

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QUEST DIAGNOSTICS INCORPORATED,
Petitioner,

v.

RAVGEN, INC.,
Patent Owner.

IPR2021-00788
Patent 7,332,277 B2

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

MAJORS, *Administrative Patent Judge.*

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

I. INTRODUCTION

Quest Diagnostics Incorporated (“Petitioner” or “Quest”),¹ on April 16, 2021, filed a Petition to institute *inter partes* review of claims 55–63, 66–69, 80–94, 96, and 126–133 of U.S. Patent No. 7,332,277 B2 (Ex. 1001, “the ’277 patent”). Paper 4 (“Pet.” or “Petition”). Ravgen, Inc. (“Patent Owner”)² filed a Preliminary Response. Paper 10 (“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 17 (Order authorizing briefing); Paper 19 (“Prelim. Reply”); Paper 20 (“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 established a reasonable likelihood of prevailing on its assertion that the challenged claims are unpatentable based on the grounds advanced here. We decline to deny the Petition on a discretionary basis as requested by Patent Owner. Thus, for reasons explained below, we institute *inter partes* review of claims 55–63, 66–69, 80–94, 96, and 126–133 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,

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.

2003. Ex. 1001, codes (21), (22), (45). The '165 Application is a continuation-in-part ("CIP") of Application No. PCT/US03/06198, filed February 28, 2003, which claims priority to several 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). Related U.S. Patent No. 7,727,720 ("the '720 patent") issued on June 1, 2010. Ex. 2041, 1671.³ The '720 patent issued on an application filed August 26, 2005, and claims priority to several ancestral applications including the '165 Application and the aforementioned provisional application filed on May 8, 2002. *Id.* at 4.

Petitioner identifies multiple lawsuits involving the '277 and '720 patents. Pet. 6; *See* IPR2021-00791, Paper 3 at 5–6. With relevance to the pre-institution arguments raised here, 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, Inc.*, No. 1:20-cv-00692-ADA (W.D. Tex.) ("the Natera lawsuit"). *Id.* According to Petitioner, Patent Owner has also asserted the '277 patent against other defendants such as Laboratory Corporation of America Holdings and Illumina, Inc. in other lawsuits pending in district courts in the Western District of Texas and the District of Delaware. Pet. 6.

Petitioner and Patent Owner also identify other matters involving the '277 and '720 patents pending before the Patent Office. Pet. 6; Paper 5, 1;

³ When citing exhibits and page numbers of exhibits herein, we may use the page numbers added to the exhibit copy when present; we may also use other citation formats (e.g., column and line, or paragraph numbers).

Paper 11, 1. Different claims of the '277 patent are challenged in IPR2021-00789 and IPR2021-00790 (both filed by Petitioner),⁴ IPR2021-00902 and IPR2021-01054 (both filed by Laboratory Corporation of America Holdings), and IPR2021-01272 (filed by Illumina, Inc.). Paper 5, 1; Paper 11, 1. The '720 patent is challenged in IPR2021-00791 (filed by Petitioner), IPR2021-01026 (filed by Laboratory Corporation of America Holdings), and IPR2021-01271 (filed by Illumina, Inc.). See IPR2021-00791, Paper 9, 1. In addition to the above, Patent Owner identifies Ex Parte Reexamination Control Nos. 90/014,792 and 90/014,703, addressing, respectively, the '277 and '720 patents. Paper 11, 1; IPR2021-00791, Paper 6, 1.

⁴ Petitioner asserts that it was justified in filing three petitions against the '277 patent. See *generally* Paper 2 (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 Paper 9 (citing the Board's Consolidated Trial Practice Guide for the proposition that a single petitioner will rarely need to file multiple petitions against the same patent). We concurrently 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.

B. Asserted Grounds of Unpatentability

Petitioner asserts four grounds of unpatentability in this Petition (Pet. 8–9), which are provided in the table below:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
81–94, 96, 133	103(a) ⁵	Chiu, ⁶ Hahn, ⁷ Abbott ⁸
81–94, 96, 133	103(a)	Lo, ⁹ Jen, ¹⁰ Abbott
55–63, 66–69, 80, 126–132	103(a)	Chiu, Hahn, Abbott, Saito ¹¹
55–63, 66–69, 80, 126–132	103(a)	Lo, Jen, Abbott, Saito

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 Rossa W. K. Chiu et al., *Effects of Blood-Processing Protocols on Fetal and Total DNA Quantification in Maternal Plasma*, 47:9 CLINICAL CHEMISTRY 1607–1613 (2001) (Ex. 1005, “Chiu”).

⁷ Sinuhe Hahn et al., *Quantification of Circulating DNA: In the Preparation Lies the Rub*, 47:9 CLINICAL CHEMISTRY 1577–1578 (2001) (Ex. 1006, “Hahn”).

⁸ Gill et al., U.S. 5,891,734, issued Apr. 6, 1999, listing Abbott Labs. as assignee (Ex. 1007, “Abbott”).

⁹ Y. M. Dennis Lo et al., *Quantitative Analysis of Fetal DNA in Maternal Plasma and Serum: Implications for Noninvasive Prenatal Diagnosis*, 62:4 AM. J. HUM. GENET. 768–775 (1998) (Ex. 1008, “Lo”).

¹⁰ Jin Jen et al., *An Overview on the Isolation and Analysis of Circulating Tumor DNA in Plasma and Serum*, 906 ANN. N.Y. ACAD. SCI. 8–12 (2000) (Ex. 1009, “Jen”).

¹¹ Hiroshi Saito et al., *Prenatal DNA diagnosis of a single-gene disorder from maternal plasma*, 356 THE LANCET 1170 (2000) (Ex. 1010, “Saito”).

Petitioner relies on the declaration of Ronald J. Wapner, M.D., among other evidence. Ex. 1002. Patent Owner responds with a declaration from Brian Van Ness, Ph.D., along with other evidence. Ex. 2001.

C. Technology Overview and the '277 Patent

The '277 patent relates to non-invasive methods for sampling DNA and detection of genetic disorders in a fetus. Ex. 1001, 1:31–39. The '277 patent explains that a variety of invasive and non-invasive techniques are available for prenatal diagnosis, including amniocentesis, fetal blood cells in maternal blood, and maternal serum alpha-feto protein. *Id.* at 2:53–57. According to the patent, however, “techniques that are non-invasive are less specific, and the techniques with high specificity and high sensitivity are highly invasive.” *Id.* at 2:57–60; *see also id.* at 3:33–37 (citing an increased fetal mortality risk of about 0.5% with amniocentesis).

The '277 patent acknowledges the prior non-invasive use of fetal cells and cell-free fetal DNA, both isolated from maternal blood, for prenatal diagnosis. *Id.* at 5:7–59. With regard to fetal cells, the patent notes that the “presence of fetal nucleated cells in maternal blood makes it possible to use these cells for noninvasive prenatal diagnosis,” and that such “cells can be sorted and analyzed by a variety of techniques to look for particular DNA sequences.” *Id.* at 5:8–13. Yet the patent states that “it is still difficult” to get many fetal cells from maternal blood and “[t]here may not be enough to reliably determine anomalies of the fetal karyotype or assay for other abnormalities.” *Id.* at 5:30–34. The '277 patent states that fetal DNA “has been detected and quantitated in maternal plasma and serum” and that “fetal

DNA present in the maternal serum and plasma is comparable to the concentration of DNA obtained from fetal cell isolation protocols.” *Id.* at 5:39–49. “However,” according to the patent, “the diagnostic and clinical applications of circulating fetal DNA is limited to genes that are present in the fetus but not in the mother” and “a need still exists for a non-invasive method that can determine the sequence of fetal DNA and provide definitive diagnosis of chromosomal abnormalities in a fetus.” *Id.* at 5:53–59.

We provide a brief overview of the components of blood, which is helpful in understanding the claims and the asserted prior art. As explained by Drs. Wapner and Van Ness, human blood includes a collection of cells—including red blood cells (RBCs) and white blood cells (WBCs)—in a fluid called plasma. Ex. 1002 ¶ 2; Ex. 2001 ¶ 22. “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 of the cellular DNA is contained within WBCs because red blood cells typically lack a nucleus and do not contain DNA; similarly platelets in the blood do not contain nuclear DNA. Ex. 1002 ¶ 39. These general features of circulating blood are depicted in the Figure 1A, reproduced below.

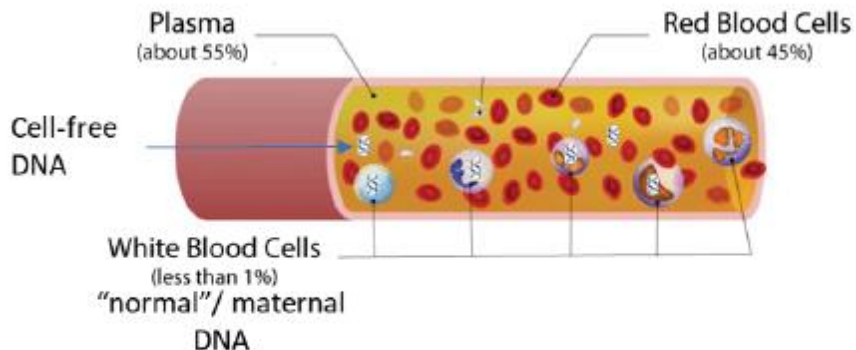


Figure 1A

Ex. 1002 ¶¶ 39–40. 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.* ¶ 41 (“**Cell-free** DNA is DNA that has been liberated (or freed) from a cell.”), ¶¶ 47–48 (discussing lysis of the cell and nuclear membranes through various means (e.g., mechanical or osmotic forces, chemical reagents) and the resulting release of cellular DNA into the surrounding medium).

As the parties’ declarants explain, in addition to circulating cell-free *maternal* DNA, pregnant women may have circulating free *fetal* DNA (“cffDNA”) within the maternal plasma. Ex. 2001 ¶ 22; Ex. 1002 ¶ 53.¹² According to Dr. Van Ness, those skilled in the art “were aware of the

¹² Dr. Wapner testifies that much of the earlier work analyzing circulating cell-free DNA related to studies of cancer, because it had been determined that cancer patients had higher amounts of free DNA than normal individuals. See, e.g., Ex. 1002 ¶¶ 49, 55–56 (discussing isolation of cell-free *tumor* DNA as distinct from cellular “germ-line” DNA from normal/non-cancerous cells), 61.

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. Citing the '277 patent, 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.”). Further, Dr. Van Ness explains, “[w]hile the increase of maternal DNA in the plasma does not decrease the amount of cell free fetal DNA, it does effectively reduce the percentage of DNA that comes from the fetus in the plasma.” *Id.*¹³

Known methods of preparing a blood sample for analysis include separating the liquid (either plasma or serum¹⁴) from the blood’s cellular components. This is depicted in Figure 1B, reproduced below.

¹³ The *fetal cellular* component represents only a small fraction of a maternal blood sample. Ex. 1001, 5:30–34; Ex. 1002 ¶ 60 (testifying that “[t]here are only 2-4 intact fetal cells” for “every 4-6 million maternal cells”); see Ex. 1008, 772 (disclosing that there are about 1.2 fetal cells/ml of maternal blood during the second trimester).

¹⁴ Serum is the fluid obtained after blood clots. Ex. 1002 ¶ 42 (“To obtain serum from a blood sample, clotted blood is centrifuged, with the clot spun to the bottom of the collection tube, leaving a straw-colored and largely cell-free liquid—the serum—above the clot.”).

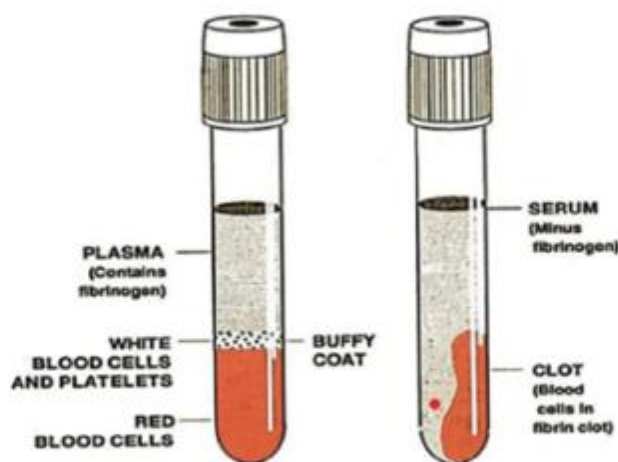


Figure 1B: plasma preparation (left); serum preparation (right).

Ex. 1002 ¶ 48. Figure 1B from Dr. Wapner's Declaration shows two collection tubes, with the tube on the left showing plasma separated from WBCs, platelets, and RBCs, and the right tube showing serum separated from the cellular material (collected in a fibrin clot). As Dr. Wapner explains, isolating plasma involves using an anticoagulant to prevent the blood's clotting, and the tube containing the whole blood sample is then centrifuged to cause RBCs to collect at the tube's bottom with WBCs and platelets forming in a thin layer (the "buffy coat") immediately above the RBC layer, with the separated plasma remaining in the upper phase or supernatant as shown in Figure 1B. *Id.* ¶ 42. Cell-free DNA in the separated plasma may then be further purified and analyzed. See Ex. 1001, 89:1–91:50 (Example 4); Ex. 1005, 1609.

The '277 patent describes a method that is said to increase the proportion or percentage of the cffDNA component in a sample from a pregnant female for subsequent analysis. According to the '277 patent, the

ability to detect chromosomal abnormalities has been “hindered by the low percentage of free fetal DNA” in maternal samples. Ex. 1001, 89:1–6.

“Increasing the percentage of free fetal DNA would enhance the detection” of mutations, trisomy, and other genetic abnormalities. *Id.* at 89:6–11.

With the aim of increasing the percentage of cffDNA relative to circulating maternal DNA in a maternal sample, the '277 patent describes adding an agent that inhibits cell lysis. Ex. 1001, 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.”); *id.* at 89:11–13 (“The percent of fetal DNA in plasma obtained from a pregnant female was determined both in the absence and presence of inhibitors of 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 patent identifies numerous agents as cell lysis inhibitors, cell membrane stabilizers, or cross-linking reagents. *See, e.g., id.* at 31:57–32:21 (listing, for example, formaldehyde, formalin, cleavable crosslinkers, cholesterol, vitamin E and its derivatives, and glucose); *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”)).

More specifically, the '277 patent provides results on the use of formalin (i.e., formaldehyde in aqueous solution) as the lysis-inhibiting agent. Ex. 1001, 89:1–91:50 (Example 4), 219:38–226:26 (Example 15). In Example 4, the patent describes collecting a 5 ml blood sample from a

pregnant subject, separating the sample into two tubes (each containing EDTA¹⁵), and adding formaldehyde (25µl/ml) to one of the tubes. *Id.* at 89:18–25. The samples were centrifuged and 800 µl of each maternal plasma sample was then used for DNA purification and further processing to determine the relative amount of cffDNA in the samples. *Id.* at 89:25–91:13. According to the '277 patent, “the percentage of fetal DNA present in the sample that was treated with only EDTA was 1.56%” and the “percentage of fetal DNA present in the sample treated with formalin and EDTA was 25%.” *Id.* at 91:14–20. The patent reports that the percent of total cffDNA in eighteen blood samples with and without formalin was then calculated, with the results (mean percentage cffDNA) provided in Table V. *Id.* at 91:35–43 (reporting, *inter alia*, 19.47% with formalin versus 7.71% without formalin); *see also id.* at 219:38–226:26 (Example 15 (reporting further results on formalin use in Table XXI)).

D. Challenged Claims

The '277 patent includes one hundred and forty claims. Thirty-seven of those claims are challenged here. Pet. 1. Independent claims 55 and 81 are illustrative of the claims challenged in this Petition and read as follows:

55. A method comprising determining the sequence of a locus of interest on free fetal DNA isolated from a sample obtained from a pregnant female, wherein said sample comprises free fetal DNA and an agent that inhibits lysis of cells, if cells are present, wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.

¹⁵ The '277 patent states that EDTA is a “magnesium chelator.” Ex. 1001, 31:52–54; Ex. 1009, 8 (describing EDTA’s use as an anticlotting agent).

81. A method for preparing a sample for analysis comprising isolating free fetal nucleic acid from a the sample, wherein said sample comprises an agent that inhibits lysis of cells, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.

Ex. 1001, 472:66–473:5, 474:52–57.

To illustrate some of the challenged dependent claims, claim 84 depends from claim 81 and adds that “the sample is obtained from a source selected from the group consisting of blood, serum, plasma, saliva, urine, tear, vaginal secretion, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascetic fluid, fecal matter, and body exudates.” *Id.* at 474:65–475:2. Claim 90 also depends from claim 81 and adds, “said cell lysis inhibitor is selected from the group consisting of glutaraldehyde, derivatives of glutaraldehyde, formaldehyde, formalin, and derivatives of formaldehyde.” *Id.* at 474:15–18.

E. Prosecution History

The independent claims challenged in this Petition (claims 55 and 81) correspond, respectively, to pending claims 58 and 87 in prosecution.

Ex. 1003, 526.

The Examiner initially rejected pending claim 87 as anticipated by Exhibit 2038 (which Patent Owner calls “the Lo Patent”¹⁶), and the Examiner rejected claims 58 and 87 as obvious over the Lo Patent and

¹⁶ We adopt Patent Owner’s terminology here for consistency. Exhibit 2038 is Patent Publication No. WO 98/39474 (“the Lo Patent”).

certain other references. Ex. 1003, 1224–27. In response, applicant argued that the Examiner had provided no evidence that EDTA in the Lo Patent’s samples inhibits cell lysis; and, citing the Specification’s Example 4, applicant argued that adding a lysis inhibitor “unexpectedly increase[d] the proportion of fetal DNA versus maternal DNA” in plasma samples. *Id.* at 1190–92, 1196.

The Examiner withdrew the rejections based on the Lo Patent, but entered new rejections for obviousness based on the combination of Amicucci (Ex. 1052) or Umansky (Ex. 2040), with Kiessling (Ex. 1004). *See id.* at 923–927 (Umansky plus Kiessling), 954–957 (Amicucci plus Kiessling). The Examiner found that Umansky taught a method of determining the sequence of a fetal locus of interest in a maternal urine sample (comprising cffDNA), but it did “not teach adding an agent that inhibits cell lysis to their maternal urine samples.” *Id.* at 924. The Examiner turned to Kiessling as teaching the addition of a fixative (e.g., formaldehyde) to “simultaneously disinfect[] and inhibit[] the lysis of cells” in Kiessling’s samples. *Id.* at 924, 929–30. The Examiner reasoned that it would have been obvious to add formaldehyde to Umansky’s methods because a skilled artisan “would have been motivated to make th[is] modification . . . in order to reduce the risk of viral infection for those laboratory personnel performing the assay(s).” *Id.* at 924; *see also id.* at 954–955 (offering substantially the same reasoning for the Amicucci combination).

In Remarks dated May 30, 2007, applicant argued that there was no motivation to combine the cited references. *See, e.g., id.* at 568–572 (response to the Umansky rejections). More specifically, applicant argued

that the DNA analyzed in the methods of Umansky (or Amicucci) and Kiessling was “quite distinct”—with the former analyzing DNA circulating outside a cell, “while the DNA in Kiessling is contained within a fixed isolated cell.” *Id.* at 570–71, 587–89. Applicant also argued there was no motivation to add a disinfecting agent “because the biological sample used in Umansky is urine, which is considered to be sterile, and Kiessling discloses a method to reduce the risk of exposure to infectious agents.” *Id.* at 571 (“[B]ecause urine is considered to be sterile . . . there is no risk of exposure to infectious agents.”).

Applicant further argued that the claimed methods satisfied a long-felt need and gave unexpected results. Applicant argued that earlier studies had “reported a mean of only 3.4% fetal DNA” in maternal plasma, which limited the clinical use of such methods. *Id.* at 569. According to applicant, the methods of claims 58 and 87 “elevate [*sic*, alleviate] this problem, and thus provide a solution to a long-felt need in the medical community” for alternative, non-invasive fetal testing. *Id.* Again citing Example 4, applicant argued the percentage of cffDNA with its method was “significantly, and unexpectedly, higher for samples treated with formalin [(25%)]” compared to a sample without formalin (1.56%). *Id.* at 570 (citing Examples 4, 15).

The Examiner, on September 26, 2007, entered a Notice of Allowability covering claims 58 and 87 and the several other claims that ultimately issued. Ex. 1003, 519–520. The Examiner’s Reasons for Allowance stated that the various claims are “deemed to be allowable in light of the applicant’s amendment filed 30 MAY 07 and the persuasive argument(s) therein.” *Id.* at 521.

Patent Owner also references portions of the '720 patent's prosecution history. Prelim. Resp. 15–16. There are some similarities between the claims of the '720 patent (pending and issued) and claims challenged in this Petition. For example, pending claim 1 of the application that issued as the '720 patent, like issued claim 81 of the '277 patent, included a step of isolating free nucleic acid and required the sample include an agent that inhibits cell lysis. *Compare* Ex. 2041, 1369, *with* Ex. 1001, 474:52–57.

There are also some similarities between the art asserted by the Examiner during prosecution of the '720 and '277 patents. For example, the Examiner initially asserted Kiessling against the pending claims of the '720 patent (but in combination with different references). *See, e.g.*, Ex. 2041, 1338 (asserting obviousness based on “Anker” in view of Kiessling).

Following those initial rejections, applicant amended the claims in a response dated December 17, 2007, and raised similar arguments to those made during the '277 patent's prosecution. *Id.* at 1380–1382 (arguing no motivation to combine because Kiessling is not focused on cell-free DNA, and nonobviousness based on a long-felt need, and unexpected results). Patent Owner emphasizes that the Examiner then withdrew the rejections and “stated that ‘***[t]he most persuasive argument(s) related to the applicant assertion that there was a long felt need and the evidence of an unexpected result***’ on pages 13 and 14 of the applicant's response.” Prelim. Resp. 15–16 (quoting (with Patent Owner's emphasis) Ex. 2041, 2459).

Whatever weight that comment from the Examiner about a long-felt need or unexpected results might carry, however, is diminished by the fact that, shortly thereafter, the Examiner withdrew the previous action (where

the comment was made) and reinstated rejections of the claims for anticipation and obviousness. Ex. 2041, 2481–2491; *see also id.* at 2527–2528 (Office Action entering new rejections based on Amicucci, Saito, or Anker, in view of Kiessling). Applicant later amended the claims and pressed similar arguments before ultimately overcoming the new rejections. *Id.* at 2608, 2617–21 (Amendment and Remarks dated June 2, 2009). But when the Examiner finally allowed the claims, there was no explicit reference to any alleged secondary considerations of nonobviousness. *Id.* at 2642 (indicating in reasons for allowance that all the pending claims were “deemed allowable over the prior art of record in light of applicant’s amendment filed 02 JUN 09 and the persuasive argument(s) therein”).

II. DISCRETION UNDER 35 U.S.C. § 325(d)

A. *Standard for Exercising Discretion under Section 325(d)*

Institution of *inter partes* review is discretionary. *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (“[T]he PTO is permitted, but never compelled, to institute an IPR proceeding.”). The Patent Office may, for example, deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that “[i]n determining whether to institute or order a proceeding under this chapter . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.”

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified

several non-exclusive factors for consideration. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“the *Becton, Dickinson* factors”). Those factors are as follows:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments.

Id.; see also Patent Trial and Appeal Board Consolidated Trial Practice Guide 61–63 (Nov. 2019), <https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf> (“CTPG”) (discussing the *Becton, Dickinson* factors).

As further explained in *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (Feb. 13, 2020) (“Advanced Bionics”) (precedential), factors (a), (b), and (d) from *Becton, Dickinson* relate to whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. Factors (c), (e), and (f) “relate to whether the petitioner has

demonstrated a material error by the Office” in its prior consideration of the art or arguments. *Id.*

Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated error. *Advanced Bionics* at 8–10. “If the petitioner fails to show that the Office erred, the Director may exercise his discretion not to institute *inter partes* review.” *Id.* at 8–9 (“If a condition in the first part of the framework [i.e., substantially same art or arguments] is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review”). “At bottom, this [§ 325(d)] framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.* at 9. On the question of material error, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.*

B. Becton, Dickinson Factors (a), (b), and (d)

Patent Owner argues that Petitioner’s grounds “rely on six prior art references that were either considered by the Patent Office during prosecution or are cumulative over references that were considered by the Patent Office.” Prelim. Resp. 29. More specifically, Patent Owner contends: (i) that Lo and Saito were considered during prosecution (*id.* at 30); (ii), that “Petitioner’s two base references in each of its grounds—Chiu and Hahn (Grounds I and III) and Lo and Jen (Grounds III and IV) . . . are cumulative over the Amicucci and Umansky references applied in rejections by the Examiner during prosecution” (*id.* at 29); and (iii) that “Abbott is

cumulative over the Kiessling reference applied in rejections by the Examiner during prosecution” (*id.* at 29). Although we agree with Patent Owner that Lo and Saito were considered during prosecution, we disagree that the other prior art relied upon by Petitioner is cumulative of the art considered during prosecution. We address each of Patent Owner’s assertions in turn.

1. Whether Lo and Saito were considered in prosecution

Lo was considered during prosecution; it is cited in the background of the ’277 patent and was identified in a February 20, 2004, Information Disclosure Statement (“IDS”). Ex. 1001, 5:40–41, Ex. 1003, 3553 (Ref. 79). Saito was listed in another IDS.¹⁷ *Id.* at 1213 (Ref. 7). This is undisputed. Pet. 3–4 (“Only Lo and Saito were disclosed to the Patent Office.”).

2. Whether Petitioner’s “base references” are cumulative of Amicucci, the Lo Patent,¹⁸ and Umansky

Petitioner relies on Hahn and Jen as teaching, *inter alia*, that it is “important to avoid contamination of the sample with other material[s]

¹⁷ Although Saito was cited in an IDS, Patent Owner does not cite any teachings in Saito that are allegedly cumulative to the highly relevant teachings of at least Hahn and Jen on which Petitioner relies, as discussed below. Thus, although Saito, like the Lo Patent, was cited, we are not persuaded, when the art advanced by Petitioner is considered as a whole, that the same (or cumulative) art and arguments were previously before the Office such that § 325(d) is sufficiently implicated.

¹⁸ In its Preliminary Sur-Reply, Patent Owner also contends that Hahn and Jen are cumulative over the Lo Patent. Prelim. Sur-Reply 3 (citing Ex. 2038). Patent Owner represents that the Lo Patent “includes the same

including non-target DNA lysed from white blood cells.” Pet. 30, 40; Prelim. Reply. 4. Patent Owner contends that the “same concept . . . was before the Examiner in at least Umansky and Amicucci.” Prelim. Sur-Reply 3. Further Patent Owner contends that “both Amicucci and the Lo Patent discuss careful DNA extraction to avoid contamination for clean plasma.” *Id.* For the reasons discussed below, Patent Owner does not persuade us that denial under § 325(d) is warranted.

We begin by considering Hahn’s teachings with respect to the contamination of blood samples with DNA from cell lysis. Hahn discloses:

[S]tudies showed that circulatory fetal DNA exists mainly in a cell-free form and is not released from dead or dying fetal cells in the maternal circulation. . . . By contrast, the amount of maternal circulatory DNA was significantly increased in serum samples compared with plasma because of the liberation of maternal DNA from maternal cells lysed during clotting.

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disclosures” as Lo (Ex. 1008). Prelim. Resp. 20. While we have not verified that the entirety of the disclosure of the Lo Patent is similar to Lo, we agree that Lo includes a passage that is substantially similar to the passage of the Lo Patent that Patent Owner identifies as cumulative Hahn and Jen. *Compare* Ex. 1008, 770 (paragraph entitled “Anticontamination Measures”), *with* Ex. 2038, 13 (paragraph entitled “Anti-contamination measures”). For purposes of this §325(d) analysis, we assume that Lo and the Lo Patent include substantially the same disclosures. That does not, however, resolve the issue of whether either Lo or the Lo Patent include the same or cumulative disclosures compared to at least Hahn and Jen—they do not as explained herein. In our discussion of discretion under § 325(d), we cite to the Lo Patent rather than Lo for consistency with Patent Owner’s briefing on this topic, which also cites the Lo Patent. Prelim. Sur-Reply 3.

From previous experiments using plasma or serum, it should be clear that the concentration of fetal DNA would not be influenced much by the procedure chosen. The contamination of the plasma sample by maternal cells or cell remnants would, however, affect the apparent concentration of maternal DNA in the sample.

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If you are examining only circulatory fetal DNA, any of several initial processing steps appears adequate. If you are considering the analysis of both circulatory fetal and maternal DNA, however, care must be taken in clearing the plasma of any maternal cellular remnants.

Ex. 1006, 1577–78. Hahn thus teaches that lysis of maternal cells can contaminate circulatory DNA in samples taken from maternal blood, that “contamination” with DNA from lysed maternal cells can affect the apparent concentration of maternal DNA in the sample, and that when performing certain analyses, plasma samples should be cleared of “maternal cellular remnants.” *Id.* Petitioner contends that these teachings would have motivated the skilled artisan to prevent contamination of a sample with DNA from lysed maternal cells by employing the “straightforward solution” of “preventing cell lysis.” Pet. 30.

We next consider Jen’s teachings with respect to the contamination of blood samples with DNA from cell lysis. Jen discloses:

Never place the blood samples in the freezer as freezing will lyse the red blood cells and release the iron, which is a major PCR inhibitor. White blood cells may also lyse, contributing to increased normal DNA contamination in the sample.

Ex. 1009, 9. Thus Jen discloses that DNA from lysed WBCs may contaminate blood samples. Petitioner contends that this teaching would

have motivated a skilled artisan to use an agent that inhibits lysis to “avoid contamination of a sample resulting from lysis.” Pet. 41.

We turn now to the references that Patent Owner contends are cumulative of Hahn and Jen. Amicucci discloses prenatal diagnosis of myotonic dystrophy using fetal DNA obtained from maternal plasma. Ex. 1052, 301. The disclosure from Amicucci that Patent Owner identifies as cumulative of Hahn’s and Jen’s teachings reads as follows:

A blood sample (~ 10 mL) was collected at 10 weeks of gestation before chorionic villus sampling (CVS) and was centrifuged at 3000g for 10 min. Plasma was carefully removed from EDTA-containing tube and centrifuged again at 3000g for 10 min. DNA was then extracted from 2 mL of the centrifuged plasma with a QIAamp Blood Kit (Qiagen). The elution volume of the final step was 300 µL.

Id. This passage can be summarized as teaching to handle blood samples carefully after they have been centrifuged.

The Lo Patent discloses a “detection method performed on a maternal serum or plasma sample from a pregnant female . . . [that] detect[s] the presence of a nucleic acid of foetal origin in the sample.” Ex. 2038, 2. The disclosure from the Lo Patent that Patent Owner identifies as cumulative of Hahn’s and Jen’s teachings reads as follows:

Anti-contamination measures

Strict precautions against PCR contamination were used (Kwok *et al* 1989). Aerosol-resistant pipette tips were used for all liquid handling. Separate areas were used for the setting up of amplification reactions, the addition of DNA template and the carrying out of amplification reactions. The 7700 Sequence Detector offered an extra level of protection in that its optical detection system obviated the need to reopen the reaction tubes following the completion of the amplification reactions, thus

minimising the possibility of carryover contamination. In addition, the TaqMan assay also included a further level of anti-contamination measure in the form of pre-amplification treatment using uracil N-glycosylase which destroyed uracil containing PCR products (Longo *et al* 1990). Multiple negative water blanks were included in every analysis.

Id. at 13. In sum, the Lo Patent teaches various physical means of preventing contamination (aerosol-resistant pipette tips, separate set up areas, and an optical detection system that does not need to be opened) as well as a pre-treatment step that uses an enzyme (N-glycosylase) to eliminate uracil containing PCR products.

Patent Owner contends that both Amicucci and the Lo Patent “discuss careful DNA extraction to avoid contamination for clean plasma.” Prelim. Sur-Reply 3. We agree. However, the disclosure of physical means used to avoid contamination from unidentified sources in Amicucci and the Lo Patent is materially different from the specific teachings in Hahn and Jen that cell lysis is a source of DNA contamination—especially Hahn’s specific and relevant teaching concerning the challenge here that lysis of maternal cells was a source of contaminating DNA relative to samples in which circulating fetal DNA is being analyzed. The Lo Patent’s use of N-glycosylase to eliminate uracil containing PCR products is also materially different from Han’s and Jen’s teachings that cell lysis is a source of DNA contamination. Patent Owner does not identify disclosure in Amicucci or the Lo Patent that specifically discloses that cell lysis is a source of contamination. This is significant because Petitioner repeatedly invokes the identification of maternal cell lysis as a known source of DNA contamination that provides reason to introduce an agent to inhibit such cell

lysis. Pet. 2–3, 30–31, 40. And, as explained below, we find such reasoning persuasive on this preliminary record. For the above reasons, we do not agree with Patent Owner that Hahn and Jen (or the combinations of Chiu with Hahn, or Lo with Jen) are cumulative to Amicucci or the Lo Patent. The relied-upon disclosure and argument concerning Hahn and Jen in the asserted combinations is sufficiently unique on this record.

Patent Owner has a stronger case on cumulateness relative to Umansky’s disclosure, which Patent Owner contends provides the same relevant “concept” as Hahn and Jen. Prelim. Sur-Reply 3. As Patent Owner points out, a portion of Umansky’s background states “[i]t can be difficult to ensure that this DNA did not originate from white blood cells as a result of their lysis during sample treatment.” Ex. 2040 ¶ 12. But that still does not weigh heavily in Patent Owner’s favor on the § 325(d) issue for at least the following two reasons.

First, Umansky’s cited disclosure is far less specific compared to at least Hahn’s, which ties the problem of maternal cell lysis and maternal DNA contamination together in a direct and explicit way to blood processing techniques that seek to distinguish and isolate the circulating fetal DNA component, as evidenced by Hahn’s excerpts above. *Second*, even if we agreed that Umansky’s disclosures concerning cell lysis and sample processing were substantially the same as Jen’s or Hahn’s, Petitioner’s rationale for combining references hardly resembles the Examiner’s in prosecution. Petitioner seizes on cell lysis and contamination as being a *known problem* (e.g., as allegedly evidenced by Hahn, etc.) to be solved by adding a known cell-lysis inhibitor (as allegedly evidenced in Abbott). The

Examiner's rationale during prosecution, in stark contrast, was based on a supposed need to add a fixing agent to avoid "viral infection" in the laboratory. *See, e.g.*, Ex. 1003, 924 (citing Kiessling's teaching on "adding an agent to a biological sample which simultaneously disinfects and inhibits the lysis of cells therein" and urging that the "ordinary artisan would have been motivated to make the modification . . . in order to reduce the risk of viral infection for those laboratory personnel performing the assay(s) of Umansky"). Therefore, the obviousness arguments during prosecution versus Petitioner's arguments are materially *different*.¹⁹

3. Whether Abbott is cumulative of Kiessling

Petitioner relies on Abbott as teaching a method for preparing blood samples using of an agent (formaldehyde) to inhibit lysis "so that non-WBC portions can be analyzed without interference from DNA freed from lysed WBCs." Pet. 30. Patent Owner argues that "[u]sing formaldehyde to simultaneously lyse red blood cells and fix white blood cells is taught by Kiessling, considered during prosecution." Prelim. Sur-Reply 4. We agree with Patent Owner that both Abbott and Kiessling disclose the use of formaldehyde to inhibit lysis. *See* Ex. 1004, 3:26–29; Ex. 1007, 12:65–13:2. However, we disagree that Abbott is cumulative to Kiessling based, at

¹⁹ We need not decide the issue of Examiner error to resolve the § 325(d) arguments here. But if Umansky taught that cell lysis and contamination was a known problem the same as Hahn or Jen (like Patent Owner argues), we would likely find it was error to have overlooked and/or not applied such a relevant disclosure over a manifestly weaker "infection" rationale.

minimum, on the manner in which the applicant sought to distinguish Kiessling during prosecution.

As discussed above, *supra* Section I(E), following a rejection over the combination of art including Amicucci or Umansky in combination with Kiessling, applicant argued that there would have been “no motivation to combine” the cited references because “the DNA analyzed in the two methods is quite distinct (*i.e.*, DNA in Umansky . . . is free and circulating outside of a cell, while the DNA analyzed in Kiessling is in and/or is released from a fixed cell).” Ex. 1003, 570–71. Based on the preliminary record, it appears that Abbott includes relevant teachings about using an agent to impede lysis so that, for example, portions of the sample outside the cells can be analyzed without interference from WBC cellular contaminants. Ex. 1007, 16:12–18, 18:12–19. Applicant’s argument during prosecution that Kiessling focused only on analyzing intracellular material belies its argument now that Abbott, which does not appear to have such limited teachings, is no more relevant than Kiessling.²⁰ For this reason, we do not agree with Patent Owner that Abbott is cumulative of Kiessling.

4. Conclusion

Having considered the prosecution history and the grounds set forth in the Petition, we determine that the Petition does not present the same or

²⁰ Insofar as Patent Owner now cites to disclosure in Kiessling that might purport to also relate to analysis of noncellular or extracellular materials (e.g., viral DNA or external markers), this would seemingly contradict the narrower characterization of Kiessling by applicant during prosecution and, thus, is entitled to little weight here. *See, e.g.*, Prelim. Resp. 39.

substantially the same prior art or arguments as were considered during prosecution. Quite the opposite, for the reasons explained above, we conclude there are enough material differences in the asserted art and arguments that a § 325(d) denial is not justified on this record. Because the first part of the framework of *Advanced Bionics* is not met, we need not further address “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics*, Paper 6 at 8–9.

Accordingly, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

III. DISCRETION UNDER 35 U.S.C. § 314(a)

A. *Standard for Exercising Discretion under Section 314(a)*

Patent Owner argues that we should exercise our discretion and deny the Petition based on the pending Quest and Natera lawsuits. Prelim. Resp. 48–58. Under § 314(a), the Director has discretion to deny institution. See *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) (“[T]he agency’s decision to deny a petition is a matter committed to the Patent Office’s discretion.”); *Harmonic*, 815 F.3d at 1367 (same).

In *NHK*, the Board denied institution relying, in part, on § 314(a) because the parallel district court proceeding was scheduled to finish before the Board reached a final decision. *NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 (PTAB Sept. 12, 2018) (precedential) (Decision on Institution). “*NHK* applies to the situation where the district court has set a trial date to occur earlier than the Board’s deadline to issue a

final written decision in an instituted proceeding.” *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 3 (PTAB Mar. 20, 2020) (precedential) (“*Fintiv*”). When determining whether to exercise discretion to deny institution under *NHK* due to an earlier trial date, we consider the following factors (“*Fintiv* factors”):

1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
2. proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision;
3. investment in the parallel proceeding by the court and the parties;
4. overlap between issues raised in the petition and in the parallel proceeding;
5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
6. other circumstances that impact the Board’s exercise of discretion, including the merits.

Id. at 6. “These factors relate to whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding.” *Id.* In evaluating these factors, we take “a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review.” *Id.* (citing CTPG 584).

We address the *Fintiv* factors below.

B. Factual Background

As discussed above, there are several other pending lawsuits involving numerous defendants accused of infringing the ’277 patent. Section I(A).

The argument between Petitioner and Patent Owner here relates primarily to two lawsuits pending in the United States District Court for the Western District of Texas—one lawsuit against Petitioner (Quest) and another lawsuit pending against Natera. Pet. 67–69; Prelim. Resp. 51–61; Prelim. Reply 6–8; Prelim. Sur-Reply 6–8. The Quest lawsuit has an “estimated” trial date of July 11, 2022. Prelim. Reply 6; Prelim. Sur-Reply 6. The Natera lawsuit, which does not involve Petitioner, is scheduled for trial on December 13, 2021. Ex. 2034, 2; Ex. 2033, 5. The statutory one-year date for a final written decision in the present matter is in October 2022.

C. Analysis of the Fintiv Factors

1. Factor 1: Whether a Stay Exists or Is Likely to Be Granted if a Proceeding Is Instituted

If a Petitioner has sought and obtained a stay of related litigation pending resolution of PTAB proceedings, that generally weighs against a discretionary denial. *See Fintiv* at 6. There is no evidence that Petitioner has requested a stay here, nor that any request for a stay has been denied. Pet. 68.²¹ This factor is neutral. *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15 at 12 (PTAB May 13, 2020) (informative) (explaining that factor 1 generally “does not weigh for or against discretionary denial” when neither party has requested a stay).

²¹ Petitioner filed a motion to transfer the Quest lawsuit (Pet. 67) and Patent Owner reports in additional briefing that such motion was recently denied (Prelim. Sur-Reply 6). The transfer motion does not, on this record, weigh significantly in our decision.

2. Factor 2: Proximity of the Court’s Trial Date to the Board’s Projected Statutory Deadline

Patent Owner argues that “the Quest Litigation has scheduled trial involving the ’277 patent to begin on July 11, 2022, three months before the statutory deadline for the Board’s Final Written Decision.” Prelim. Resp. 54.²² Patent Owner contends this earlier trial date favors discretionary denial. We disagree.

Based on the evidence before us, the July 11, 2022, date for trial is only *estimated*. Prelim. Reply 6. The schedule submitted here is unsigned by the court. Ex. 2035, 14. Although we usually take courts’ trial schedules at “face value,”²³ that is not necessarily so with trial dates that are only estimates. *See, e.g., Progenity, Inc. v. Natera, Inc.*, IPR2021-00279, Paper 12 at 29 (PTAB June 11, 2021) (concluding “there is no trial date scheduled for the parallel proceeding” based on an email from the court’s clerk merely providing an estimated trial date); *Intel Corp., v. FG SRC LLC*, IPR2020-01449, Paper 13 at 15 (PTAB Mar. 3, 2021) (explaining that estimated trial dates are not firm trial dates). Therefore, “[w]hether the trial takes place before, contemporaneously with, or after our final written decision statutory deadline involves speculation.” *Progenity*, IPR2021-00279 at 29.

In additional briefing, the parties further dispute whether trial is likely to commence on July 11, 2022. Petitioner contends the presiding judge (Judge Albright) has more pending patent cases on his docket than any other

²² We further consider the Natera lawsuit in light of the *Fintiv* factors, below in our discussion under Factor 6.

²³ *Fintiv*, IPR2020-00019, Paper 15 at 13 (informative).

district court in the country, and that roughly 200 cases are scheduled for trial between now and the estimated trial date—including multiple additional cases that are also tentatively scheduled for trial on July 11, 2022. Prelim. Reply 7. Patent Owner responds that, although some of Judge Albright’s trials have been rescheduled to later dates, some cases have proceeded as scheduled and some have started earlier than scheduled. Prelim. Sur-Reply 7. From this, Patent Owner contends the court has signaled it plans to bring patent cases to trial at or near their estimated trial dates. *Id.*

Petitioner raises legitimate questions about whether the court will be able to hold trial for the Quest lawsuit on July 11, 2022. But we cannot answer those questions. Nor can we say whether Patent Owner’s forecasts about potential trial timing will hold true. How the court might manage its large docket of patent cases, including scheduling any trial in this matter, involves guesswork from us on this record. In any event, even if the July 11, 2022, date had been firmly set, it is still within a few months of the Board’s deadlines and, balanced with other considerations (e.g., Petitioner’s diligence, low investment, and absence of overlapping validity arguments) discussed below, it would not weigh heavily in favor of discretionary denial.

Given the significant uncertainty about when trial in the district court might occur for the Quest lawsuit, we determine that this factor does not weigh in favor of discretionary denial.

3. Factor 3: Investment in the Parallel Proceeding by the Court and Parties

Petitioner contends that the Quest lawsuit is in its infancy. Pet. 67–68. According to Petitioner, fact discovery has not opened, and (as of the

date of the Petition’s filing) contentions had not been exchanged. *Id.*; Prelim. Reply 6 (noting that final infringement or invalidity contentions have not been served, and that no claim construction has yet issued from the court).²⁴ Thus, Petitioner argues, the investment so far has been minimal. Pet. 67–68. Petitioner also emphasizes that it acted “expeditiously” and filed the Petition “only *six months*” after Patent Owner served its complaint and well before the one-year statutory bar. *Id.*

Patent Owner argues that, by the time of any decision on institution, a *Markman* hearing will have been held, and a *Markman* order will be forthcoming in the Quest lawsuit. Prelim. Resp. 55. Patent Owner then pivots to discussing the Natera lawsuit. *Id.* at 56; Prelim. Sur-Reply 8.

We agree with Petitioner that investment in the Quest lawsuit, particularly as related to any validity issues, has been low. Even taking the unsigned, proposed scheduling order as a guide about case deadlines proposed therein by Patent Owner (Ravgen), as of this institution decision, fact discovery opened on September 16, 2021, and will not close until February 2022. Ex. 2031, 16–17. Expert discovery will not open until February 2022 and will close in April 2022 at the earliest. *Id.* A *Markman* order has been entered but most of the investment from the court and the parties in the Quest lawsuit, especially on invalidity issues, still lies ahead.

Moreover, Petitioner’s diligence in filing promptly weighs heavily against discretionary denial. The Board has previously explained that, “[i]f

²⁴ After the parties submitted their supplemental pre-institution briefing, Petitioner informed us that the court has now entered a claim construction order, which we authorized to be submitted as an exhibit. Ex. 1062.

the evidence shows that the petitioner filed expeditiously, such as promptly after becoming aware of the claims being asserted, this fact has weighed against” discretionary denial. *Fintiv* at 11–12 (noting that filing at or around the time of a patent owner’s response to invalidity contentions may reveal a lack of diligence). Petitioner filed this challenge even *before* it had received preliminary infringement contentions from Patent Owner identifying the claims Patent Owner intended to assert. Ex. 2031, 14 (listing the deadline for Patent Owner to serve preliminary infringement contentions as April 30, 2021 (the Petition was filed April 16, 2021); *see also* Paper 2 (explaining, at the time of filing, that “PO has not yet identified the claims it intends to assert or served infringement contentions”).²⁵

We determine that this factor does not weigh in favor of discretionary denial of the Petition.

4. Factor 4: Overlap Between Issues Raised in the Petition and in the Parallel Proceeding

Patent Owner argues that there is substantial overlap in the claims asserted and challenged in the Quest lawsuit, and the claims challenged by Petitioner here. Prelim. Resp. 57. Patent Owner further argues “there is complete overlap between the arguments and evidence in the Petition and those at issue in the Quest Litigation.” *Id.* at 59.

²⁵ To be clear, we are not suggesting that petitioners must or should file IPRs before even knowing what claims are asserted against them in order to show diligence. There may be good reasons to wait (e.g., on preliminary infringement contentions) before filing to increase efficiencies and avoid challenges to claims that are never truly in dispute between the parties.

It is undisputed that there is significant overlap between the validity issues and claims asserted here and in the Quest lawsuit. Nevertheless, Petitioner stipulates that “if the Petition is instituted, it will not seek to invalidate the challenged claims in district court based on the same grounds set forth in this Petition.” Prelim. Reply 7; Pet. 68.

Petitioner’s stipulation, although not as comprehensive as the stipulation discussed in the Board’s *Sotera Wireless*²⁶ decision, still mitigates to some degree concerns of duplicative efforts and possibly conflicting decisions between the Board and the court in the Quest lawsuit. Indeed, Petitioner’s stipulation echoes the one cited in *Sand Revolution II, LLC v. Continental Intermodal Group-Trucking LLC*, IPR2019-01393, Paper 24 at 16 (PTAB June 16, 2020) (informative), which the Board determined weighed marginally against discretionary denial.

Consistent with *Sand Revolution II*, the Board has not mandated that a stipulation must be as broad as the one in *Sotera Wireless* or cover the same scope as the estoppel provisions of § 315(e) in order to be considered in a *Fintiv* analysis. We are unpersuaded by Patent Owner’s contentions to the contrary. Prelim. Sur-Reply 7–8. Patent Owner also argues that Petitioner’s stipulation does not stop other defendants from asserting the same prior art. *Id.* That is true but not decisive because those are parties that Petitioner cannot control, and parties that Patent Owner chose to separately sue.

²⁶ *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at (PTAB Dec. 1, 2020) (precedential).

Accordingly, despite the overlap, in view of Petitioner's stipulation, we determine this factor to not weigh in favor of discretionary denial.

5. Factor 5: Whether the Petition and the Defendant in the Parallel Proceeding Are the Same Party

Petitioner is the defendant in the Quest lawsuit. Prelim. Resp. 60. Factor 5, thus, favors discretionary denial, assuming that the Quest lawsuit would reach trial before a final written decision in this proceeding, about which, for reasons explained above, we decline to speculate. *Fintiv*, IPR2020-00019, Paper 15 at 15 (“Because the petitioner and the defendant in the parallel proceeding are the same party, this factor weighs in favor of discretionary denial.”).

6. Factor 6: Other Circumstances that Impact the Board's Exercise of Discretion, Including the Merits

Petitioner argues “the merits of this Petition warrant institution” and the “challenged claims are fully taught by grounds not before the Patent Office” previously. Pet. 68. Patent Owner cross-references its arguments for denial under § 325(d) and further contends that Petitioner “fails to meaningfully address the substantial evidence of secondary indicia” showing nonobviousness. Prelim. Resp. 61.

We have considered Patent Owner's § 325(d) arguments, but they do not weigh in favor of discretionary denial under § 314(a) for reasons explained above.

On the merits, Patent Owner does not at this time contest that Petitioner's asserted prior art teaches or suggests the subject matter of the challenged claims. Patent Owner, instead, refers to alleged secondary

considerations of nonobviousness (e.g., unexpected results). *See, e.g.*, Prelim. Resp. 5–11. Such considerations, while possibly promising for Patent Owner, require further development, including on the key issue of nexus, as discussed below. And Patent Owner is incorrect in suggesting that Petitioner has failed to respond to the evidence at this preliminary stage. To the contrary, Petitioner points out, for example, that other investigators have questioned Patent Owner’s testing and, in their own studies, were unable to replicate the allegedly surprising results. Pet. 65–66; *see also* Prelim Reply 5 n.2 (contending that Patent Owner’s argument about other researchers applying different test conditions (Prelim. Resp. 8–9) fails because the claims purport to encompass such conditions). Petitioner further contends that, even considering Patent Owner’s results, they are not commensurate with the scope of the claims because, for example, the results are specific to “a **single** type of cell lysis inhibitor (formaldehyde),” yet the claims cover numerous inhibitors. Pet. 65. Those and other issues require further evidentiary development through trial.

Petitioner has met its institution burden as addressed below, but we are not prepared on this preliminary record to characterize the merits of Petitioner’s challenge as especially “strong.” At the same time, we do not see glaring weaknesses in Petitioner’s case based on the arguments made to date. The merits are neutral to marginally weighing against discretionary denial for purposes of the *Fintiv* analysis.

Considering the Natera lawsuit under the *Fintiv* rubric, we agree with Patent Owner that some considerations favor denial. In particular, *Fintiv* factors 2 (proximity of trial date) and 3 (investment) arguably weigh against

instituting trial on this Petition. The trial date in the Natera lawsuit is currently set for December 13, 2021, and, by the time of this Decision, almost all pretrial work will be complete. Prelim. Resp. 55–56 (noting dispositive motions due September 24, 2021, and a joint pretrial order due on October 28, 2021). That investment is substantial. However, it appears that little, if any, of this substantial investment relates the issues presented by the Petition.

We find that the extent of overlap (factor 4) between the invalidity challenges in the Natera lawsuit and this Petition is not substantial. Many of the claims challenged in this Petition are challenged in the Natera lawsuit (although the Natera lawsuit includes many more not at issue here). Ex. 2043 (Natera’s Invalidity Contentions) 5. But turning to the relevant prior art, the overlap is minor. The Hahn reference, which is pivotal in Petitioner’s case, is nowhere in Natera’s contentions. Chiu is mentioned but never in any combination with Hahn or Abbott. *See, e.g., id.* at 18, 45–46.

Patent Owner points out that Natera asserts a combination of the Lo Patent, Jen, and Abbott, which Patent Owner compares to Petitioner’s assertion of Lo, Jen, and Abbott. Prelim. Resp. 58. Natera’s assertion must, however, be put in context. Natera’s invalidity contentions are over 300 pages long (even in the excerpted copy of record), and include over 50 different patent and non-patent publications listed as prior art against the ’277 patent that allegedly “anticipate and/or render obvious” the claims. *See generally* Ex. 2043; *id.* at 16–23. Indeed, there are over 70 *different bases* of alleged anticipation and obviousness listed in those contentions. *Id.* at 24–50. The last one of such bases is a combination of the Lo Patent, Jen, and

Abbott. *Id.* at 46. And, all those seventy-plus prior art bases are in addition to other invalidity challenges set forth in the contentions, including challenges under § 101 and § 112. *Id.* at 50–57.

The notion that most, much less all, of Natera’s myriad invalidity bases listed in its contentions will be litigated at trial to a verdict and judgment is implausible. In fact, reflecting the practical reality that only so many issues can be presented at a trial of limited duration, the court’s order in the Natera lawsuit requires that parties “meet and confer to discuss narrowing the number of claims asserted and prior art references at issue [in the final contentions] to *triable limits*.” Ex. 2033, 4 (emphasis added) (encouraging the parties to contact the clerk to discuss each side’s trial time). Presumably infringement issues on the two asserted patents will be tried too, further limiting the time available to address whatever subset of validity arguments Natera might ultimately decide to advance.

To be sure, Natera has made an investment in identifying some overlapping references in its ocean of invalidity contentions. But beyond that, the parties’ and court’s investment to date in those references or in any grounds that substantially overlap with grounds asserted by Petitioner here is unclear. Nor is it clear that any overlapping references and combinations will actually be litigated at trial; if anything, it is doubtful. At bottom, on this record, the risk of duplicating work or inconsistency between the Board

resolving Petitioner’s challenge and the court resolving Natera’s invalidity arguments at trial appears to be minimal.²⁷

Although the proximity of the trial date and the investment by the parties in the Natera litigation weigh in favor of exercising discretion to deny institution, those considerations are less weighty when paired with the absence of significant overlap, the fact that Quest is *not a party* to that case (factor 5), and the fact that Quest has no control over what might be argued there or how that lawsuit might end.

Plus, as explained above, Quest moved quickly to file its own IPR petition—the first challenging the ’277 patent—which detracts from the weight we might otherwise accord to the Natera lawsuit in deciding whether discretionary denial is appropriate.²⁸ Efficiency is important, but so is

²⁷ Even if Natera did further advance a challenge based on the Lo Patent, Jen, and Abbott, and even assuming that is substantially the same as Petitioner’s challenge based on Lo, Jen, and Abbott, the Board may never need to reach that particular challenge because Petitioner may first prevail on its primary challenge to the same claims based on the combination of Chiu, Hahn, and Abbott, which is undisputedly not presented in the Natera lawsuit. *Boston Scientific Scimed, Inc. v. Cook Group Inc.*, 809 F. App’x 984, 990 (Fed. Cir. 2020) (“We agree that the Board need not address issues that are not necessary to the resolution of the proceeding” once Petitioner has prevailed on all its challenged claims).

²⁸ Patent Owner repeatedly cites the Board’s decision in *Mylan Labs. Ltd. v. Janssen Pharm. NV*, IPR2020-00440, Paper 17 (PTAB Sept. 16, 2020), which Patent Owner sees as analogous to the present case. Prelim. Resp. 52, 54, 56; Prelim. Sur-Reply 8. *Mylan* is inapposite for at least the reasons that, unlike Petitioner here, the petitioner in *Mylan* waited until well after contentions were exchanged before filing, there was no apparent stipulation to not pursue any instituted grounds in the related litigation, and the extent

“fairness.” *Fintiv* at 6. Under the specific circumstances here, including where the Petitioner was especially diligent in presenting sufficiently unique invalidity challenges, and the Petitioner has no apparent relation to or control over Natera, we determine that the circumstances related to the Natera lawsuit do not overall tilt the analysis in favor of denial. For the above reasons, this factor does not favor discretionary denial.

7. Balancing the *Fintiv* Factors

We have considered the circumstances before us in light of the *Fintiv* factors. Altogether, considering and balancing the factors holistically, we decline to invoke our authority to deny the Petition on a discretionary basis under § 314(a).

IV. 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

of overlap with the related lawsuits appears to have been greater in *Mylan*. *Mylan*, IPR2020-00440, Paper 17 at 15–21. Moreover, the *Mylan* decision is not precedent binding on this panel in any event.

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).

B. 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 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, with 2-3 years of relevant research experience in an academic or industry setting in, *e.g.*, prenatal or cancer diagnosis.

Pet. 22–23 (citing Ex. 1002 ¶ 118). Patent Owner does not directly oppose Petitioner’s proposal. Prelim. Resp. 23. Patent Owner’s own proposal is similar but 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 cited 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)). We also note that Patent Owner’s declarant, Dr. Van Ness, testifies that the parties’ proposed POSA levels are not “materially different” and that his opinions would not change under either proposal. Ex. 2001 ¶ 21.

C. 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.*

Petitioner does not identify any claim terms as needing construction. Pet. 24–25. Patent Owner directs us to Petitioner’s argument in the Quest lawsuit that, if the term “an agent that impedes cell lysis” is not indefinite, it

should be construed as a mean-plus-function term. Prelim. Resp. 23–24 (citing Ex. 2036, 2–7). Patent Owner contends that Petitioner’s failure to propose a means-plus-function claim construction for the term “agent that impedes cell lysis” is “fatal because the Petition does not provide Petitioner’s required identifications under 37 C.F.R. § 42.104(b)(3).” *Id.* at 25. We are not persuaded.

At this point in the proceeding, neither party asserts that the term “agent that impedes cell lysis” is a mean-plus-function claim limitation. Pet. 23 (asserting that “no terms need be construed for purposes of resolving the issues in this Petition because the prior art discloses all limitations under any plausible construction”); Prelim. Resp. 23 n. 2 (noting that “Patent Owner’s silence regarding the appropriate construction of any term should not be taken as an agreement with Petitioner’s apparent construction”), 24 n. 4 (noting that “[i]n the Natera Litigation, neither party contended that this claim term is a mean[s]-plus-function term”); Prelim. Reply 1–3 (addressing Patent Owner’s arguments without proposing a claim construction); Prelim. Sur-Reply 1–2 (addressing Petitioner’s arguments without proposing a claim construction).

Given that neither party currently contends before us that the term “agent that impedes cell lysis” is a means-plus-function term, it would seem incongruous to deny the Petition on the basis that it does not set forth a means-plus-function claim construction. The district court also recently declined to interpret the term that way. *See generally* Ex. 1062. And we see no sufficient basis to disagree with the court on that issue—particularly absent substantive claim construction briefing from the parties to us

addressing whether the phrase in question should be construed under 35 U.S.C. § 112(f) (former § 112 ¶ 6).

There is also no apparent need to provide a further explicit construction of the term to resolve the case. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy’”). Indeed, the primary agent in the prior art that Petitioner cites as meeting the limitation “agent that impedes cell lysis”— i.e., formaldehyde—is expressly identified in the ’277 patent as such an “agent that impedes cell lysis.” Ex. 1001, 6:51–58 (listing formaldehyde among other agents). Patent Owner does not dispute this. Prelim. Resp. 8 (identifying formaldehyde as “an agent that impedes cell lysis”). Accordingly, we can determine whether the prior art discloses “an agent that impedes cell lysis” without expressly construing that term.

For the reasons discussed above, we are not persuaded that Petitioner’s failure to further construe the term an “agent that impedes cell lysis” is fatal to its Petition. At this stage, we determine that no explicit construction of any claim term is necessary to resolve this case. *Nidec*, 868 F.3d at 1017; *Wellman*, 642 F.3d at 1361.

D. Overview of the Asserted Prior Art

1. Chiu (Exhibit 1005)

Chiu is an article about molecular diagnostics and genetics, published in Clinical Chemistry in 2001. See generally Ex. 1005. Chiu relates to a study on the effects of blood-processing protocols on the quantification of fetal and total DNA in maternal plasma. *Id.* at 1607–1608 (“[I]t is the objective of this study to investigate the effects of different blood-processing protocols on the quantitative analysis of total and fetal DNA in maternal plasma, as well as the effect on the relative proportions of cellular and cell-free DNA.”).

Chiu discloses that its study was prompted by several scientific reports and questions. Those matters include, *inter alia*, “the discovery of fetal DNA in maternal plasma and serum in 1997 . . . [and] numerous reports [that] have confirmed its potential application for noninvasive prenatal diagnosis.” *Id.* at 1607 (noting applications such as for disorders of autosomal dominant inheritance and achondroplasia). Citing prior studies, Chiu reports that “it has been shown that fetal DNA represents a substantial portion of the total DNA in maternal plasma, contributing ~ 3.4% and ~ 6.2% of total plasma DNA in early and late pregnancy, respectively.” *Id.* Based on such prior investigations, Chiu addresses “whether plasma is truly acellular” and “whether fetal DNA circulates predominately in a cellular or cell-free form in maternal plasma.” *Id.* at 1608. Because studies may rely on quantification of fetal DNA in maternal plasma, Chiu discloses that “it would be of prime importance to investigate whether the apparent maternal

plasma DNA concentration would be affected by different sample processing protocols.” *Id.*

Chiu discloses the use of different protocols to process blood samples and separate maternal plasma, including centrifugation, microcentrifugation, filtration, and Percoll density-gradient separation. *Id.* at 1608–09. Certain genes (β -globin and *SRY*)²⁹ in the separated plasma were then isolated and amplified via PCR for determination of the levels of fetal and total DNA in the samples. *Id.*

From the data, Chiu discloses that “different blood-processing protocols have a significant impact on the quantification of *β -globin*, but not *SRY* sequences in plasma.” *Id.* at 1612. “In other words, by altering the blood-processing protocol, quantification of total, but not fetal, DNA is affected.” *Id.* Chiu explains, for example, that “centrifugation alone, by various speeds (1600g and 800g) led to total DNA concentrations that were significantly different and higher than those of filtered plasma ($P < 0.05$).” *Id.* Chiu teaches, “[t]herefore, it can be deduced that despite centrifugation, some of the maternal cells could remain in plasma, leading to an increase in the total DNA in plasma.” *Id.* (“[C]entrifugation alone is not effective in removing all the cells in plasma, and the number of cells that remain in plasma after processing is variable.”). Chiu teaches that the “lack of difference in fetal DNA concentration among the different [sample-

²⁹ These genes could be used as proxies for determining the percentage of fetal to total DNA because the β -globin gene is present in maternal and fetal DNA, and the *SRY* gene only in the fetal DNA. Ex. 1005, 1608, 1612; Ex. 1002 ¶ 89.

processing] treatment groups . . . suggests that most of the fetal DNA circulates in an extracellular form.” *Id.* (“[I]ntact fetal cells contribute only a very small proportion of the quantifiable fetal DNA”); *see also id.* (disclosing that “fetal cells are detectable at a frequency of . . . ~ 2 fetal cells/mL of Percoll-derived maternal plasma”). Chiu concludes that “[d]ifferent protocols of blood sample processing impart a significant effect on the quantification of total DNA in maternal plasma.” *Id.* at 1613.

2. Hahn (Exhibit 1006)

Hahn is an editorial in Clinical Chemistry from 2001. *See generally* Ex. 1006. Hahn relates generally to quantification of circulating DNA and, like Chiu, the effects and significance of sample-processing protocols. *Id.* Citing the 1997 observation of cell-free fetal DNA circulating in maternal plasma, Hahn teaches that “[t]his observation has been one of the most important for those attempting to develop safe and efficacious methods for prenatal diagnosis fetal genetic traits,” especially compared to methods that “rely on invasive procedures such as amniocentesis.” Ex. 1006, 1577. Hahn contrasts approaches “using fetal cells enriched from the blood of pregnant women” (which have “been hampered by the extreme scarcity of these cells”) with approaches that rely on circulating fetal DNA, which “could be detected in as little as 10 μ L of maternal plasma.” *Id.* (“[T]his approach was readily seized on by various research groups, who in rapid succession showed that circulatory fetal DNA can be reliably used for the determination of fetal sex, rhesus D status, and inherited Mendelian disorders.”).

Hahn discusses prior studies showing that blood-processing protocol significantly affects the amount of total circulating DNA, but not fetal DNA

in the sample. *Id.* Thus, as Hahn explains, “circulatory fetal DNA exists mainly in a cell-free form and is not released from dead or dying fetal cells in the maternal circulation.” *Id.* (citing Chiu, among other references, and remarking, “[a]s expected, no significant difference was noted in the concentrations of circulatory fetal DNA, clearly indicating that this is mainly in an acellular form”). Hahn discloses, “[b]y contrast, the amount of maternal circulatory DNA was significantly increased in serum samples compared with plasma because of the liberation of maternal DNA from maternal cells lysed during clotting.” *Id.*

Hahn discloses that “[t]he quantification of both fetal and maternal circulatory DNA . . . raised the question of how the plasma sample should best be prepared for extraction of circulatory DNA.” *Id.* Further to that point, Hahn teaches that “contamination of the plasma sample by maternal cells or cell remnants would . . . affect the apparent concentration of maternal DNA in the sample.” *Id.* And, after reviewing Chiu’s study in greater detail, Hahn discloses that “[i]f you are considering the analysis of both circulatory fetal and maternal DNA . . . , care must be taken in clearing the plasma of any maternal cellular remnants.” *Id.* at 1577–78.

3. Abbott (Exhibit 1007)

Abbott is a U.S. patent issued on April 6, 1999. Ex. 1007, codes (45) (73). Abbott discloses “methods and devices for performing automated blood cell analysis by integrating ‘impedance,’ ‘light scattering,’ and ‘fluorescence’ analysis and flow cytometric techniques.” Ex. 1007, 1:20–23. Abbott teaches that it is advantageous to “gently fix the white cells [in a blood sample] at the same time that the red cells are being lysed.” *Id.* at

14:51–55. This advantage is achieved with a “multipurpose reagent system.” *Id.* at 12:65–13:2 (disclosing a “multipurpose reagent system [that] can substantially completely and rapidly lyse red blood cells, while concurrently substantially preserving white cell morphology and the antigenicity of lymphocyte surface antigens”); 13:46–60 (disclosing reagents for “concurrently lysing red blood cells and fixing white blood cells”). Abbott’s “multipurpose reagent system” includes a short-chain aliphatic aldehyde, such as formaldehyde, which “fix[es] white blood cells and substantially preserve[s] their membrane integrity.” *Id.* at 13:62–14:3. According to Abbott, “even fragile white cells, such as those seen in chronic lymphocytic leukemia patients, are stabilized in the multi-purpose reagent system.” *Id.* at 14:56–60.

4. Lo (Exhibit 1008)

Lo is an article published in 1998 in The American Journal of Human Genetics. Ex. 1008. Lo discloses a “real-time quantitative PCR assay to measure the concentration of fetal DNA in maternal plasma and serum.” Ex. 1008, 768. According to Lo, analysis of fetal DNA can be used for “fetal sex determination” and for “prenatal diagnosis” of various disorders, including “sex-linked disorders,” “autosomal dominant disorders,” and “autosomal recessive genetic disorders” like “certain hemoglobinopathies,” and “cystic fibrosis.” *Id.* at 773–774. Fetal DNA can be detected in both maternal plasma and maternal serum. *Id.* at 772 (“The high concentration of fetal DNA in maternal plasma and serum has allowed us to detect reliably the presence of fetal genetic material.”). However, maternal serum has a higher quantity of “background maternal DNA.” *Id.* Therefore, it may be

preferable to use maternal plasma rather than maternal serum for “robust fetal DNA detection.” *Id.*

5. Jen (Exhibit 1009)

Jen is an article published in 2000 in the Annals of the New York Academy of Sciences. Ex. 1009. Jen discloses that tumor DNA circulating in peripheral blood can be detected in plasma or serum and may have diagnostic and prognostic value. *Id.* at 8. According to Jen, blood samples intended to be analyzed for the presence of tumor DNA should “never” be placed “in the freezer as freezing will lyse the red blood cells and release the iron, which is a major PCR inhibitor.” *Id.* at 9. “White blood cells may also lyse, contributing to increased normal DNA contamination in the sample.” *Id.*

6. Saito (Exhibit 1010)

Saito is a publication from 2000 in The Lancet. Ex. 1010. Saito relates to prenatal assessment of point mutations to the FGFR3 gene, which mutations are associated with achondroplasia (a short-limb disorder). *Id.* (disclosing that DNA analysis has determined that particular mutations to nucleotide 1138 in the gene encoding fibroblast growth factor receptor 3 (FGFR3) appear in more than 90% of subjects with achondroplasia).

Saito teaches that “maternal plasma may have the potential to provide for non-invasive prenatal diagnosis of single-gene disorders in which the mother does not have genomic alterations in the target sequence.” *Id.* Saito determined the sequence of a locus (i.e., a segment including nucleotide location 1138) of the FGFR3 gene and amplified the relevant segment with

PCR and an appropriate primer. *Id.* Saito discloses that the mutation was detected in maternal plasma and determined that the likely source of the mutation was fetal DNA. *Id.* (“No mutation was found in maternal leucocytes, suggesting that the mutant allele in maternal plasma DNA originated from the fetus”). Thus, Saito states: “We have successfully carried out a non-invasive prenatal DNA diagnosis of a single-gene disorder, achondroplasia, from maternal plasma.” *Id.*

E. Obviousness over Chiu, Hahn, and Abbott

Petitioner asserts that claims 81–94, 96, and 133 are unpatentable as obvious over the combination of Chiu, Hahn, and Abbott. Pet. 23–36; see *id.* at 25–33 (claim 81), 33–36 (claims depending from claim 81).

We provided an overview of the prior art above. We turn first to Petitioner’s analysis of the unpatentability of the claims, beginning with independent claim 81. We then address the challenged dependent claims. And, finally, we will discuss Patent Owner’s contentions about secondary considerations (e.g., alleged unexpected results with the claimed invention).

1. Claim 81

Petitioner shows, based on the present record, where each of the limitations of claim 81 is taught or suggested in the combination of Chiu, Hahn, and Abbott. Pet. 23–28. Petitioner shows where Chiu and Hahn teach the preamble’s language³⁰ of a “method of preparing a sample for

³⁰ We need not decide whether the preamble is limiting because there is no present dispute that it is disclosed in the asserted prior art.

analysis.” *Id.* at 25–26. For example, Petitioner cites Chiu’s teaching of collecting blood samples from healthy pregnant subjects and processing samples through different means (e.g., centrifugation or microcentrifugation) to separate the plasma component. *Id.* (citing Chiu, 1607). Moreover, Petitioner shows where Chiu and Hahn teach isolating free fetal nucleic acid from a separated plasma sample, meeting the claimed “isolating” step. *Id.* at 27 (citing, for example, Hahn’s disclosures about extraction of circulatory DNA from a maternal plasma sample to quantify fetal DNA).

Turning to the two “wherein” clauses of claim 81, which relate to the sample comprising “an agent that inhibits lysis of cells, if cells are present” and that the agent is selected from a “group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor,” Petitioner cites to Abbott. *Id.* at 27–28. Petitioner shows, for example, that Abbott discloses the use of formaldehyde as a cell-lysis inhibitor and fixative for WBCs in a blood sample. *Id.* (citing, e.g., Abbott, 12:65–13:2 (using a reagent system to lyse red blood cells while simultaneously preserving WBC morphology), 13:62–14:6 (using formaldehyde, to preserve membrane integrity of WBCs), 16:12–18 (using reagent system to inhibit WBC lysis and resulting “interference” of WBC’s DNA relative to another measured component)).

Petitioner also provides evidence-backed reasoning to support its argument that a skilled artisan would have had reasons for adding a cell-lysis inhibitor to the methods suggested by Chiu and Hahn. Pet. 28–33. In general, Petitioner contends that, based on the combined teachings of Chiu and Hahn, a skilled artisan would have recognized the problem caused by lysis of maternal cells, liberation of maternal DNA from WBCs, and

“contamination” of the sample with such DNA. *Id.* at 29 (“A POSA considering Chiu would naturally consider Hahn’s teaching that avoiding such contamination would result in a more effective [cffDNA] sampling method”). Petitioner contends a skilled artisan would have considered Abbott as identifying a “straightforward solution (preventing [WBC] cell lysis) to the need expressly identified by the combination of Chiu and Hahn (the need to avoid contamination of a sample with maternal DNA due to maternal cell lysis)” and, thus, would have modified the method of Chiu and Hahn accordingly with a reasonable expectation of success. *Id.* at 30–32.

Petitioner’s assertions above are backed by the cited prior art and by the testimony of its declarant, Dr. Wapner, which is uncontested and which we find credible at this preliminary stage. *See, e.g.*, Ex. 1002 ¶¶ 123–152. Patent Owner does not, at present, contest Petitioner’s argument and evidence on the points above. Rather, Patent Owner points to alleged secondary considerations of nonobviousness, which we address in greater detail below. Prelim. Resp. 5–12.

2. Dependent claims 82–94, 96, and 133

Petitioner contends that the limitations added in dependent claims 82–94, 96, and 133 are taught or suggested in the prior art, and that the skilled artisan would have predictably modified the prior art to the extent needed to arrive at the claimed subject matter. Pet. 33–35. Petitioner’s contentions are, at this stage, uncontested by Patent Owner (except for citing alleged secondary considerations addressed below). We have considered Petitioner’s argument and find that it is backed by documentary and testimonial support that is sufficient for institution purposes on this record.

3. Secondary Considerations of Nonobviousness

Patent Owner contends that secondary considerations (such as long-felt need, unexpected results, and initial skepticism about such results) show that the claims are nonobvious. Prelim. Resp. 5–12. Petitioner, however, contends that formaldehyde has been used for decades as a cell lysis inhibitor, and the fact that it inhibited lysis of cells to reduce background contamination of a sample by maternal cellular DNA is not unexpected. Pet. 63–64. Petitioner also contends that Patent Owner’s results are questionable and could not be validated by multiple laboratories; moreover, Petitioner argues that the data is not commensurate in scope with the claims for at least the reason that testing was limited to a single lysis-inhibiting agent—formaldehyde. *Id.* at 65–66.

To begin, we observe that objective indicia of nonobviousness, such as unexpected results, are “only relevant to the obviousness inquiry ‘if there is a nexus between the claimed invention and the [objective indicia].’” *In re Affinity Labs of Tex., LLC*, 856 F.3d 883, 901 (Fed. Cir. 2017) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006)). “The patentee bears the burden of showing that a nexus exists.” *WMS Gaming Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999); *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (explaining that nexus may be presumed “when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them”) (internal quotations marks and citation omitted).

There are material issues surrounding Patent Owner’s alleged objective indicia of nonobviousness that are better resolved through trial on a more complete evidentiary record. We explain below.

One issue is whether there is a sufficient nexus between, for example, the allegedly unexpected results and the claims. At this stage, Petitioner is correct that Patent Owner’s data appears limited to testing with formaldehyde/formalin, yet the claims are far broader than that. Ex. 1001, 91:14–23 (noting 25% cffDNA in the formalin sample versus 1.5% in the sample without formalin). Claim 81, for example, is not limited to the use of formaldehyde as the agent. The claim instead uses functional language to characterize the agent—“an agent that inhibits lysis of cells . . . said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.” *Id.* at 474:51–57.³¹ Such functional language renders the claim scope quite broad—encompassing the myriad additional stabilizer, cross-linker, and lysis inhibitor compounds listed in the Specification, and maybe more. *See, e.g., id.* at 31:57–32:21, 226–229 (Table XXIII).

Patent Owner contends that, “[u]nder Petitioner’s logic” about the claims not being commensurate in scope with the data, “there would never be objective indicia evidence for a claim that covers more than one embodiment.” Prelim. Resp. 50. But Patent Owner’s argument misses the mark. Whether a nexus exists, and the correspondence needed between a

³¹ *See Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1362–63 (Fed. Cir. 2021) (discussing implications for a nexus showing when claims use functional as opposed to structural language and noting that “[a] claim to ‘anything that works’ hardly has a nexus to any particular product”).

claim and alleged objective indicia evidence exists along a spectrum. The evidence here appears to be relatively limited (specific results with formaldehyde) yet the claims are quite broad. And, at present, there is an insufficient evidentiary basis to support a conclusion that other embodiments falling within the broad claim scope would produce substantially the same results as the formaldehyde embodiment. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (holding that there must be an evidentiary basis to show that other embodiments within the scope of the claims will behave the same).

There are other potential nexus issues beyond Patent Owner's results being limited to the use of formaldehyde. One such issue relates to the reproducibility of Patent Owner's results. Petitioner contends the results could not be reproduced by other researchers, citing studies by Chung (Ex. 1038) and Chinnapapagari (Ex. 1053). Pet. 66. Patent Owner responds that, in fact, others were able to show formaldehyde provides a significant increase in the percentage of cffDNA, affirming Dr. Dhallan's (the inventor's) results. Prelim. Resp. 9 (citing, e.g., Exs. 2008, 2009, 2010); Ex. 2007, 1–2 (competing correspondence from researchers about the disputed data).

Patent Owner downplays the inconsistent results from the studies cited by Petitioner, arguing “there were significant differences between Dr. Dhallan's approach and the methodologies of labs that doubted Dr. Dhallan's results.” Prelim. Resp. 8–9 (noting that the “other labs tested samples much sooner after extracting” blood). That only highlights the nexus issue. The challenged claims would appear to encompass the methodologies in the studies cited by Petitioner—there is, for example, no

recitation in claims 55 or 81 of *when* the samples must be taken or processed. Prelim. Reply 5 n.2. And, on the preliminary record, there is evidence to suggest that timing is a key factor to whether any improved or allegedly surprising results will or will not arise. For example, a study by Zhang, reports “no difference” in fetal and total DNA concentrations “between blood portions with and without formaldehyde addition” when processed at 6 hours. Ex. 2009, 3–4; *see also id.* at 2 (Table 1). At “36 h[ours], however, the blood portions with formaldehyde addition demonstrated a significant decrease in the concentration of total DNA and a marked increase in the concentration of fetal DNA compared with those without formaldehyde addition ($p < 0.05$).” *Id.* at 4. Zhang, thus, concludes that “formaldehyde addition will offer no beneficial effect if blood samples are processed without delay,” but if there is “[u]ndue delay (>24 h)” in processing, formaldehyde addition may provide an improvement. *Id.* (“Therefore, only in such situations [(i.e., undue delay in processing)] can formaldehyde addition offer advantages.”); *see also* Ex. 2008, 1 (“Addition of formaldehyde does not significantly enhance the proportion of cell free fetal DNA when blood specimens are processed without delay.”).³²

³² This is not to say that the above nexus issues may be the only ones. For example, Dr. Dhallan writes about other “critical” yet seemingly unclaimed aspects of the method. Ex. 1035, 1117–18 (identifying the time between venipuncture and formaldehyde addition; listing other criteria used like zero-brake centrifugation and other “careful processing protocols”); Ex. 1001, 223:63–224:14 (same). If appropriate, the parties may consider developing evidence on such matters through trial.

On the topic of skepticism, we agree with Patent Owner that evidence suggests some were skeptical of Dr. Dhallan's results. *See, e.g.*, Ex. 2007, 1 (“One of the most remarkable aspects of the report by . . . [Dr.] Dhallan . . . is the substantial increase in the proportion of fetal DNA that is achieved by simply adding formaldehyde to the tubes.”). Some of that skepticism about the results may, however, have been justified. As discussed above, other researchers were not able to reproduce them. *Id.* (citing inconsistent studies and describing as “curious that there is no mentioning of this controversy in the *Lancet* paper”). Or, it may just reflect a common desire among scientists for more detail and for independent verification. Ex. 2007, 1–2 (“Before jumping to conclusions . . . we will require a more detailed protocol and a logically explained mode of action for the formaldehyde treatment.”). Such matters are better addressed on a full record.

If Dr. Dhallan's results are valid (e.g., 1.56% without formalin versus 25% with formalin), we are somewhat skeptical that such results are merely a difference in degree as argued by Petitioner. Pet. 64. Petitioner contends that a skilled artisan would expect formaldehyde to inhibit lysis of maternal WBCs and, thus, lower contamination from maternal DNA in a blood sample, and we generally agree on this preliminary record. Pet. 63–64. But that does not necessarily explain why one would expect the particular increase in cffDNA percentage that Patent Owner cites in its results. As with the above issues, we will address this further on a more developed record through trial as needed.

Patent Owner also contends that its invention satisfied a long-felt but unmet need, that it received praise, and that the invention has been widely

adopted in the industry. Prelim. Resp. 5–7, 9–12. Patent Owner’s argument and evidence on these points raise similar nexus issues as discussed above. The evidence again appears limited to Patent Owner’s specific method that uses formaldehyde. We will revisit as necessary based on a full record. We note the following points, however, to provide some guidance to the parties.

Regarding the alleged long-felt need, Patent Owner’s evidence focuses on the use of fetal *cells* from maternal plasma, and the shortcomings of that approach. Prelim. Resp. 6 (citing Ex. 2005 for the proposition that recovery of fetal cells is difficult and not clinically practical). But, even based on the preliminary record, there appear to be other non-invasive techniques that used, for example, circulating *cell-free* fetal DNA isolated from maternal plasma for diagnostic purposes. Petitioner cites the publications by Chiu and Hahn and the non-invasive methods that they specifically describe or exemplify and that were already known and used for prenatal diagnoses. Pet. 66; Ex. 1002 ¶ 422; *see also* Ex. 1034, 1135 (describing, e.g., maternal serum analyte screening as a commonly used technique, which the ’277 patent acknowledges is a preexisting technique (Ex. 1001, 3:59–4:59)). And Chiu and Hahn indicate that techniques using cffDNA do not suffer the same problems as with fetal cells, with the former providing much higher amounts of fetal DNA for diagnostic purposes. *See, e.g.*, Ex. 1006, 1577. Even assuming that Patent Owner’s method is an improvement over existing non-invasive diagnostic techniques, that does not necessarily explain or show that it meets the alleged need yet other methods did not. If Patent Owner continues to advance this argument, it would benefit from further evidentiary development.

The preliminary evidence on praise also appears to be specific to the use of formaldehyde, raising questions on nexus as discussed above. *See, e.g.*, Ex. 2004, 1–2. There are, however, multiple laudatory statements in evidence, suggesting promise with that method. Ex. 1034, 1135–36 (suggesting “major clinical implications” and “tremendous promise” with an increased percentage of cffDNA). As with Patent Owner’s other alleged secondary considerations, we conclude that it is prudent to wait until the record is more developed to determine what actual weight, if any, the alleged praise should carry in the final obviousness analysis.

Lastly, Patent Owner contends that “the industry has widely adopted the invention.” Prelim. Resp. 11. According to Patent Owner, companies including Quest, Illumina, and Natera (among others) “use blood collection tubes sourced from Streck.” *Id.* Patent Owner argues those tubes use a “unique preservative” that inhibits cell lysis to permit cell-free DNA analysis. *Id.* (citing Ex. 2025, 2); *see also id.* (citing documents (Ex. 2027; Ex. 2030) concerning tubes allegedly made by Roche that include a “[p]roprietary solution” that prevents cells lysis). It is unclear at present how this alleged use is objective indicia of nonobviousness. Patent Owner does not characterize the use as due to any copying, licensing, or as evidence of commercial success—categories recognized in the precedents. Alleged use of a patented technology, without more, generally carries little or no weight in the obviousness inquiry. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) (“Not every competing product that arguably falls within the scope of a patent is evidence of copying. Otherwise every infringement suit would automatically confirm

the nonobviousness of the patent.”). Moreover, Patent Owner’s argument about industry use still falls short on the matter of nexus. *See Fox Factory*, 944 F.3d at 1377 (holding that a showing of nexus cannot be made by simply showing that “the patent claims broadly cover the product that is the subject of the evidence of secondary considerations”).

For the reasons discussed above, we find that Patent Owner’s argument and evidence on secondary considerations of obviousness is entitled to little weight at this stage. We will reevaluate, if appropriate and to the extent the arguments are preserved, on a full trial record. Based on the preliminary record, the alleged secondary considerations do not outweigh the evidence of obviousness relied upon by Petitioner. Petitioner has established a reasonable likelihood that it will prevail in showing that at least claim 81 is obvious.

F. Obviousness over Lo, Jen, and Abbott

Petitioner asserts that claims 81–94, 96, and 133 would have been obvious over Lo, Jen and Abbott. Pet. 36–44. Petitioner provides documentary and testimonial evidence to back its assertions, which we have considered and which are uncontested by Patent Owner at present. *Id.*; *see also*, for example, Ex. 1002 ¶¶ 199–225. Patent Owner’s contentions about secondary considerations of nonobviousness do not avoid institution for substantially the same reasons discussed above under Section IV(E). Also, if trial is instituted it must be instituted on all challenged claims and grounds. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1354 (2018).

G. Obviousness over Chiu, Hahn, Abbott, and Saito; Obviousness over Lo, Jen, Abbott, and Saito

Petitioner asserts that claims 55–63, 66–69, 80, and 126–132 would have been obvious over: (i) the combination of Chiu, Hahn, Abbott, and Saito (Pet. 45–56); and (ii) the combination of Lo, Jen, Abbott, and Saito (56–60).

The subject matter of independent claim 55 is similar to independent claim 81, except claim 55 requires “determining the sequence of a locus of interest on free fetal DNA” for the isolated DNA sample, and the sample be “obtained from a pregnant female.” Ex. 1001, 472:66–473:5. Petitioner explains, without dispute at this stage from Patent Owner, where Saito teaches determining a sequence of a locus of interest (e.g., a single nucleotide polymorphism or “SNP” at a certain position of the FGFR3 gene). *See, e.g.*, Pet. 46 (citing Saito, 1170). Petitioner also explains sufficiently where the other references disclose obtaining a sample from a pregnant female. *Id.* at 48, 57. Petitioner explains, with supporting and undisputed evidence, why a skilled artisan would have been motivated to combine Saito’s teachings with the combinations of either Chiu, Hahn, and Abbott (*id.* at 48–51), or Lo, Jen, and Abbott (*id.* at 58–60) to arrive at the claimed subject matter. Petitioner also provides undisputed evidence-backed contentions covering the challenged claims that depend from claim 55. *Id.* at 51–56, 60–63. Based on the present record, Petitioner has established a reasonable likelihood of success in showing that at least claim 55 is unpatentable for obviousness based on the grounds advanced.

Patent Owner's contentions about secondary considerations do not avoid institution for substantially the same reasons discussed above under Section IV(E)(3). There are similar issues with Patent Owner's argument and evidence (e.g., nexus showing) that also apply to at least claim 55. In any event, if trial is instituted it must be instituted on all challenged claims and grounds. *See SAS*, 138 S. Ct. at 1354.

V. CONCLUSION

On this preliminary record, Petitioner has established a reasonable likelihood of prevailing in showing that at least one of the challenged claims is unpatentable based on the grounds advanced in the Petition.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *granted*, and we institute *inter partes* review of claims 55–63, 66–69, 80–94, 96, and 126–133 based on the grounds asserted in this Petition;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is given of the institution of trial, which will commence on the entry date of this Decision.

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