throughput parallel analysis***." *Id.* at 53–54 (citing Ex. 1026 ('406 application), 6:27–30). Petitioner thus argues that Rabinowitz "***makes clear that the named inventors did not consider any DNA sequencing method to be suitable for high-throughput analysis***." *Id.* at 54. Petitioner further argues that, "[t]o the extent sequencing is mentioned in the provisional applications, those applications also teach that the then-available sequencing methods were not conducive to high-throughput applications." *Id.* at 55.

Patent Owner disagrees, arguing that the Specification must be read in conjunction with the discussion of pyrosequencing in the '741 provisional, which states:

> Pyrosequencing. For a review of the method, see http://www.pyrosequencing.com/. The main advantages to pyrosequencing include an extremely fast turnaround and unambiguous SNP calls, since you actually produce a sequence. The disadvantage of pyrosequencing, as with Taqman, is that ***the assay is not necessarily conducive to high-throughput analysis (unless $1 million machines are purchased)***. This may change as technology evolves.

Ex. 1039, 32 (emphasis added); PO Resp. 69–70. Patent Owner argues that this disclosure in the '741 provisional "clearly teaches that pyrosequencing ***is*** conducive to high-throughput analysis ***if $1 million machines are purchased***." PO Resp. 70. Patent Owner thus concludes that a person of ordinary skill in the art reading these disclosures together[23] "would understand that the inventors believed that pyrosequencing ***was*** a high-throughput method of DNA sequencing . . . that ***could*** be used to practice the claimed methods, but that it would be expensive to do so." *Id.* at 71; *see also* Ex. 2012 (Quackenbush Decl.) ¶ 280 (supporting Patent Owner's argument).

On this record, we agree with Patent Owner and Dr. Quackenbush that the '406 application and '741 provisional together demonstrate to persons of

[23] The '741 provisional is incorporated by reference into the '406 application. Ex. 1026, 1:5–13.

ordinary skill that the inventors understood pyrosequencing could be used for high-throughput sequencing, if expensive machines were purchased. In other words, the '741 provisional gives context to the statement in the '406 application, and we agree with Dr. Quackenbush that "'[s]uitability', as the provisional makes clear to a person of ordinary skill in the art, is a cost issue, rather than a technical one." Ex. 2012 (Quackenbush Decl.) ¶ 277; *see also id.* ¶¶ 276–80 (opining on disclosures in the '741 provisional).

Petitioner's expert, Dr. Peters, asserts that the '741 provisional lacks "evidence that the inventors believed a high-throughput sequencing approach could be used in conjunction with the claimed methodology." Ex. 1004 (Peters Decl.) ¶ 227. We are not persuaded by this testimony, because Dr. Peters neither specifically addresses the language cited above from the '741 provisional, nor controverts Dr. Quackenbush's opinion that a person of ordinary skill would have understood that language to indicate that pyrosequencing could be used in high-throughput applications, if expensive machines were purchased. *See* Ex. 2012 (Quackenbush Decl.) ¶¶ 276–77, 280, 283, 284.

Although Petitioner argues that the cited passage in the '741 provisional is "equivocal" and "disparaging," it does not explain in detail why this is so. Reply 26. Petitioner additionally argues that the cited passage "does not state that pyrosequencing is useful for high-throughput analysis using a 'small amount of genetic material' that generates 'noisy

genetic data' as claimed in the '592 patent, and therefore fails to support the challenged claims." *Id.* Petitioner, however, has not alleged, much less persuasively established, that pyrosequencing could not be used in the claimed method.

Considering the arguments and evidence of record, we determine that the '406 application and '741 provisional provide adequate written description support for the "high throughput DNA sequencing" limitation because together, they reasonably convey to those of ordinary skill in the art that pyrosequencing could be used for high throughput DNA sequencing (if expensive machines were purchased). Ex. 2012 (Quackenbush Decl.) ¶¶ 276–80, 284.

In our Institution Decision, we invited the parties to address whether the disclosure of pyrosequencing sufficiently supports the claimed genus of "high throughput DNA sequencing" recited in claim 1. Inst. Dec. 46; *see also Ariad Pharms., Inc.*, 598 F.3d 1336, 1350 ("Sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."). On the full trial record, neither party addresses this issue.

Petitioner, however, bears the ultimate burden of proving unpatentability of the challenged claims by a preponderance of the evidence, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC*,

800 F.3d at 1378. Once Patent Owner came forward with arguments and evidence in support of its entitlement to the claimed priority date, the burden shifted back to Petitioner to convince the Board that Patent Owner is not entitled to the benefit of that date.[24] *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327–28 (Fed. Cir. 2008). Despite having had the opportunity to address the issue in its Reply, Petitioner has not alleged, let alone persuaded us, that the disclosure of pyrosequencing is insufficient to support the claimed genus. *See* Patent Trial and Appeal Board Consolidated Trial Practice Guide ("TPG") 73 (November 2019) (noting that in its reply brief, petitioner may address issues discussed in the institution decision).[25] "Failure to prove the matter as required by the applicable standard means that the party with the burden of persuasion loses on that point—thus, if the

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[24] Citing *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008), Petitioner states that Patent Owner has the burden to establish entitlement to an earlier priority date. Pet. 51. To the extent Petitioner is arguing that Patent Owner bears the burden of persuasion on this issue, we disagree. The Federal Circuit has explained that *PowerOasis* addressed the burden of production, not the burden of persuasion. *See Tech. Licensing Corp.*, 545 F.3d at 1328–29 ("That ultimate burden [of persuasion on invalidity] never shifts, however much the burden of going forward may jump from one party to another as the issues in the case are raised and developed. Correctly understood, *PowerOasis* is fully consistent with this understanding . . . .").

[25] The TPG is available at https://www.uspto.gov/TrialPracticeGuide Consolidated.

fact trier of the issue is left uncertain, the party with the burden loses." *Tech. Licensing Corp.*, 545 F.3d at 1327.

In sum, on this record, Petitioner has not demonstrated by a preponderance of the evidence that the '592 Patent lacks adequate written description support for the "high throughput DNA sequencing" limitation recited in claim 1, and thus has not demonstrated that Rabinowitz is prior art to the challenged claims. For these reasons, Petitioner's obviousness challenge based on Rabinowitz fails on this record.

III. OBJECTIONS TO DEMONSTRATIVES

Prior to the oral argument, Patent Owner submitted objections to certain of Petitioner's demonstratives. *See* Ex. 3002 (email submitting Patent Owner's objections). These objections generally allege that certain demonstratives improperly contain new theories and arguments. *See id.*

Demonstratives are not evidence. *See* TPG 84 ("Demonstrative exhibits used at the final hearing are aids to oral argument and not evidence . . . ."). In this Final Written Decision, we rely on the arguments properly presented in the parties' briefs and the evidence of record, not on the demonstratives. Therefore, we overrule Patent Owner's objections.

IV. PETITIONER'S MOTION TO EXCLUDE

Petitioner moves to exclude the entirety of Dr. Quackenbush's Declaration (Exhibit 2012) under Federal Rules of Evidence ("FRE") 702, 401, and/or 403. Paper 48, 1. Patent Owner opposes. Paper 49. Petitioner,

as the moving party, bears the burden of establishing that it is entitled to the requested relief. 37 C.F.R. §§ 42.20(c), 42.62(a).

Petitioner argues that Dr. Quackenbush's declaration should be excluded because "he has no experience in fetal diagnostics," and could not opine on cross-examination about the accuracy of noninvasive prenatal diagnostic testing in the 2005–06 timeframe. Paper 48, 1 (citing Ex. 1058 (Quackenbush deposition), 27:21–22, 28:3–4, 203:23–204:9, 205:15–23). Petitioner argues that, "[w]ithout relevant experience in fetal diagnostics, and without understanding the state of the art or benchmarks for testing at the time, Dr. Quackenbush lacks the 'scientific, technical, or other specialized knowledge' required by FRE 702." *Id.* at 2. Petitioner also points to "[e]xemplary paragraphs that should be excluded" under FRE 702, 401, and 403 because they purportedly contradict, are inconsistent with other evidence of record, apply incorrect legal standards, or are misleading and confusing. *Id.*; *see also id.* at 2–15 (addressing "exemplary paragraphs").

Patent Owner responds by summarizing Dr. Quackenbush's qualifications and experience and arguing that he has sufficient "'knowledge, skill, experience, training, and education' of a 'specialized nature' in the techniques of the '592 patent and prior art (e.g. amplification, genotyping, and analysis of genetic data) for his testimony to be helpful to the Board." Paper 49, 1–2 (quoting *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010)). Patent Owner also argues that Petitioner's Motion "raises a host of new arguments in what amounts to an

unauthorized sur-sur reply." *Id.* at 5. Patent Owner also argues that Dr. Quackenbush's testimony is correct in view of the evidence of record and is not misleading. *Id.* at 5–15.

We have considered the parties' arguments and evidence and, as explained below, we deny Petitioner's motion to exclude.

As an initial matter, to the extent Petitioner employs its motion as a vehicle to clarify or bolster arguments made in its briefs (Paper 48, 2–15), we reject that endeavor as inappropriate. We limit our analysis of the issues raised in the substantive briefs to the information properly and timely raised by the parties in those briefs.

As to Dr. Quackenbush's qualifications, although Petitioner characterizes his expertise as relating to statistics, the record reflects that he also has adequate experience in the fields of genetics and biotechnology. For example, he is Professor of Computational Biology and Bioinformatics, the Chair of the Department of Biostatistics, and the Director of the Health Data Science Center at the Harvard TH Chan School of Public Health. Ex. 2013, 1. He has almost three decades of experience in research and teaching in the fields of genetics and biotechnology (*id.* at 1–8, 12), has published hundreds of articles in these fields (*id.* at 13–52), was the Editor-in-Chief of the journal Genomics for over a decade (*id.* at 8), and has served as a peer reviewer, or on the editorial board, of a dozen other publications relating to genetics and biotechnology (*id.* at 7–8). Paper 49, 2. Given that experience in genetics and biotechnology, we find that Dr. Quackenbush has sufficient

specialized knowledge, experience, and education in the techniques of the '592 Patent and prior art, such as DNA amplification, genotyping, and analysis of genetic data, for his testimony to be helpful to us. Moreover, even if Dr. Quackenbush did not personally work in fetal diagnostics at the relevant time, there is no requirement that a declarant must actually be a person of ordinary skill in the art to present testimony as to what such a person would have understood at the time of the invention. *See, e.g.*, *SEB S.A.*, 594 F.3d at 1373 (stating there is no requirement of a perfect match between an expert's experience and the field of the art in question, provided the expert has "sufficient relevant technical experience" to testify).

The remaining arguments raised in Petitioner's motion relate to the sufficiency, rather than admissibility, of evidence. Such arguments are improperly advanced in a motion to exclude. *See* TPG 79 (stating that a motion to exclude may not be used to challenge the sufficiency of the evidence to prove a particular fact); *see also Corning Inc. v. DSM IP Assets B.V.*, IPR2013-00053, Paper 66 at 19 (PTAB May 1, 2014) ("[T]he Board, sitting as a non-jury tribunal, is well-positioned to determine and assign appropriate weight to the evidence presented in this trial."). Moreover, "there is a strong public policy for making all information filed in an administrative proceeding available to the public." *Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2012-00010, Paper 59 at 40 (PTAB February 24, 2014). Rather than excluding evidence that is allegedly

confusing, misleading, or incorrect, we simply give it the appropriate weight in our analysis.

Accordingly, for the reasons discussed above, we deny Petitioner's motion to exclude Dr. Quackenbush's declaration.

V. OTHER

Patent Owner "objects to the appointment of APJs by the Office as unconstitutional under *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019)." PO Resp. 72.

We decline to consider Patent Owner's constitutional challenge, because the issue has been addressed by the Federal Circuit. *Arthrex*, 941 F.3d at 1328.

VI. CONCLUSION[26]

Based on the information presented, we conclude that on this record, Petitioner has not shown by a preponderance of the evidence that claims 1–27 of the '592 Patent are unpatentable for obviousness.

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[26] 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*. *See* 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).

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–12, 15–17, 19–23, 27	103(a)	Dhallan		1–12, 15–17, 19–23, 27
18	103(a)	Dhallan, Bianchi		18
24–26	103(a)	Dhallan, Sham		24–26
1–27	103(a)	Rabinowitz		1–27
Overall Outcome				1–27

VII. ORDER

It is hereby

ORDERED that claims 1–27 of U.S. Patent No. 8,682,592 B2 have not been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is *denied*; and

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

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