

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QUEST DIAGNOSTICS INCORPORATED,
Petitioner,

v.

RAVGEN, INC.,
Patent Owner.

IPR2021-00790
Patent 7,332,277 B2

Before ZHENYU YANG, TIMOTHY G. MAJORS, and DAVID COTTA,
Administrative Patent Judges.

MAJORS, *Administrative Patent Judge.*

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

I. INTRODUCTION

Quest Diagnostics Incorporated (“Petitioner” or “Quest”),¹ on April 19, 2021, filed a Petition to institute *inter partes* review of claims 8–13, 125, 139, and 140 of U.S. Patent No. 7,332,277 B2 (Ex. 1201, “the ’277 patent”). Paper 4 (“Pet.” or “Petition”). Ravgen, Inc. (“Patent Owner”)² filed a Preliminary Response. Paper 9 (“Prelim. Resp.”). With our authorization, Petitioner and Patent Owner filed a respective Preliminary Reply and Preliminary Sur-Reply addressing certain matters raised in the Preliminary Response. Paper 15 (Order authorizing briefing); Paper 17 (“Prelim. Reply”); Paper 18 (“Prelim. Sur-Reply”).

Under 35 U.S.C. § 314(a), *inter partes* review may not be instituted unless the Petition “shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Petitioner has not on this record established a reasonable likelihood of prevailing on the grounds advanced here. Thus, for reasons explained below, we do not institute *inter partes* review of claims 8–13, 125, 139, and 140 of the ’277 patent.

A. Related Patents & Proceedings

The ’277 patent issued February 19, 2008, from U.S. Patent Application No. 10/661,165 (“the ’165 Application”), filed September 11, 2003. Ex. 1201, codes (21), (22), (45). The ’165 Application is a continuation-in-part of Application No. PCT/US03/06198, filed February

¹ Petitioner identifies itself as the real party-in-interest. Pet. 5.

² Patent Owner identifies itself as the real party-in-interest. Paper 5, 1.

28, 2003, which claims priority to other applications with filing dates in 2002 and 2003, and two provisional applications filed May 8, 2002, and March 1, 2002. *Id.* at codes (60), (62). United States Patent No. 7,727,720 (“the ’720 patent”) is related to the ’277 patent.

Petitioner identifies multiple lawsuits involving the ’277 patent. Pet. 5. Those lawsuits include: *Ravgen, Inc. v. Quest Diagnostics*, No. 6:20-cv-00972-ADA (W.D. Tex.) (“the Quest lawsuit”), and *Ravgen, Inc. v. Natera, Inc. and NSTX*, No. 1:20-cv-00692-ADA (W.D. Tex.) (“the Natera lawsuit”). *Id.* (listing other lawsuits).³

The parties also identify other matters involving the ’277 patent pending before the Patent Office. Pet. 5; Paper 5, 1; Paper 10, 1. Different claims of the ’277 patent are challenged in IPR2021-00788 and IPR2021-00789 (both filed by Petitioner),⁴ IPR2021-00902 and IPR2021-01054 (both filed by Laboratory Corporation of America), and IPR2021-01272 (filed by Illumina, Inc.). Paper 5, 1; Paper 10, 1. In addition to the above, Patent

³ The ’720 patent is also asserted in the related lawsuits, it is challenged by Petitioner in IPR2021-00791, and is subject to Ex Parte Reexamination Control No. 90/014,703. IPR2021-00791, Paper 6, 1.

⁴ Petitioner asserts that it was justified in filing three petitions against the ’277 patent. *See generally* Paper 3 (citing, *inter alia*, the number of claims, and complexity; ranking the 788 petition first in priority). Patent Owner argues that three petitions from Petitioner were unnecessary and, thus, that at least the 789 and 790 petitions should be denied. *See generally* Paper 8. We deny the 789 and 790 petitions on their merits, leaving only the 788 case. We, therefore, decline to further address Patent Owner’s argument that the petitions should be denied for being excessive in number.

Owner identifies Ex Parte Reexamination Control No. 90/014,792 as relating to the present proceeding. Paper 10, 1.

B. Asserted Grounds of Unpatentability

Petitioner asserts one ground of unpatentability in this Petition (Pet. 8), which is provided in the table below:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
8–13, 125, 139, 140	103(a) ⁵	Adinolfi, ⁶ Pertl, ⁷ Abbott ⁸

Petitioner relies on the declaration of Ronald J. Wapner, M.D. (Ex. 1202), and Patent Owner responds with a declaration from Brian Van Ness, Ph.D. (Ex. 2001).

C. Technology Overview & the '277 Patent

The '277 patent relates generally to non-invasive methods for DNA sampling and detection of genetic abnormalities in a fetus. Ex. 1201, 1:31–39. The '277 patent explains that a variety of techniques (both invasive and

⁵ The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), amended 35 U.S.C. §§ 102 and 103. Based on the filing date of the '277 patent, we apply the pre-AIA versions of §§ 102 and 103.

⁶ Matteo Adinolfi et al., *Rapid Detection of Aneuploidies by Microsatellite and the Quantitative Fluorescent Polymerase Chain Reaction*, 17:13 PRENATAL DIAGNOSIS 1299–1311 (1997) (Ex. 1212, “Adinolfi”).

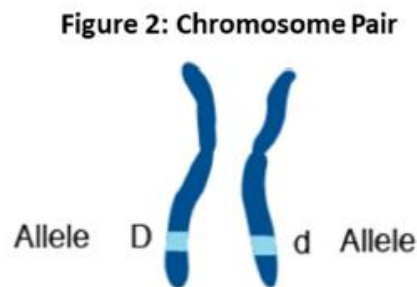
⁷ Barbara Pertl et al., *Detection of male and female fetal DNA in maternal plasma by multiplex fluorescent polymerase chain reaction amplification of short tandem repeats*, 106 HUM. GENET. 45–49 (2000) (Ex. 1211, “Pertl”).

⁸ Gill et al., US 5,891,734, issued Apr. 6, 1999, which lists Abbott Laboratories as assignee (Ex. 1207, “Abbott”).

non-invasive) are available for obtaining samples of DNA and using in prenatal diagnosis, including amniocentesis, and those that use fetal blood cells or cell-free fetal DNA in maternal blood. *Id.* at 2:53–57, 5:7–59.

As discussed below, claim 1 from which the challenged claims depend relates to methods of quantitating ratios of alleles (e.g., alternative versions of genes) in samples from a pregnant female that contain a mixture of fetal and maternal DNA and, from those ratios, detecting fetal chromosomal abnormalities. Dr. Van Ness explains that, with prior methods, “DNA in a mixed sample of unknown proportions of fetal and maternal DNA could not easily be distinguished in a way that would inform chromosomal abnormalities in the fetus.” Ex. 2001 ¶ 27 (citing Ex. 1201, 67:11–22). According to the ’277 patent, with the methods claimed “[t]he percentage of fetal DNA present in the sample from the pregnant female can be calculated by determining the ratio of alleles at a heterozygous locus of interest on a chromosome that is not typically associated with a chromosomal abnormality.” Ex. 1201, 67:18–22; *id.* at 70:19–23 (“[T]he present invention provides a method that allows the ratio of maternal to fetal alleles at loci of interest, including SNPs, to be calculated.”). The ’277 patent discloses methods that purport to allow for determination of fetal chromosomal abnormalities based on allelic ratios in mixed samples with both fetal and maternal DNA. *See, e.g., id.* at 67:57–68:19 (showing quantification of ratios of alleles in maternal samples with 40% fetal DNA; noting that “if the fetal DNA is 40% of the DNA in the maternal blood, the expected ratio without a trisomy is 0.25”).

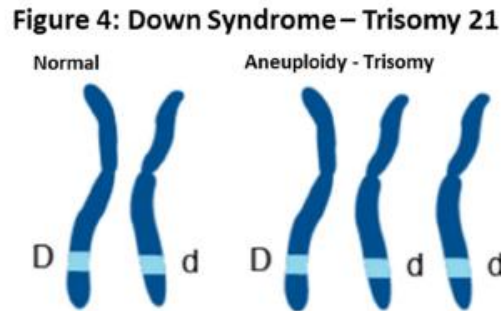
We provide a brief overview of chromosomes and alleles, with reference to Dr. Wapner's testimony. Chromosomes are the biological structures that carry an individual's genes—normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Ex. 1202 ¶ 29. Generally each pair has one chromosome inherited from the individual's father and one from the mother. *Id.* An "allele" is one or more alternate versions of a particular locus (e.g., a gene or portion of a gene) on a chromosome. *Id.* ¶ 32. This is illustrated on the chromosome pair in Figure 2 (reproduced below).



Ex. 1202 ¶ 33. Figure 2 above from Dr. Wapner's Declaration depicts a chromosome pair with "Allele D" on the left and "Allele d" on the right—both alleles reflecting a hypothetical locus or gene shaded in light blue on corresponding portions of the chromosome pair. *Id.* If two alleles are the same at a given locus, they are considered "homozygous" at that locus (e.g., D, D; or d, d); if the alleles are different at that locus (like shown above with D, d), they are "*heterozygous.*" *Id.* ¶ 34.

One form of chromosomal abnormality is "aneuploidy," which is a numerical abnormality where there are too few or too many chromosomes. *Id.* ¶ 36. One type of aneuploidy is "trisomy," where the individual has three copies of a chromosome instead of the usual two. Down Syndrome is

a type of trisomy and individuals with Down Syndrome have three copies of chromosome 21. *Id.* ¶ 37. This is shown in the Figure 4 (reproduced below).



Ex. 1202 ¶ 37. Figure 4 from Dr. Wapner’s Declaration is reproduced above, and it depicts a “[n]ormal” pair of chromosomes on the left (with alleles “D” and “d” at a heterozygous locus for that pair), and a set of three chromosomes are shown on the right for “Trisomy” (with an additional allele “d” at the locus on the extra chromosome at the far right). *Id.*

We also provide, with further reference to the testimony of Drs. Wapner and Van Ness, a brief overview of the components of human blood because blood samples are often used to obtain cellular or extracellular DNA for diagnostic purposes relevant to the claimed subject matter. *See, e.g.*, Ex. 1201, 5:7–59. “The vast majority of human DNA in blood is contained within the cells; however, some DNA may be found circulating outside of the cells in plasma and is considered extracellular, cell-free, or free.” Ex. 2001 ¶ 22. Most cellular DNA is contained within white blood cells (“WBCs”) because red blood cells (“RBCs”) typically lack a nucleus and do not contain DNA; similarly platelets in the blood do not

contain nuclear DNA. Ex. 1202 ¶ 48. These general features of circulating blood are depicted in the figure below.

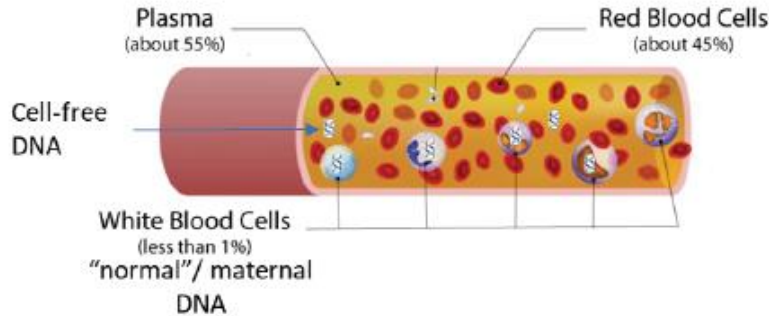


Figure 1A

Ex. 1202 ¶ 48. Figure 1A of Dr. Wapner’s Declaration is a cross-sectional illustration of maternal blood circulating within a vessel, with plasma shown in orange, and arrows pointing to (i) RBCs, (ii) WBCs, most of which still contain their nuclear DNA, and (iii) circulating cell-free DNA. *Id.* ¶¶ 55–56 (discussing lysis of the cell and nuclear membranes and the resulting release of cellular DNA into the surrounding medium).

Maternal plasma may contain circulating cell-free maternal DNA and also circulating free *fetal* DNA (“cffDNA”). Ex. 2001 ¶ 22. According to Dr. Van Ness, those skilled in the art “were aware of the presence of such circulating free DNA and its potential use as a diagnostic tool for prenatal or other disorders,” but “the percentage of free DNA in blood samples was too small to render accurate detection or diagnosis.” Ex. 2001 ¶ 23. Dr. Van Ness testifies that “this is in part due to lysis of [predominantly maternal] cells within the blood during collection and preparation of a sample for analysis,” which causes the cells to release their contents including maternal

cellular DNA into the plasma. *Id.* (“In the case of maternal blood, this increases the amount of maternal DNA in the plasma.”).

The ’277 patent describes methods said to increase the percentage of the cffDNA in a sample from a pregnant female for improved detection of chromosomal abnormalities. Ex. 1201, 89:6–11. To increase the percentage of cffDNA relative to circulating maternal DNA in a sample of maternal blood, for example, the ’277 patent describes adding an agent that inhibits cell lysis. Ex. 1201, 219:38–44 (Example 15) (“[T]he use of cell lysis inhibitors, cell membrane stabilizers, or cross-linking reagents can be used to increase the percentage of fetal DNA in the maternal blood.”), 469:46–51 (claim 8 (reciting addition of an agent that inhibits cell lysis)). The ’277 patent explains that, “[w]hile lysis of both maternal and fetal cells is inhibited, the vast majority of cells [in a maternal blood sample] are maternal, and thus by reducing the lysis of maternal cells, there is a relative increase in the percentage of free fetal DNA.” *Id.* at 32:36–39. The ’277 patent identifies numerous agents as cell lysis inhibitors. *See, e.g., id.* at 31:57–32:21 (listing formaldehyde, formalin, cleavable crosslinkers, cholesterol, vitamin E and its derivatives, and glucose, among other agents); *see also id.* at 226:27–229:20 (Table XXIII (“A representative list of cross-linkers that can be used to impede maternal cell lysis”)).

D. Challenged Claims

Nine of the ’277 patent’s one hundred and forty claims are challenged here. Pet. 1. The claims challenged in this Petitioner are all dependent claims. Claim 8 is illustrative and it depends from claim 4 and independent

claim 1. (Claims 1 and 4 are not challenged here, but are challenged in related IPR2021-0789). Claims 1, 4, and 8 are reproduced below:

1. A method for detecting the presence or absence of a fetal chromosomal abnormality, said method comprising:
quantitating a ratio of the relative amount of alleles at a heterozygous locus of interest in a mixture of template DNA, wherein said mixture comprises maternal DNA and fetal DNA, and wherein said mixture of maternal DNA and fetal DNA has been obtained from a sample from a pregnant female, and further wherein said heterozygous locus of interest has been identified by determining the sequence of alleles at the locus of interest, and wherein said ratio indicates the presence or absence of a fetal chromosomal abnormality.
4. The method of claim 1, wherein the template DNA is obtained from a sample selected from the group consisting of: a blood, serum, plasma, saliva, urine, tear, vaginal secretion, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascitic fluid, fecal matter, and body exudates.
8. The method of claim 4, wherein said sample is mixed with an agent that inhibits cell lysis to inhibit the lysis of cells, if cells are present, wherein the agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.

Ex. 1201, 469:10–21, 429:29–35, 429:46–51. Independent claim 116 (not challenged here) is similar to claim 1. *Id.* at 477:1–13. Challenged claims 9–13 and 125 depend indirectly from claim 1; claims 139 and 140 depend from claim 1 or claim 116. *Id.* at 469:52–65, 477:33–35, 478:32–35.

E. Prosecution History

Independent claims 1 and 116 (from which the challenged claims depend) correspond, respectively, to claims 1 and 152 that were pending

during prosecution of the '277 patent. Ex. 1203, 526.⁹ The Examiner rejected pending claims 1 and 152 as obvious over either “Umansky” or “Amicucci,” in combination with “Saiki.” *Id.* at 909–910, 943–944. Claim 8 (pending claim 9) was originally rejected as obvious over Umansky, Saiki, and “Kiessling.” *Id.* at 526, 917.

We discuss the rejection of claim 1 based on the Umansky-Saiki combination as illustrative and particularly significant relative to the issues raised in this Petition. The Examiner determined that Umansky taught a method with all the limitations of claim 1 but was “silent as regards how to express the relative amount of the alleles at the heterogeneous locus of interest.” *Id.* at 909 (citing disclosure in Umansky about detection of inherited diseases (e.g., Marfan Syndrome or Sickle Cell Anemia) of the fetus by analysis of fetal DNA in a maternal fluid sample). According to the Examiner, Saiki taught methods for diagnosing “sickle cell anemia wherein the relative amount of the alleles at a heterozygous locus of interest are determined . . . and results of the assay are expressed as a ratio.” *Id.* at 910.

Applicant responded with an amendment to both claims 1 and 152. *Id.* at 536, 554. Applicant then made several responsive remarks. First, applicant stated that “[c]laim 1 has been amended to more clearly indicate that the alleles, which are quantified and used to calculate a ratio, comprise a mixture of maternal DNA and fetal DNA.” *Id.* at 559 (stating same for claim 152). Second, applicant argued that the combination of Umansky and

⁹ Citations to the prosecution history (Ex. 1203) use the page numbers added to the exhibit copy rather than the original pagination.

Saiki “does not teach or suggest a method comprising all of the [claim] elements.” *Id.* at 563. Applicant argued Saiki relied on “determining the relative amount of alleles in a homogeneous sample, and expressing the results of the assay as a ratio,” such that the ratio “is calculated using a homogeneous DNA sample, and the ratio calculated represents alleles from a single individual.” *Id.* Applicant asserted that, “[i]n contrast, the methods [of the claims] taught herein comprise calculating a ratio of the relative amount of alleles in a heterogeneous mixture of DNA, i.e., maternal DNA and fetal DNA,” where “[t]he methods taught in the present invention comprise determining a ratio, wherein the ratio represents alleles from both the mother and the fetus.” *Id.* at 563–64. According to applicant, Umansky and Saiki “fail[ed] to teach or suggest this element, either alone or in combination.” *Id.* at 564 (“Thus, the methods described in the present application detect chromosomal abnormalities using a method that comprises, inter alia, quantitating a ratio of alleles in a heterogeneous mixture of DNA, wherein the ratio represents alleles from more than one individual.”); *see also id.* at 563–65 (arguing dependent claims nonobvious based on dependency from claims 1 or 152), 566–67 (arguing claim 9 was nonobvious for the same reasons given for claim 1, among other reasons).

Shortly thereafter, the Examiner allowed the claims. Ex. 1203, 519–520. The Examiner’s Reasons for Allowance stated that the claims are “deemed to be allowable in light of applicant’s amendment filed 30 MAY 07 and the persuasive argument(s) therein.” *Id.* at 521.

II. ANALYSIS

A. *Principles of Law*

“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) (citing 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”)).

A claim is unpatentable under 35 U.S.C. § 103(a) if 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 to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A. *Person of Ordinary Skill in the Art (“POSA”)*

In determining the level of skill in the art, we consider the problems encountered in the art, the art’s solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the

educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner contends:

A person of ordinary skill in the art (“POSA”) in the field of the ’277 Patent would be a Ph.D., M.D. or M.D./Ph.D., with a doctoral degree or Board certification in medical genetics, human genetics, molecular genetics, clinical genetics or related fields, and with 2-3 years of relevant research experience in an academic or industry setting in, e.g., the field of prenatal diagnosis or cancer diagnosis.

Pet. 38 (citing Ex. 1202 ¶ 101). Patent Owner does not directly oppose this definition. Prelim. Resp. 31. Patent Owner’s proposal describes the fields of advanced study as including “area[s] such as genetics, biochemistry, molecular biology, cell biology, or microbiology.” *Id.* Patent Owner proposes that a POSA would have “at least one to two years of work” in those areas and, alternatively, that a POSA “could have a Bachelor’s degree in one of the foregoing areas and at least three to four years of work in” such areas. *Id.* (citing Ex. 2001 ¶ 19).

Petitioner’s proposal of the POSA level is more precise and appears to be generally consistent with the prior art. Accordingly, we adopt it for purposes of this Decision. *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

We interpret 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) (2020). 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.* “[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” See *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

According to Petitioner, “no terms need to be construed for purposes of resolving the issues in this Petition because the prior art discloses all limitations under any plausible construction.” Pet. 33. Patent Owner, in discussing the prosecution history and in its merits argument, raises an issue that touches on claim interpretation, which we address in Section II(D).

We decline to further address Patent Owner’s argument that the Petition is defective under 37 C.F.R. § 42.104(b)(3) as to certain claims for not identifying how such claims are to be construed. Prelim. Resp. 45. (asserting that Petitioner argued in a related lawsuit that the phrase “an agent that inhibits lysis of cells” (e.g., in claim 8) should be construed as a means-plus-function term, but that Petitioner has not identified the claimed function and structure in this Petition). Because we determine, on this record, that Petitioner has not established that it is reasonably likely to prevail with its

challenge to the claims for other reasons (*see* Section II(D)), Patent Owner’s argument about Rule 42.104(b)(3) is not decisive.

C. Overview of the Asserted Prior Art

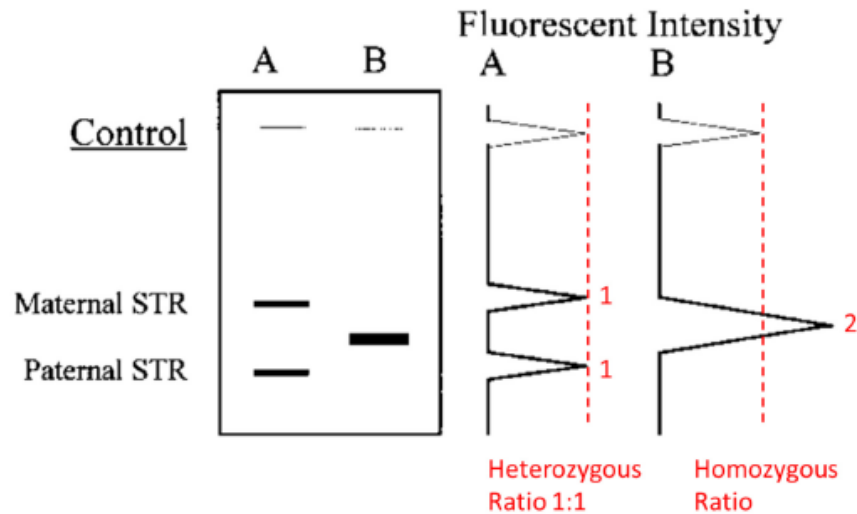
1. Adinolfi (Exhibit 1212)

Adinolfi is a publication from 1997 and relates to a method for rapid detection of aneuploidies using quantitative fluorescent polymerase chain reaction (“QF-PCR”). Ex. 1212, 1299. Adinolfi uses QF-PCR to analyze short tandem repeats (“STRs”)¹⁰ to detect fetal aneuploidies, such as on chromosomes 21 and 13. *Id.*

Adinolfi teaches amplification of STRs by PCR, and detection of fluorescent activity for the STRs. *Id.* at 1301 (disclosing “incorporation of fluorochromes into the products of PCR amplification *via* . . . primers specific for each STR”). Adinolfi discloses that fluorescent activity for two different alleles at one locus will generate two “peaks” following amplification and DNA scanning. *Id.*; *see also id.* at Fig. 1. According to Adinolfi, “in normal heterozygotes the ratio of the fluorescent activity of the two peaks should be close to 1:1.” *Id.* (“If the STR marker is highly polymorphic, few normal subjects should be homozygotes and show one peak of activity (Figs. 1 and 2).”). However, “[i]n a trisomic patient, the three doses of an STR marker can be detected either as three peaks . . . with a ratio of 1:1:1 (trisomic allelic) or as a pattern of two peaks with a ratio of 2:1 (trisomic diallelic).” *Id.*

¹⁰ STRs are short sequences of DNA, normally of 2–5 base pairs in length, which are repeated numerous times. Ex. 1201, 74:14–19.

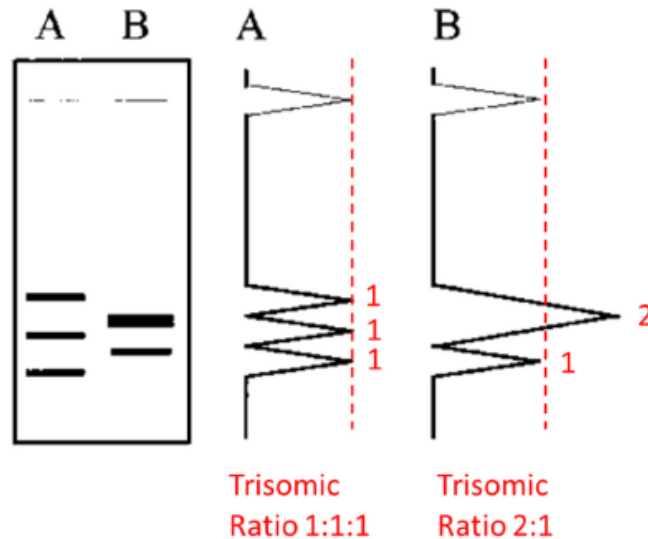
To illustrate the differences in normal diploid samples and samples indicating trisomy in the fetus as taught in Adinolfi, we reproduce excerpts of Adinolfi's Figure 1 below, with annotations in red added by Petitioner.



Pet. 31; Ex. 1212, 1301 (Fig. 1). The annotated image above is a schematic representation of testing samples "A" and "B" with results of electrophoresis on the left, and fluorescent intensities (represented as peaks for a control and respective maternal and paternal STRs) depicted on the right. Ex. 1212, 1301. As shown, sample "A" includes two different peaks of roughly equal height representing the relative amount of two different fetal alleles, which Petitioner annotates in red as being a "Heterozygous Ratio 1:1." *Id.*; Pet. 31. Sample B includes a single, larger fluorescent peak, which Petitioner annotates as having a value of "2" (intensity of 2:1 relative to control) and as showing a "Homozygous Ratio." Pet. 31; Ex. 1212, 1301. Adinolfi describes these samples as being "Normal Diploid Samples." *Id.*

Adinolfi also discloses conducting QF-PCR on samples and generating fluorescent peaks that are indicative of trisomy (e.g., Down

Syndrome) in a fetus. Ex. 1212, 1301–02. This is shown in another excerpt of Adinolfi’s Fig. 1, with annotations in red provided by Petitioner.



Id.; Pet. 33–34. The excerpt above shows electrophoresis results on the left, in the middle, three equally-sized fluorescent peaks for sample “A” in a “Trisomic Ratio 1:1:1” and, at the far right, sample “B” with one large peak and one smaller peak, reflecting a “Trisomic Ratio 2:1.” *Id.*; Ex. 1212, 1301. Thus, as depicted, the trisomic patient produces either three peaks that represent three different alleles (a ratio of 1:1:1 in sample A), or two peaks at a ratio of 2:1 that represent duplicate copies of one STR allele and only a single copy of another allele (as in sample B). *Id.*; *see also* Ex. 1202 ¶ 90.

Adinolfi teaches taking fetal samples through invasive techniques (e.g., obtaining amniotic fluid samples, chorionic villus samples, or umbilical cord blood samples). Ex. 1212, 1306–07. Adinolfi discloses “maternal contamination” was present in a few samples. *Id.* at 1307. According to Adinolfi, “[o]ne amniotic fluid sample” was “visibly contaminated with [maternal] blood” and “showed an unusual triallelic

pattern with the chromosome 13 markers.” *Id.* Adinolfi teaches that “[s]ince in the case of contaminated samples we always analyse the maternal STR profile, it was possible to exclude trisomy 13 and conclude that the unusual pattern was due to maternal contamination.” *Id.*

2. Pertl (Exhibit 1211)

Pertl is a study published in 2000, and relates to methods for detecting fetal DNA in maternal plasma. Ex. 1211, 45. The purpose of Pertl’s “study was to develop a fluorescent polymerase chain reaction (PCR) assay for the detection of circulating fetal DNA in maternal plasma.” *Id.* According to Pertl, “[m]ultiplex fluorescent PCR was used to detect fetus-specific alleles in the corresponding maternal plasma samples” and “[f]etus-specific alleles were found in all maternal plasma samples studied.” *Id.*

Pertl teaches that “[t]his approach may have implications for non-invasive prenatal diagnosis.” *Id.* at 45. According to Pertl, the “results demonstrate the feasibility of detection of male and female fetal DNA in maternal plasma with the use of highly polymorphic STR markers and fluorescent multiplex PCR.” *Id.* at 48. Pertl discloses that “the potential of quantitative analysis of fetal DNA in maternal plasma/serum using fluorescent PCR has still to be investigated.” *Id.*

3. Abbott (Exhibit 1207)

Abbott is a U.S. patent that issued in 1999. Ex. 1207, code (45). Abbott discloses automated methods for differentiating cells in whole blood samples. *Id.* at Abstr. Abbott describes, for example, use of a multipurpose reagent system for analysis of nucleated peripheral blood cells. *Id.* at 12:62–

65. Abbott teaches that its reagent system can “preserv[e] white cell morphology” and “fix white blood cells.” *Id.* at 12:65–13:2, 14:2–3, 14:42–46. Exemplary ingredients of Abbott’s reagent system includes aldehydes, like “formaldehyde.” *Id.* at 13:62–65. Petitioner’s declarant, Dr. Wapner, testifies that a POSA would know that “preserving” cell morphology and “fixing” WBCs with a chemical agent, like disclosed in Abbott, means that the agent inhibits cell lysis. Ex. 1202 ¶¶ 80–85 (testifying that formaldehyde is a well-known agent used to fix and prevent lysis of cells).

D. Obviousness over Adinolfi, Pertl, and Abbott

Petitioner asserts that claims 8–13, 125, 139, and 140 are unpatentable as obvious over Adinolfi and Pertl, in further view of Abbott. Pet. 39–68; *see id.* at 40–63 (dependent claim 8), 63–68 (other dependent claims).

The asserted prior art is summarized above. As noted above, claim 8 depends from independent claim 1 and dependent claim 4. *See supra* Section I(D). We start with Petitioner’s contentions and then move to Patent Owner’s responsive arguments and our analysis for those claims.

1. Claim 8

We discuss Petitioner’s challenge to claim 8 in greater detail below, but Petitioner summarizes it as follows:

In sum, (1) Adinolfi discloses an effective technique for identifying and quantifying chromosomal abnormalities; (2) Pertl discloses the benefit of using that technique on maternal plasma containing a mixture of maternal and fetal DNA—namely, that it was safer and less invasive than using DNA obtained by amniocentesis; and (3) Abbott discloses using a cell lysis inhibitor, like formaldehyde, to avoid interference from

maternal DNA lysed from WBCs in analyzing the fetal DNA. Accordingly, a POSA would have been motivated to combine the references to achieve the purported invention.

Pet. 61.

To show that the combination of Adinolfi, Pertl, and Abbott renders obvious the subject matter of dependent claim 8, Petitioner must first show that the asserted art teaches or suggests all the limitations of claims 1 and 4, from which claim 8 depends. Petitioner splits claim 1's language into six parts—[A] through [F]. Pet. 40–54. Petitioner addresses the language added by claim 4 as part [G] (“The method of claim 1, wherein the template DNA is obtained from a sample selected from . . . blood, serum, plasma, [etc.]”). *Id.* at 54. And finally, Petitioner addresses the language added in claim 8 as part [H] (“The method of claim 4, wherein said sample is mixed with an agent that inhibits cell lysis . . .”). *Id.* at 55–63.

Petitioner invokes the teachings of Abbott as satisfying the limitations of claim 8, but only for part [H] of the claim. *Id.* at 55–63. For parts [A]–[F] (claim 1's language) and [G] (claim 4's language), Petitioner relies on Adinolfi's and Pertl's disclosures, not Abbott's. *Id.* at 40–54.

Petitioner argues, without dispute, that Adinolfi teaches the claim's preamble, which it describes a part [A]: “A method for detecting the presence or absence of a fetal chromosomal abnormality.” *Id.* at 40–41 (citing Ex 1212, 1299 (Fig. 3)).¹¹

¹¹ Absent a dispute, we need not decide whether this preamble language is limiting. In addressing the different portions of the claim, Petitioner also

Petitioner argues that Adinolfi discloses what Petitioner has designated part “[B]” of the claim, reciting “quantitating a ratio of the relative amount of alleles at a heterozygous locus of interest.” *Id.* at 41–44. According to Petitioner, Adinolfi meets this claim language because it teaches, *inter alia*, using QF-PCR to produce fluorescent peaks for heterozygous alleles that will exhibit a 1:1 ratio in normal samples and a trisomic ratio (1:1:1 or 2:1) in samples with a trisomy. *Id.* (“Experimental data in Adinolfi discloses both a 1:1:1[] ratio and a 2:1 ratio in fetal DNA.”) (citing, for example, Ex. 1212, 1301–02, Figs. 2A and 2B). Petitioner cites similar teachings in Adinolfi as meeting part [F] of the claim, which recites “wherein said ratio indicates the presence or absence of a fetal chromosomal abnormality.” *Id.* at 50–51 (“Adinolfi further discloses that a 1:1:1 ratio or a 2:1 ratio indicates the **presence** of a trisomy, a fetal chromosomal abnormality.”) (citing Ex. 1212, 1301; Ex. 1202 ¶¶ 134–140).

The claim also recites “in a mixture of template DNA, wherein said mixture comprises maternal DNA and fetal DNA,” which language Petitioner designates as part “[C].” Pet. 44–46. Relevant to part [C], Petitioner contends that, during prosecution, Patent Owner obtained the ’277 patent based on the argument “that the prior art did not teach the limitation of a mixture of template DNA, wherein said mixture comprises maternal

makes several assertions to the effect that some of the techniques disclosed in Adinolfi or Pertl are the same as those described in the Specification. *See, e.g.*, 41 (“[T]he method disclosed in Adinolfi is identical to the QF-PCR/STR method disclosed in an embodiment of the ’277 patent.”) (citing Ex. 1201, 74:14–75:17). We discuss below.

DNA and fetal DNA.”¹² *Id.* at 44–45. And Petitioner contends Pertl teaches what was argued as missing during prosecution. *Id.*

To show that the art asserted here meets the language of part [C] of the claim, Petitioner contends Pertl discloses the use of QF-PCR for the purpose of detecting fetal DNA in samples that include both maternal DNA and fetal DNA. *Id.* at 45 (citing Ex. 1211, 45–46); Ex. 1202 ¶¶ 119–124. According to Petitioner, Pertl recognized that detecting and analyzing free fetal DNA from maternal plasma could be an alternative source of fetal material for prenatal diagnosis. Prelim. Resp. 45. In a footnote, Petitioner also asserts that “Adinolfi likewise disclosed one study that analyzed a sample that contained a mixture of fetal and maternal DNA.” *Id.* at 45 n.6.

Petitioner argues that Adinolfi also discloses parts [D] and [E] of the claim. Pet. 46–50; Ex. 1202 ¶¶ 125–133. According to Petitioner, Pertl discloses obtaining a sample from a pregnant female as in part [D], and Adinolfi teaches determining the sequences of heterozygous alleles at a locus of interest for part [E]. Pet. 48 (“Absent such sequencing [of alleles], one could not perform the PCR analysis” nor use the specific primers in Adinolfi) (citing Ex. 1212, 1301 (Table 1 (listing loci))).

Having asserted that Adinolfi and Pertl teach or suggest parts [A]–[F] (i.e., the recitations of claim 1), Petitioner moves to part “[G]” of claim 8.

¹² We disagree with this characterization of the file history as discussed further below; *see also* Pet. 63 (asserting “[d]uring prosecution, PO expressly argued that the claims were not obvious . . . because none of the references disclosed the use of samples containing a mix of fetal and maternal DNA.”).

Pet. 54. Petitioner argues that Pertl discloses obtaining blood samples from pregnant women and separating maternal plasma from the samples. *Id.* (citing Ex. 1211, 46 (teaching extraction of DNA from plasma samples)). Thus, Petitioner contends, Pertl teaches use of maternal plasma samples as recited in claim 8's part [G] (i.e., claim 4's added language). *Id.*

Lastly, Petitioner addresses part "[H]" of claim 8 and, here, cites to Abbott's disclosures. Pet. 55. Petitioner contends that "Abbott discloses an agent that **inhibits lysis of cells.**" *Id.* (citing Ex. 1207, 12:65–13:2; Ex. 1202 ¶¶ 145–146). Moreover, Petitioner contends, Abbott teaches use of such a lysis inhibitor to preserve white blood cell (WBC) morphology and to prevent DNA within WBCs from interfering with analysis of extracellular portions of a sample. *Id.* (citing, e.g., Ex. 1207, 13:45–53, 14:42–60). According to Petitioner, Abbott teaches a use of formaldehyde, a well-known lysis inhibitor, in Abbott's reagent system. *Id.*; Ex. 1207, 13:62–14:6; Ex. 1202 ¶ 148.

Petitioner, thus, contends that Adinolfi, Pertl, and Abbott teach the subject matter of claim 8 (and necessarily claims 1 and 4 from which claim 8 depends). And Petitioner argues a POSA would have been motivated to combine those references with a reasonable expectation of success. Pet. 56–62. According to Petitioner, Adinolfi's testing involved taking samples invasively (via amniocentesis), but it was known that invasive techniques posed greater risks in pregnancy. *Id.* at 56–57. Petitioner argues that Pertl disclosed *non-invasive* approaches that were capable of detecting fetal alleles in maternal plasma, and suggested free fetal DNA could be an alternative source of fetal DNA for prenatal diagnosis. *Id.* at 57 (citing, e.g.,

Ex. 1211, 45); Ex. 1202 ¶¶ 151–153. Also, Petitioner contends a POSA would have been motivated to investigate use of fetal DNA in maternal plasma for possible prenatal diagnoses because cell-free DNA “had already been proven as a diagnostic tool.” Pet. 57–58. Petitioner contends it would have been obvious to add a cell-lysis inhibitor like disclosed in Abbott to advance the goal of careful sample preparation and minimize contamination of the sample with excess maternal DNA liberated from maternal cells due to lysis. *Id.* (citing, e.g., Ex. 1206, 1577; Ex. 1202 ¶¶ 155–157).

Patent Owner raises several counterarguments. Prelim. Resp. 32–45. First, Patent Owner contends the Petition does not establish that Adinolfi and Pertl render obvious all the requirements of the claims. *Id.* at 32–33 (“Petitioner here fails to map the asserted prior art onto the Challenged Claims,” instead “breaking [the claim language] into small disjointed pieces” and “never identifies how the supposed combination . . . would meet the limitations of the claims **read as a whole**.”). In making this argument, Patent Owner focuses on whether Petitioner has shown that Adinolfi and Pertl teach all the limitations of independent claim 1 (what Petitioner calls parts [A]–[F]), from which challenged claim 8 depends.¹³ As explained above, Petitioner does not rely on the additional Abbott reference for teaching or rendering obvious the limitations of claim 1.

According to Patent Owner, “Petitioner fails to show that Adinolfi discloses quantitating the ratio as claimed” because “Adinolfi’s approach

¹³ Patent Owner also notes that “Petitioner maps only independent claim 1, and not independent claim 116, when addressing the Challenged Claims.” Prelim. Resp. 32 n.3.

attempts to determine the presence or absence of chromosomal abnormalities in a sample of **only fetal DNA**” which “are not applicable to mixed samples having both maternal and fetal DNA (and thus alleles from more than one individual).” *Id.* at 34–36. Moreover, Patent Owner contends, “[i]f a POSA were to apply Adinolfi’s approach to a mixed sample, the resulting ratio could not be interpreted because Adinolfi’s expected 1:1 ratio applies only to fetal DNA samples (that include alleles only from the fetus)—**not** mixed samples (that include alleles from both the fetus and the mother).” *Id.* at 36 (citing Ex. 2001 ¶¶ 102–107); *see also id.* at 36–37 (contending that, to the extent Adinolfi disclosed one contaminated sample, whatever peaks or ratio that sample may have produced could not be relied upon as indicating whether trisomy was present).

Second, Patent Owner argues that Pertl does not remedy Adinolfi’s shortcomings. Prelim. Resp. 39. Patent Owner contends that “Petitioner fails to show that Pertl discloses quantitating any ratio, much less the ratio claimed in the ’277 patent.” *Id.* According to Patent Owner, Pertl’s methods were limited to **detecting** fetal DNA in maternal plasma, not quantitating ratios of alleles in any mixed samples to indicate chromosomal abnormalities. *Id.* at 39–40; Ex. 2001 ¶ 110; Ex. 1211, 46–48.

Third, Patent Owner argues “Petitioner fails to explain **how** a POSA would have combined Adinolfi and Pertl” to arrive at the method actually claimed. Prelim. Resp. 40–41. Patent Owner contends that “Adinolfi’s ratio of alleles is potentially useful **only** for assessing chromosomal abnormalities in a sample of fetal DNA, **without maternal DNA**” and “Pertl does not disclose quantitating any ratio at all.” *Id.* at 40; Ex. 2001 ¶¶ 107, 110. And,

Patent Owner contends, “Petitioner does not explain with particularity any way in which a POSA would have modified the QF-PCR analysis in Adinolfi to produce meaningful results using the mixed samples in Pertl.” Prelim. Resp. 40.

Patent Owner also argues that the Petition does not establish a sufficient motivation to combine the asserted references with a reasonable expectation of arriving at the claimed subject matter. Prelim. Resp. 42–45. Patent Owner contends that Adinolfi focused its design on only fetal DNA—describing maternal DNA as contamination to be avoided—yet Petitioner posits that Adinolfi’s method would somehow be modified to intentionally add contaminating genetic material. *Id.* at 42–43. Patent Owner contends “Adinolfi was unable to apply its quantitative analysis to mixed samples and instead required a [separate] workaround . . . to draw a conclusion in view of the unreliable ratios obtained.” *Id.* at 44. To the extent Pertl is relied upon, Patent Owner also highlights Pertl’s disclosure that the potential of quantitative analysis on fetal DNA in maternal plasma “**has still to be investigated.**” *Id.* (citing Ex. 1211, 48); Ex. 2001 ¶ 115.

Based on the grounds advanced and the record here, we determine that Petitioner has not met its institution burden. We agree with Patent Owner that Petitioner has not shown that the method claimed is taught in the asserted combination of Adinolfi, Pertl, and Abbott. Like Patent Owner, we emphasize the deficiencies with Petitioner’s argument that the combination of Adinolfi and Pertl teaches all the limitations of independent claim 1—as Petitioner’s success with that argument is a prerequisite to showing dependent claim 8 challenged here would have been obvious.

In particular, we reference the following language of claim 1, which Patent Owner calls out in its papers: “quantitating a ratio of the relative amount of alleles at a heterozygous locus of interest in a mixture of template DNA, wherein said mixture comprises maternal DNA and fetal DNA . . . wherein said ratio indicates the presence or absence of a fetal chromosomal abnormality.” Prelim. Resp. 33; *see supra* Section I(D). On this record, considering this language in context and in view of the intrinsic evidence, especially the prosecution history, we determine that this claim language requires that the quantitated ratio is a ratio of alleles from both maternal and fetal DNA in the mixture. And it is that quantitated ratio that must “indicate[] the presence or absence of a fetal chromosomal abnormality.”

As an initial matter, Petitioner’s challenge here does not account adequately for the amendment and argument made during prosecution in route to securing allowance of the challenged claims. To the extent Petitioner mentions the prosecution history, we do not agree with its characterizations. Petitioner suggests that the issue during prosecution was whether the art taught detecting chromosomal abnormalities in samples containing a ***mixture of both fetal and maternal DNA***. Pet. 29–30, 44, 63. But considering Patent Owner’s argument and Dr. Van Ness’s testimony, and upon our review of the file history, the challenged claims were amended (with related argument from applicant) specifically to address and overcome a *different* issue. Prelim. Resp. 23–24; Ex. 2001 ¶¶ 36–46.

It is clear that the issue applicant’s arguments and amendments during prosecution sought to overcome was whether the asserted prior art taught quantitating a ratio of the relative amount of alleles in a mixed sample—

where the *ratio* represents alleles not just from one individual, but *alleles from both the mother and the fetus*. See, e.g., Ex. 1203, 563–64. Indeed, the applicant argued explicitly that the claims were amended “to indicate more clearly that the alleles, which are quantified and used to calculate a ratio, comprises a mixture of maternal DNA and fetal DNA.” *Id.* at 559 (explaining amendment to pending claim 1). If that left any doubt, applicant argued expressly that, “[i]n contrast” to the cited prior art, “the methods taught herein comprise calculating a ratio of the relative amount of alleles in a heterogeneous mixture of DNA . . . wherein ***the ratio represents alleles from both the mother and the fetus.***” *Id.* at 563–564 (emphasis added); see also *id.* at 564 (“[T]he methods described in the present application detect chromosomal abnormalities using a method that comprises . . . quantitating a ratio of alleles in a heterogeneous mixture of DNA, wherein ***the ratio represents alleles from more than one individual.*** This element is neither taught nor suggested” by the cited prior art) (emphasis added).

Those representations of applicant make sense when considering the art cited against the claims during prosecution, and why applicant believed they were needed to distinguish that art. The Examiner cited Umansky (or, alternatively, Amicucci) as teaching the claimed subject matter, including the language that “template DNA comprises a mixture of maternal DNA and fetal DNA.” *Id.* at 910 (“This limitation is inherent to Umansky in that both maternal and fetal free DNA present in the maternal blood stream will pass over into [a] maternal urine” sample), 943–44. The issue, thus, was not (as Petitioner suggests) whether the prior art taught methods for detecting chromosomal abnormalities in a sample that included both fetal and

maternal DNA. The Examiner determined, and the applicant did not dispute, that at least Umansky taught that. *See, e.g., id.* at 909–10. The deficiency of Umansky (or Amicucci), according to the Examiner, was that neither taught how to express *the relative amounts of alleles in ratios* as claimed to indicate the abnormality. *Id.* For that, the Examiner turned to Saiki as teaching quantitating the amounts of alleles and expressing as a ratio to indicate a chromosomal abnormality (i.e., sickle cell anemia). *Id.* But Saiki’s deficiency, applicant later argued after amending and clarifying its claim scope, was that it only taught how to calculate ratios indicative of a chromosomal abnormality in a homogeneous DNA sample—where “**the ratio calculated represents alleles from a single individual.**” *Id.* at 563 (emphasis added). Thus, applicant’s repeated representations that the claimed invention was, in direct contrast, drawn to quantitating ratios that represent the alleles from more than one individual (i.e., mother and fetus) was key to the alleged distinction of the claims over the cited art. After such arguments, the claims were allowed.

Petitioner contends that certain disclosures in the Specification are allegedly comparable to some of the techniques in Adinolfi or Pertl. *See, e.g.,* Pet. 36–37 (citing Ex. 1201, 75:2–4). But we are not persuaded on this record that such disclosures change the result on the meaning of the claims when the aforementioned amended claim language and the prosecution history is taken into account. Even if, for argument’s sake, these disclosures in the Specification might be read as relating to quantitating alleles of a single individual or using homogeneous samples, such disclosures would

appear to be related to alternative embodiments outside the scope of these claims based on the file history as discussed above.¹⁴

Turning to Petitioner’s asserted prior art, Petitioner admits “Adinolfi was not specifically designed to test a mixture of maternal and fetal DNA and largely involved fetal samples obtained via amniocentesis.” IPR2021-00789, Paper 4 at 45; Prelim. Resp. 3–4, 34. Insofar as Adinolfi quantitated allelic ratios and used those ratios as indicating a fetal chromosomal abnormality, its rapid detection method is limited to samples with only fetal DNA. Pet. 41–42, 50–51 (citing Adinolfi’s detected ratios of 1:1 as indicating a normal sample, and 1:1:1 or 2:1 as indicating trisomy); Prelim. Resp. 35 (“Adinolfi’s Figure 1 (in which the peaks correspond only to alleles from the same individual (*i.e.*, the fetus))”). We agree with Dr. Van Ness that Adinolfi’s conclusions about the presence of trisomy based on an observed ratio of 1:1:1 or 2:1 “is valid . . . only if the observed peaks reflect alleles from the same individual (*i.e.*, the fetus), in which case only a 1:1 ratio would be normal at a heterozygous locus.” Ex. 2001 ¶ 102; *see also id.* ¶ 103 (“This is in contrast to the ’277 Patent, which recognized that the expected ratio of alleles ***in a mixed sample*** changes in accordance with

¹⁴ We find, on this record, the statements in the prosecution history are also clear about the scope of the challenged claims in contrast to the cited art, where ratios indicating a chromosomal abnormality were quantitated for alleles only on one subject’s DNA, likely also amounting to a disclaimer against recapturing such scope. *Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 798 (Fed. Cir 2019) (“[T]o operate as a disclaimer, the statement in the prosecution history must be clear and unambiguous, and constitute a clear disavowal of scope.”).

changes in the sample’s proportion of fetal DNA.”). The cited teachings of Adinolfi do not meet the claim limitations, which recite, *inter alia*, “quantitating a ratio of the relative amount of alleles . . . in a mixture of template DNA, wherein the mixture comprises maternal DNA and fetal DNA . . . and wherein said ratio indicates the presence or absence of a fetal chromosomal abnormality.”

Petitioner briefly mentions one sample in Adinolfi that included fetal and maternal DNA. Pet. 45 n.6.¹⁵ But we agree with Patent Owner that Adinolfi’s disclosure of this “contaminated” sample does not satisfy the limitations of claim 1. Prelim. Resp. 36–38; Ex. 1212, 1307. As discussed above (Section II(C)(1)), Adinolfi describes one fetal sample taken via amniocentesis that was visibly contaminated with maternal blood. Adinolfi reports that QF-PCR revealed an “unusual triallelic pattern” (*i.e.*, three peaks) with that sample. *Id.* Even if that pattern was interpreted as quantitating a ratio of alleles in a mixed sample of both fetal and maternal DNA, it still does not meet the claim language because, as is clear from Adinolfi, such a “ratio” **does not** “indicate[] the presence or absence of a fetal chromosomal abnormality” (Petitioner’s part “[F]” of the claim). Quite the opposite, reliance on that triallelic pattern would have *incorrectly* led to a diagnosis of aneuploidy. Prelim. Resp. 37; Ex. 2001 ¶¶ 76–78. Indeed, Adinolfi did not rely on that pattern. *Id.* It was only through a separate

¹⁵ Petitioner puts greater emphasis on this one contaminated sample in Adinolfi as allegedly satisfying the claim limitations in the related challenge from IPR2021-00789, in which claim 1 is expressly challenged as obvious over Adinolfi and Pertl. IPR2021-00789, Paper 4 at 37–38.

“workaround” analyzing the maternal DNA profile that Adinolfi was able to rule out trisomy and determine that there was no fetal abnormality. Prelim. Resp. 37–38; Ex. 1212, 1307; Ex. 2001 ¶¶ 76–78, 106.

Petitioner relies on Pertl primarily for its disclosures of *detecting* fetal alleles in *mixed samples* with both fetal and maternal DNA. Pet. 44–45. As argued persuasively by Patent Owner, Petitioner does not contend or show that Pertl teaches “quantitating a ratio of the relative amount of alleles at a heterozygous locus of interest” in a mixed sample or “wherein said ratio indicates the presence or absence of a fetal chromosomal abnormality.” Prelim. Resp. 39. We agree with Patent Owner that “Pertl’s goal was simply **detection**, aiming ‘to develop a **fetal DNA detection method** that can be used independently of the fetal gender.’” *Id.* (quoting (with Patent Owner’s emphasis) Ex. 1211, 46); Ex. 2001 ¶¶ 108–110. Pertl does not, therefore, close the gaps between Adinolfi’s disclosures and the claimed method as discussed above.

To the extent Pertl even mentions quantitative analysis, it states: “the *potential of quantitative analysis of fetal DNA in maternal plasma/serum* using fluorescent PCR *has still to be investigated*.” Ex. 1211, 48 (emphasis added). This statement, coming three years after Adinolfi and made by one of Adinolfi’s co-authors, undermines Petitioner’s position that Adinolfi and Pertl would have been predictably combined with a reasonable expectation of success of arriving at the method as claimed. Ex. 1211, 45; Ex. 2001 ¶¶ 115–116. And Petitioner neither argues nor shows that Abbott includes any relevant teachings on quantitating ratios of alleles in a mixture of fetal

and maternal DNA that might overcome the deficiencies of Adinolfi and Pertl on that subject as addressed above.

Finally, we agree with Patent Owner that “Petitioner fails to explain **how** a POSA would have combined Adinolfi and Pertl to reconcile their teachings and arrive at the Challenged Claims.” Prelim. Resp. 40–41. The Petition must lay out its challenge with “particularity.” *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (“It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the “evidence that supports the grounds for the challenge to each claim.”) (quoting 35 U.S.C. § 312(a)(3)). Adinolfi’s ratio could indicate trisomy (or absence of trisomy) in samples of fetal DNA *without* contaminating maternal DNA. Pertl discloses detecting fetal alleles in samples with both maternal and fetal DNA, but does not disclose quantitating allelic ratios in such samples to indicate any abnormality. On this record, the Petition simply does not provide a sufficient evidence-backed theory on how Adinolfi and Pertl would be combined to predictably quantitate ratios of alleles in a mixed sample such that the ratio indicates if a chromosomal abnormality is present.¹⁶ Doing so might be straightforward. Or there may have been known or unknown complexities still to be explored. *See, e.g.*, Ex. 1211, 48 (disclosing years after Adinolfi that quantitative analysis of fetal DNA in maternal plasma using QF-PCR had not yet been investigated).

¹⁶ Petitioner does not assert that Abbott discloses this language of claim 1 or dependent claim 8 as already discussed.

Put differently, we are not persuaded on this record that Petitioner has shown how the art would have been combined with a reasonable expectation of success in arriving at the claimed subject matter.

For the above reasons, Petitioner has not established a reasonable likelihood of prevailing on its challenge to claim 8 (given its dependency on claim 1) on this record. Thus, Petitioner has not met its institution burden on claim 8 on this record.

2. Claims 9–13, 125, 139, and 140

Petitioner contends that dependent claims 9–13, 125, 139, and 140 would have been obvious over Adinolfi, Pertl, and Abbott. Pet. 63–68. Petitioner’s challenge to these additional claims relies on mapping of limitations of claim 8 (including the threshold mapping of parts [A]–[F] for independent claim 1’s language). *Id.* Petitioner’s challenge to the additional dependent claims does not overcome the aforementioned deficiencies and is lacking on this record for the same reasons as addressed above. We, thus, determine that Petitioner has not met its burden to show that dependent claims 9–13, 125, 139, and 140 are unpatentable.

3. Secondary Considerations of Nonobviousness

Patent Owner contends that secondary considerations show that the claims are nonobvious. Prelim. Resp. 9–20. We do not further address this argument because we determine Petitioner has not met its institution burden on other issues necessary to prevail on the obviousness challenge. See *Hamilton Beach Brands, Inc. v. f’real Foods, LLC*, 908 F.3d 1328, 1343 (Fed. Cir. 2018) (holding “objective indicia of nonobviousness” “need not

[be] address[ed]” because the court “affirm[ed] the Board’s findings regarding the failure of the prior art to teach or suggest all [claim] limitations”).

III. CONCLUSION

Petitioner has not established a reasonable likelihood of prevailing in showing that the challenged claims are unpatentable.¹⁷

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and we do not institute *inter partes* review of any claim of the ’277 patent based on the grounds asserted in this Petition.

¹⁷ Considering the merits, Petitioner has not met its institution burden on this record. We decline to reach the argument that the Petition should be denied on the basis of discretion under § 314(a). Prelim. Resp. 48–58.

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