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Paper 20
Date: April 22, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STRECK, INC.,
Petitioner,

v.

RAVGEN, INC.,
Patent Owner.

IPR2021-01577
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

Streck, Inc. ("Petitioner" or "Streck"),[1] on September 28, 2021, filed a Petition to institute *inter partes* review of claims 55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, and 133 of U.S. Patent No. 7,332,277 B2 (Ex. 1001, "the '277 patent"). Paper 3 ("Pet." or "Petition"). Ravgen, Inc. ("Patent Owner")[2] filed a Preliminary Response. Paper 12 ("Prelim. Resp.").

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." Based on the preliminary record, it is reasonably likely that Petitioner will prevail in showing that one or more of the challenged claims are unpatentable. We decline to deny the Petition on a discretionary basis or as time-barred as argued by Patent Owner. Thus, for reasons explained below, we institute *inter partes* review of claims 55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, and 133 of the '277 patent.

A. Related Patents & Proceedings

The '277 patent issued February 19, 2008, from U.S. Application No. 10/661,165 ("the '165 Application") filed September 11, 2003. Ex. 1001, codes (21), (22), (45). The '277 patent claims priority to several other applications, and the earliest application listed in the '277 patent's priority chain is a provisional application filed on March 1, 2002. *Id.* at code (60).

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[1] Petitioner identifies Streck Laboratories, Inc. as the real party-in-interest. Pet. 1.

[2] Patent Owner identifies itself as the real party-in-interest. Paper 4, 1.

Related U.S. Patent No. 7,727,720 ("the '720 patent"), which also claims priority to the '165 Application, issued on June 1, 2010. *See* IPR2021-00791, Paper 20 at 2–3.

The parties identify multiple lawsuits involving the '277 patent. Pet. 1–2; Paper 18, 1–2. Those lawsuits include: *Ravgen, Inc. v. Natera, Inc.*, No. 1:20-cv-00692-ADA (W.D. Tex.); *Ravgen, Inc. v. Laboratory Corp. of America Holdings*, No. 6:20-cv-00969-ADA (W.D. Tex.); and *Ravgen, Inc. v. Quest Diagnostics*, No. 6:20-cv-00972-ADA (W.D. Tex.);[3] and *Ravgen, Inc. v. Illumina, Inc.*, No. 1-20-cv-01644 (D. Del.). Paper 18, 1–2 (identifying other lawsuits against, *inter alia*, PerkinElmer Inc., Bioo Scientific Corporation, Myriad Genetics, Inc., Progenity, Inc., Ariosa Diagnostics, Inc., Roche Molecular Systems, in the Western District of Texas or the District of Delaware).

The parties also identify other matters involving the '277 patent before the Patent Office. Pet. 2; Paper 18, 2. Claims of the '277 patent have also been challenged in IPR2021-00788, -00789, and -00790 (all filed by Quest), IPR2021-00902 and -01054 (both filed by Labcorp), and IPR2021-01272 (filed by Illumina). Pet. 2. On October 19, 2021, we instituted trial in IPR2021-00788, Paper 23 (covering claims 55–63, 66–69, 80–94, 96, and 126–133), and denied institution in IPR2021-00789 and IPR2021-00790. On November 5, 2021, we instituted trial in IPR2021-00902 and -01054 (covering, collectively, claims 55–63, 66–69, 80–96, and 127–133). We

[3] The Quest lawsuit has since been transferred to another district. *Ravgen v. Quest Diagnostics*, No. 2:21-cv-09011-RGK-GJS (C.D. Cal.).

instituted trial in IPR2021-01272, Paper 14 (covering claims 55–63, 66–69, 80–91, 94–96, 126–130, 132, and 133), on January 26, 2022. Patent Owner also identifies *Ex Parte* Reexamination Control No. 90/014,792, filed by Natera, as related to the '277 patent. Prelim. Resp. 11. That reexamination has since been stayed during the pendency of the related IPRs. *See* IPR2021-00902, Paper 24.

The related '720 patent was also asserted in the lawsuits identified above (*see* IPR2021-01271, Paper 1, 2–3), and claims of the '720 patent are challenged in IPR2021-00791 (filed by Quest), -01026 (filed by Labcorp), and -01271 (filed by Illumina), all of which are instituted and ongoing. Natera and Foundation Medicine have, respectively, also challenged claims of the '720 patent in *Ex Parte* Reexamination Control Nos. 90/014,703 and 90/014,869. Prelim. Resp. 11–12. Those reexaminations are now stayed. IPR2021-00791, Paper 25; IPR2021-01026, Paper 17.

B. Asserted Grounds of Unpatentability

Petitioner asserts three grounds of unpatentability in this Petition (Pet. 4), which are provided in the table below:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, 133	103(a)[4]	Pertl,[5] Granger[6]
55–59, 61, 68, 69, 80–86, 89, 94, 126–130	102(a)	Chiu[7]
55–59, 61, 68, 69, 80–86, 89, 94, 126–130	103(a)	Chiu, Lee[8]

[4] 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.
[5] Barbara Pertl et al., *Detection of male and female fetal DNA in maternal plasma by multiplex fluorescent polymerase chain reaction amplification of short tandem repeats*, 106 HUM. GENET. 45–49 (2000) (Ex. 1010, "Pertl").
[6] Granger et al., WO 97/45729, published Dec. 4, 1997 (Ex. 1012, "Granger").
[7] Rossa W. K. Chiu et al., *Effects of Blood-Processing Protocols on Fetal and Total DNA Quantification in Maternal Plasma*, 47:9 CLINICAL CHEMISTRY 1607–13 (2001) (Ex. 1010, "Chiu").
[8] Tzong-Hae Lee et al., *Quantitation of genomic DNA in plasma and serum samples: higher concentrations of genomic DNA found in serum than in plasma*, 41 TRANSFUSION 276–82 (2001) (Ex. 1015, "Lee").

Petitioner also relies on the declaration of Dr. Bruce Patterson, among other evidence. Ex. 1009. Patent Owner has not, at this time, submitted rebuttal testimony.

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 invasive and non-invasive techniques are available for prenatal diagnosis, including amniocentesis, and analysis of fetal cells in maternal blood. *Id.* at 2:53–57. According to the patent, "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, 3:33–37 (citing higher fetal mortality risk with amniocentesis).

By the late 1990s, and before the '277 patent, researchers had known that cell-free *fetal* DNA ("cffDNA") and maternal cell-free DNA ("cfDNA") may be found in circulating maternal blood. Ex. 1001, 55:39–56; Ex. 1009 ¶¶ 44–46. For example, researchers had determined that cffDNA was present in maternal plasma in a range of about 3.4%–6.2% (as a percent of total circulating DNA). Ex. 1001, 222:37–43; Ex. 1011, 1607 (citing studies by Dr. Dennis Lo). It was also known that, although intact fetal *cells* may be found in maternal plasma, most fetal DNA in maternal plasma exists in its cell-free form. Ex. 1011, 1612 (disclosing that "intact fetal cells contribute only a very small proportion of the quantifiable fetal DNA").

To analyze cell-free DNA from blood, a blood sample is ordinarily collected (e.g., from a subject's vein) and then further processed. Ex. 1009

¶¶ 38–39, 44–45. Dr. Patterson explains that it was routine to add compounds like ethylenediaminetetraacetic acid ("EDTA") to stabilize such samples. Ex. 1009 ¶¶ 42–43 ("EDTA stabilizes blood in its fluid form and prevents destruction of cells contained in the sample."); Ex. 1011, 1608 (teaching that "venous blood samples . . . were collected into EDTA tubes").

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. Ex. 1001, 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.

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. *Id.* at 89:1–6. "Increasing the percentage of free fetal DNA would enhance the detection" of 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. *Id.* at 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."). 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, cholesterol, and glucose).

The '277 patent provides results on the addition of formalin (i.e., formaldehyde in aqueous solution) as the lysis-inhibiting agent. *Id.* at 89:1–91:60 (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 EDTA[9]), and adding

[9] The '277 patent states that EDTA is a "magnesium chelator." Ex. 1001, 31:52–54.

formaldehyde (25μl/ml) to one of the tubes. *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"), 89:18–25. The samples were centrifuged and 800 μl of each maternal plasma sample was then further processed to determine the relative amount of cffDNA present. *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.

D. Challenged Claims

Independent claims 55 and 81 are illustrative 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.
>
> 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.

E. Prosecution History

During prosecution, the Examiner rejected several pending claims as anticipated by, or obvious over, the "Lo" reference.[10] Ex. 2223, 1224, 1227. In response, applicant argued that the Examiner had provided no evidence that EDTA in Lo's samples inhibits cell lysis. *Id.* at 1191 ("[T]he Office has provided absolutely no documentary evidence or rationale in support of its assertion that EDTA is an agent that inhibits cell lysis.").

Applicant also argued that "the assertion by the Office that EDTA is a cell lysis inhibitor is simply incorrect." *Id.* at 1192. Applicant then stated:

> EDTA is not an "agent that inhibits cell lysis." Rather, EDTA is a well-known chelator of calcium and magnesium. EDTA is routinely added to blood during the blood collection process as an anticoagulant due to its ability to chelate calcium. In fact, EDTA is sometimes included as an ingredient in cell lysis buffers. . . . EDTA is clearly referred to as a chelator in Applicant's specification, not as a cell lysis inhibitor (see, e.g., paragraph [0165] of Applicant's specification), whereas multiple examples of agents that inhibit cell lysis are provided separately (see, e.g., paragraphs [0166] to [0167]).

Id. at 1192. Applicant raised a related argument in an interview with the Examiner. *Id.* at 1020 ("As regards Claims 58, 87 and 152 the applicant pointed out they [*sic*] EDTA could not be defined as a cell lysis inhibitor but rather was simply an anticoagulant"). Thus, applicant argued during

[10] Claims 55 and 81 correspond, respectively, to pending claims 58 and 87 in prosecution. Ex. 2223, 526. The citations to Exhibit 2223 and 2041 are to the page numbers added to the exhibit copies, not the original pagination.

prosecution that EDTA does not satisfy the limitation of "an agent that inhibits cell lysis" as claimed. *Id.* at 1192.

The Examiner withdrew the rejections based on Lo, but entered new rejections for obviousness based on the combination of "Amicucci" or "Umansky," with "Kiessling." *Id.* at 923–927, 954–957. The Examiner found that Amicucci and Umansky taught all the claim limitations except "an agent that inhibits cell lysis," which the Examiner found was taught in Kiessling based on its disclosure on formaldehyde as an agent to fix (i.e., inhibit the lysis of) white blood cells (WBCs). *Id.*

In response, applicant argued that there was no motivation to combine the newly cited references. *See, e.g.*, *id.* at 570–571. Among other things, applicant argued that the DNA analyzed in Umansky and Kiessling was "quite distinct" in each reference because Umansky analyzed fetal DNA circulating outside a cell, "while the DNA analyzed in Kiessling is in and/or is released from a fixed cell." *Id.*; *see also id.* at 589 (advancing similar argument for the Amicucci combination). Applicant also argued that the claimed method addressed a long-felt need and produced unexpected results. *Id.* at 569–570 (arguing the method was an alternative to invasive prenatal testing, and, by adding formalin as an agent that inhibits lysis, the percentage of cffDNA was 25%, compared to 1.56% without formalin).

The Examiner, on September 26, 2007, entered a Notice of Allowability. *Id.* at 519–521. The Examiner stated that the 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 the related '720 patent's prosecution history. Prelim. Resp. 7–10. There, the Examiner initially rejected the pending claims over Kiessling (but in combination with different references than discussed above). *See, e.g.*, Ex. 2041, 1334–1339. In a rejection of the claims as obvious over Adams in view of Kiessling, the Examiner stated that Adams taught the claimed subject matter "except these authors do not teach adding an agent that impedes cell lysis to the sample." *Id.* at 1345. The Examiner relied on Kiessling as disclosing an agent that fixes white blood cells (i.e., formaldehyde) that met the "agent" limitation as claimed. *Id.* In response, applicant argued, *inter alia*, that its invention satisfied a long-felt need and provided unexpected results. *Id.* at 1380–81.

The Examiner withdrew the rejections discussed above and entered a new round of rejections. Ex. 2041, 2527–2532. Those rejections included combinations based on, *inter alia*, either Amicucci or Holodniy, in further combination with Kiessling. *Id.* The Examiner, in making these rejections, stated: "these authors [e.g., Amicucci or Holodniy] do not teach that their samples comprise an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from a defined group which includes a cell lysis inhibitor." Ex. 2041, 2527–2530. For the "agent" limitation, the Examiner again turned to Kiessling's use of formaldehyde as a fixing compound. *Id.* Patent Owner now notes, however, that Amicucci disclosed that blood samples were processed in EDTA tubes and Holodniy disclosed that blood samples were collected in tubes with the "anticoagulant chelator" acid-citrate-dextrose ("ACD"). Prelim. Resp. 8–9 (citing Ex. 2046, 301, and

Ex. 2020, 3511 ("samples were collected in VACUTAINER . . . blood collection tubes that contained acid citrate dextrose") (emphasis omitted).

Applicant amended the claims to specify that the free nucleic acid is isolated from the sample's "non-cellular fraction," argued that the cited art failed to teach all the claim limitations, that there were no reasons to combine the art, and argued that the claims met a long-felt need and produced unexpected results. Ex. 2041, 2608–2632. Applicant remarked, for example, that "Holodniy . . . fail[s] to teach or suggest a method for detecting free nucleic acid comprising, *inter alia*, isolating free nucleic acid from a non-cellular fraction of a sample, wherein an agent that impedes cell lysis has been added." *Id.* at 2625. Ultimately the claims were allowed with the Examiner stating that "none of the references of record alone teach all of the [claim] limitations" and "[n]either does the prior art or record, in any combination, reasonably suggest the method(s)" claimed. *Id.* at 2661.

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

A. Standards for Exercising Discretion under Section 314(a)

Under Section 314(a), the Director has discretion to deny institution. *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 272 (2016) ("[T]he agency's decision to deny a petition is a matter committed to the Patent Office's discretion."). Indeed, "the PTO is permitted, but never compelled, to institute an IPR proceeding." *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016).

The Director, and the Board under the Director's delegated authority, may deny institution in a variety of circumstances. For example, it is within

the Board's discretion to deny serial petitions that challenge the same patent. Such discretion is explained in *General Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential as to Section II.B.4.i) ("*General Plastic*") as well as in the Board's Consolidated Trial Practice Guide ("CTPG").[11] *General Plastic* at 16–19 (discussing factors for consideration); CTPG 56–61 (same).

When deciding whether discretionary denial based on serial-petitioning activity is appropriate, we consider the factors set forth in *General Plastic*, which include:

> 1. whether the same petitioner previously filed a petition directed to the same claims of the same patent;
>
> 2. whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
>
> 3. whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;
>
> 4. the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
>
> 5. whether the petitioner provides adequate explanation for the time elapsed between the filing of the multiple petitions directed to the same claims of the same patent;
>
> 6. the finite resources of the Board; and

[11] Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), available at https://go.usa.gov/xpvPF.

> 7. the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic at 16–19. The above seven factors are non-exclusive. *Id.* Moreover, "[t]he *General Plastic* factors, alone or in combination, are not dispositive, but part of a balanced assessment of all relevant circumstances in the case, including the merits." CTPG at 58.

Patent Owner argues, applying the factors set forth in *General Plastic*, that we should deny the Petition on a discretionary basis under § 314(a). Prelim. Resp. 50–60. We decline to do so for the reasons explained below.

B. Analysis of the General Plastic Factors

1. Factor 1: Whether the same petitioner previously filed a petition directed to the same claims of the same patent

This Petition is Streck's only petition challenging the claims of the '277 patent. Pet. 66. Under such circumstances, the Board ordinarily weighs *General Plastic* Factor 1 against discretionary denial. *See Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7 at 7–8 (PTAB Sept. 5, 2018).

Nevertheless, "our application of the *General Plastic* factors is not limited solely to instances when multiple petitions are filed by the same petitioner." *Valve Corp. v. Elec. Scripting Prods., Inc.*, IPR2019-00062, Paper 11 at 2 (PTAB April 2, 2019) (precedential) ("*Valve*"). Where "different petitioners challenge the same patent, we consider any relationship between those petitioners when weighing the *General Plastic* factors." *Id.* This is explained in the *Valve* decision, where the Board found that "[t]he complete overlap in the challenged claims and the significant

relationship between Valve [(follow-on petitioner)] and HTC [(first petitioner)] favor denying institution." *Id.* at 10.

Anticipating Patent Owner's argument for discretionary denial, Petitioner acknowledges the filing of other petitions against the '277 patent by some of Petitioner's customers, but Petitioner contends that it is not a party to those petitions and that its challenge relies on prior art combinations not asserted in those other matters. Pet. 61–62. Petitioner further argues that it "has not been accused of infringement," it "has denied it owes an obligation to indemnify any prior petitioner," it "has not used the Board's decisions on earlier petitions as a roadmap," and "the current Petition does not overlap entirely with most of these [prior] filings." *Id.* at 63–64. Petitioner, thus, argues that there is no "significant relationship" with the prior petitioners or other circumstances, such as discussed in *Valve* and its progeny, that would justify denying this Petition on a discretionary basis. *Id.*

Patent Owner responds that there is a "significant relationship" between Streck and its customers that have filed prior challenges to the '277 patent. Prelim. Resp. 51–52. According to Patent Owner, customers Quest, LabCorp, Illumina, and Natera all use, as a "key component," Streck's blood collection tubes in those customers' genetic testing methods accused of infringing the patent. *Id.* at 51 (citing, e.g., Ex. 2196 (Complaint against Quest) ¶¶ 41–56). Patent Owner also contends that Streck has helped at least Natera in its defense against Patent Owner's infringement allegations. *Id.* (citing experiments performed by Streck employees and its current declarant, Dr. Patterson); *see generally* Ex. 2066 (Patent Owner Ravgen's Motion to Strike). Patent Owner argues that demands for

indemnification to Streck "remain unresolved." Prelim. Resp. 52; Ex. 1013 ¶ 7. And, Patent Owner contends, there is claim overlap and overlap among the prior art and unpatentability theories between this Petition and the prior petitions. Prelim. Resp. 52–53. Accordingly, Patent Owner argues that *General Plastic* Factor 1 should be weighed in favor of discretionary denial.

We do not agree that *General Plastic* Factor 1 favors discretionary denial on this record. To be sure, Streck's tubes feature prominently in Patent Owner's infringement allegations against Quest, Natera, and other customers. *See* Exs. 2065, 2178, 2179, and 2196 (identifying, collectively, Streck's tubes dozens of times). And, as evidenced by the filing of its own petition, Streck is also interested in seeing claims of the '277 patent held unpatentable. But Streck is not a defendant in any action brought by Patent Owner related to the '277 patent. Nor is there any assertion or indication that Streck's blood collection tubes infringe the methods claimed in the '277 patent. These facts, at minimum, distinguish this case from *Valve*. *Valve* at 9–10 (explaining that Valve and HTC were co-defendants sued at the same time in the same case, based on the same allegedly infringing devices that HTC and Valve co-developed).

There is also no evidence that Streck is indemnifying any of its customers against Patent Owner's accusations. The evidence is to the contrary—Streck has denied any indemnity demands. Ex. 1013 ¶ 7 (testifying "Streck has denied those [indemnity] claims in light of the absence of any such duty" in its supplier agreements). A disagreement, if one exists, between Streck and a customer about Streck's rejection of any

indemnity tender, leaving the issue unresolved as legal/contractual matter, does not tilt the analysis toward discretionary denial here. Prelim. Resp. 52.

We accept, for our analysis, Patent Owner's assertion that Streck has provided some experimental or testing assistance to its customer Natera at Natera's direction. Prelim. Resp. 10–11, 52. Although such assistance may point to a degree of cooperation between customer and supplier related to Patent Owner's lawsuit, as we elsewhere pointed out, Streck's testing ostensibly related to how Streck's tubes are designed and work, not invalidity issues. Paper 14, 3. That Streck provided limited technical assistance about Streck's own products, a topic about which Streck would be uniquely familiar, is unremarkable. Accordingly, we find that the relationship between Streck and Natera falls short of the "significant relationship" contemplated in *Valve*. Natera's reexamination request on the '277 patent does not weigh in favor of discretionary denial.[12]

As to the other customers, there is no evidence that Streck has provided them assistance with either their respective petitions or in the lawsuits where those customers are defendants. Although Patent Owner invites us to infer that Streck is providing the same sort of technical assistance to Quest, Labcorp, and Illumina as it did with Natera, we decline to do so. Those other customers source blood collection tubes from Streck, and use of Streck's tubes is cited by Patent Owner in its infringement

[12] It is also notable that Natera's reexamination request was stayed at its inception. IPR2021-00902, Paper 24 (stay order), 9 (explaining that no office action had yet been entered). So, as between Streck and Natera, Streck's challenge to the '277 patent is the only one now moving forward.

allegations as allegedly satisfying one limitation of the challenged claims. Those facts do not add up to a "significant relationship" between the parties that would justify weighing those customers' earlier petitions against Streck and in favor of discretionary denial.

Lastly, we agree with Patent Owner that there is some substantive overlap in Streck's and the prior petitioners' challenges. Comparing Streck's petition and the Quest, Labcorp, and Illumina petitions, there is significant overlap between the challenged claims. All of the claims challenged by Streck are currently at issue in Quest's ongoing IPR. *See supra* Section I(A) (listing related matters and claims challenged). And the only claims challenged by Streck that are missing in Labcorp's IPRs and Illumina's IPR are, respectively, dependent claims 126 and 92.

There is also some overlap in asserted prior art and similarities in the unpatentability theories. Streck, for example, asserts that independent claims 55 and 81 would have been obvious over Pertl and Granger. Pet. 4. The combination of Pertl and Granger is not before us in any of Quest's, Labcorp's, or Illumina's challenges to the '277 patent. Streck's obviousness theory based on Pertl and Granger is, however, somewhat similar to, for example, Quest's challenge to claim 55 as obvious over Chiu, Hahn, and Abbott. Streck relies on Pertl, turning to Granger primarily for its addition of formaldehyde (i.e., the claimed "agent") to further stabilize maternal white blood cells. Pet. 22–25; *see also id.* at 26 (citing Chiu as a motivating reference and as evidence of known cell lysis). *Id.* at 26. Quest, on the other hand, cites Chiu and Hahn, and turns to Abbott for the addition of

formaldehyde as a known white blood cell stabilizing agent. IPR2021-00788, Paper 4, 25–28.

There are also other differences in the unpatentability theories between this Petition and the earlier petitions. Streck argues, for example, that claims 55 and 81 are anticipated by Chiu—a theory not advanced in any prior petition. And Streck challenges claims 55 and 81 as obvious over the combination of Chiu and Lee, urging substitution of acid-citrate-dextrose (ACD) for EDTA. Pet. 49–51. Streck's argument on Chiu and Lee raises some similar issues to what we have seen before; for example, whether ACD (or dextrose/glucose in ACD) is the claimed "agent," is an issue raised in Illumina's § 102 challenge based on Landes. IPR2021-01272, Paper 14, 51–57. The combination of Chiu and Lee, and Streck's substitution theory is, however, new before us. We find that any similarity in Streck's Petition and earlier challenges does not tip this factor in favor of denial.

Notwithstanding the substantial claim overlap, and some overlap in the prior art and unpatentability theories between this Petition and earlier challenges to the '277 patent, we find that Streck's connection with its customers (Quest, Labcorp, Illumina, and Natera) does not rise to the level of a "significant relationship." *Valve* at 10. Accounting for all the considerations above, we conclude on this record that factor 1 does not weigh in favor of discretionary denial.

2. Factors 2, 4, and 5

Factors 2, 4, and 5 relate to a petitioner's earlier knowledge of prior art asserted in a later petition, the time between a petitioner learning of the later-asserted art and the later-filed petition, and a petitioner's explanation

for any delay between filings. *General Plastic* at 16–19. However, where a later petitioner is not the same party as, or significantly related to, the earlier petitioner(s), Factors 2, 4, and 5 are less relevant in the overall *General Plastic* analysis. *Qualcomm Inc. v. Monterey Research, LLC*, IPR2020-01493, Paper 11 at 17 (PTAB Mar. 8, 2021); *Unified Patents*, IPR2018-00548, Paper 7 at 7–8.

Patent Owner argues that Petitioner would have had knowledge of most of the prior art asserted here based on the filings by Petitioner's various customers between April and May 2021, which asserted those prior art references against the '277 patent. Prelim. Resp. 55. That is a reasonable supposition by Patent Owner. Petitioner admits that it retained Dr. Patterson "shortly after Quest and Lab Corp. filed their petitions" in April and May 2021. Pet. 65. Patent Owner also subpoenaed Streck for documents and a deposition concerning, *inter alia*, details about Streck's tubes on February 16, 2021, in connection to the Natera lawsuit. Ex. 2229. From these facts, we infer that Streck was aware of the '277 patent by at least February 2021, and became aware of the Quest and LabCorp petitions shortly after they were filed in April or May. Streck, thus, likely knew about or, with diligence could have discovered, most if not all of the prior art asserted here by roughly May 2021. A window of four to five months for Streck to analyze the patent and prior art and prepare its own petition is, however, not unreasonable under the circumstances.

For the reasons above, we determine that Factors 2, 4, and 5 do not weigh in favor of discretionary denial on this record.

3. Factor 3: whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition

"Under the third *General Plastic* factor, the Board considers the extent to which a later petitioner had the opportunity to 'tailor its arguments to address issues identified by patent owner and/or the Board during a prior proceeding.'" Prelim. Resp. 56 (quoting *NetApp, Inc. v. Realtime Data LLC*, IPR2017-01354, Paper 16 at 11 (PTAB Nov. 14, 2017)). Petitioner had the opportunity to study and tailor its present arguments based on issues identified by Patent Owner during earlier proceedings. Indeed, by the time Streck filed its petition, Patent Owner had filed five preliminary responses to petitions filed by Quest and Labcorp challenging the '277 patent. According to Patent Owner, those papers "gave Petitioner a ***road map***" for preparing the instant Petition. Prelim. Resp. 56.

Streck's opportunity to study Patent Owner's various responses before Streck filed its own petition does raise fairness concerns. On the other hand, although Streck had the opportunity to study those responses and tailor its petition accordingly, it is not apparent that Streck did in fact tailor this Petition to address issues raised by Patent Owner previously. For example, Patent Owner's responses in IPR2021-00788, IPR2021-00902, and IPR2021-01054 cited repeatedly to alleged objective indicia of non-obviousness. *See, e.g.*, IPR2021-00902, Paper 9, 5–10, 20–25 (arguing Labcorp's petition should be denied for not addressing, *inter alia*, alleged unexpected results). If Streck was "roadmapping," one might have expected

Streck to offer a prebuttal to Patent Owner's earlier arguments on objective indicia. Streck did not do so. In fact, as it did in prior preliminary responses, Patent Owner argues this Petition should be denied for failing to address objective indicia. Prelim. Resp. 44–49. Perhaps Streck did not address Patent Owner's argument on that issue precisely to avoid the appearance of roadmapping. But such an approach was not without risk because, when this Petition was filed, the Board had yet to institute any proceeding against the '277 patent and, thus, had not yet signaled its preliminary views on the alleged objective indicia evidence.

As another example, Streck provided no express argument on claim construction to support Streck's position that EDTA is the claimed "agent" that inhibits cell lysis. Yet, in a prior response, Patent Owner argued that such "agent" could not be interpreted to encompass "anticoagulant chelator compounds such as EDTA and ACD." IPR2021-01026, Paper 7, 17–26. Here again, if Streck was "roadmapping," one might have expected it to directly confront Patent Owner's position that the claimed "agent" excludes EDTA. Illustrating the risk to Petitioner's case in not addressing this argument, as explained below, we agree with Patent Owner that EDTA is not an "agent" as claimed and, on this record, we find that at least one of Petitioner's grounds is likely to fail.

Patent Owner sees roadmapping in Streck's Petition based on Patent Owner's past arguments "distinguishing Pertl." Prelim. Resp. 56–57. We do not agree. Patent Owner's prior arguments about Pertl were made in its response to one of Quest's petitions, and were specific to a different set of claims, none of which are challenged here. *See*, *e.g.*, IPR2021-00790,

Paper 21, 4 (order denying institution of challenge based on Adinolfi in combination with Pertl). Patent Owner fails to make any clear connection between what it argued previously about Pertl and how Streck purports to tailor this Petition to address Patent Owner's past arguments. Patent Owner speculates that Streck "repurposed" Pertl to bring an obviousness challenge that otherwise resembles prior petitioners' challenges relying largely on Chiu. Prelim. Resp. 57 (noting that Streck's argument cites repeatedly to Chiu notwithstanding the asserted combination of Pertl and Granger). At the time Streck filed, however, the Board had not yet instituted any proceeding and it is not clear to us that Streck shifted its position based on any alleged deficiency that Patent Owner identified earlier with Chiu or grounds based on Chiu. *General Plastic* at 17 (criticizing follow-on petitions that seek to "us[e] our [(i.e., the Board's)] decisions as a roadmap, until a ground is found that results in the grant of review"); *see also id.* at 17 n.14 (citing cases that explain "a decision on a petition . . . is not simply part of a feedback loop by which a petitioner may perfect its challenges through a subsequent filing") (citation omitted).

Streck's opportunity to study numerous filings challenging the '277 patent along Patent Owner's responses to them weighs somewhat in favor of denial. But, as discussed above, it is not evident that Streck used those papers for roadmapping to any unfair advantage. We determine that Factor 3 is neutral on this record.

4. Factors 6 and 7

General Plastic Factors 6 and 7 relate to the Board's resources and the requirement to issue a timely final written decision. *General Plastic* at 16.

Patent Owner argues that we should deny institution because the Board's resources are generally better spent on initial petitions, and the time for coordinating this proceeding with the schedules of the earlier cases has passed. Prelim. Resp. 58–60 (arguing it is wasteful to institute yet another challenge, especially in view of material overlap with prior petitions). Patent Owner also argues that Petitioner could have, but did not, move to join any of the earlier cases. *Id.* at 59–60.

We agree with Patent Owner to a point. Because there is overlap in the claims and similarities in several of petitioners' unpatentability theories, it is arguably inefficient and wasteful to institute yet another trial. Petitioner could have possibly avoided such inefficiencies by, for example, filing the present Petition earlier, or foregoing its present challenges (to the extent distinct) and joining another earlier-filed petition. On the other hand, that there are numerous petitions against the '277 patent filed on a staggered basis is not unusual based on the number, scope, and timing of Patent Owner's lawsuits. Pet. 67–68 (asserting that Patent Owner's litigation against seven companies "threatens . . . important industries and the medical care they support"). Despite the number of petitions, we see no present obstacle to reaching a final decision on this Petition within the timeframe set by statute. There are also some efficiencies gained based on the Board's familiarity with the '277 patent and prior art at this time, and at least two of Streck's three grounds appear to have merit as we discuss below.

Under the circumstances in this case, we weigh Factor 6 as somewhat in favor of discretionary denial and Factor 7 as neutral to minimally against discretionary denial.

5. Conclusion

After considering all the *General Plastic* factors, we decline to deny the Petition on a discretionary basis. Factor 6 is the only factor that weighs in favor of denial, but not so much that it overrides other considerations on this record that weigh against discretionary denial.

III. 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*, 815 F.3d at 1363 (citing 35 U.S.C. § 312(a)(3)).

To show anticipation under 35 U.S.C. § 102, each and every claim element, arranged as in the claim, must be found in a single piece of prior art. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008).

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

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 proposes the following POSA definition:

> [A POSA] would have at least a bachelor's degree in Chemistry, Biochemistry, Biology, Microbiology, Molecular Biology, Genetics or related fields, as well as either an advanced degree in those fields or in Medicine (M.S., Ph.D., or M.D.), or at least 2-3 years' experience in research or clinical laboratories with respect to pathology, virology, immunology, oncology, hematology or other disciplines concerned with the analysis of body fluid or tissue samples, including detection/analysis of nucleic acids, and would have had experience with available techniques for handling, storing and processing biological samples, including blood samples, for use in laboratory analyses.

Pet. 8 (quoting Ex. 1009 ¶ 34). Patent Owner neither contests this definition nor proposes its own definition in this proceeding. We adopt Petitioner's uncontested proposal for purposes of this Decision.[13]

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[13] On this record, we think it likely that a POSA would have some practical experience (e.g., 1–2 years) in a laboratory working with the subject matter proposed in Petitioner's definition (e.g., detection/analysis of nucleic acids in tissue samples, including blood samples) even where the POSA has an advanced degree. We note this to clarify because Petitioner's POSA definition might otherwise be read to encompass one with minimal practical experience in that subject matter. We adopted somewhat differently phrased definitions for the POSA in the Quest, Labcorp, and Illumina cases based on

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) (2021). 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 "proposes [that] no claim language requires express construction to resolve the grounds herein." Pet. 9.

Patent Owner argues that, in applying the prior art to the claims, Petitioner interprets the claims "too broadly." Prelim. Resp. 19. In particular, Patent Owner argues that Petitioner's interpretation of the phrase "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" to encompass alleged "anticoagulant chelators," such as EDTA or ACD (acid citrate dextrose) is impermissibly broad. *Id.* Patent Owner contends that Petitioner's interpretation departs from the district court's claim construction in the Natera litigation, which concluded that EDTA and other anticoagulant chelators are not encompassed by the claimed "agent" limitation. *Id.*; Ex. 2040, 1, 4–6 ("[T]he Court holds that EDTA and other chelators used as anticoagulants are not within the scope of

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the parties' positions there. *See, e.g.*, IPR2021-00788, Paper 23 at 42–43; IPR2021-01054, Paper 11 at 33–35; IPR2021-01272, Paper 14 at 39. We do not see that the relatively minor differences in the proposed POSA levels would alter the outcome of this Decision.

the 'agent' limitation."). And, Patent Owner contends, the exclusion of EDTA and other anticoagulant chelators is justified based on the intrinsic evidence as well as extrinsic evidence (insofar as EDTA and ACD are commonly referred to in the art as anticoagulants and allegedly not cell lysis inhibitors). Prelim. Resp. 20–28.

We agree in part with Patent Owner. The intrinsic evidence unambiguously demonstrates that EDTA is not the claimed "agent." The '277 patent expressly describes EDTA as a "magnesium chelator" compound that may be added during blood processing. Ex. 1001, 31:52–56.[14] The patent never describes EDTA as a cell lysis inhibitor, membrane stabilizer, or cross-linker, which are described separately—listing many examples of compounds with those functionalities. *See, e.g.*, *id.* at 31:57–32:21. Moreover, the '277 patent, in illustrating the stated advantage of adding an agent that inhibits cell lysis, describes comparative testing on blood samples with and without such agent. *Id.* at 89:1–34 (Example 4). In Example 4, the patent describes determining "[t]he percent of fetal DNA in plasma obtained from a pregnant female . . . *both in the absence and presence of inhibitors of cell lysis*." *Id.* at 89:11–13 (emphasis added). That example describes obtaining two DNA templates: one from a blood sample taken in a tube treated *with only EDTA* and another treated *with EDTA and formaldehyde*. *Id.* Because the EDTA-only tube is used as a control in this example, and formaldehyde is undisputedly listed in the '277 patent as "an

[14] In addition to listing EDTA as a "magnesium chelator," the '277 patent discloses that "[o]ptionally, a calcium chelator, including but not limited to EGTA, can be added." Ex. 1001, 31:52–56.

agent that inhibits lysis of cells," this disclosure in the patent strongly suggests that EDTA is not the "agent" as claimed. *See, e.g.*, *id.* at 31:57–59 ("In another embodiment, a cell lysis inhibitor is added to the maternal blood including but not limited to formaldehyde . . . .").

If the Specification of the '277 patent left any question whether EDTA is encompassed by the "agent" limitation, the prosecution history leaves no doubt that it is not. During prosecution, the Examiner rejected the relevant claims over the "Lo" reference, with Lo's use of EDTA-containing tubes expressly cited as meeting the "agent" limitation. *See supra* Section I(E). In response, applicant argued that "the assertion by the Office that EDTA is a cell lysis inhibitor is simply incorrect," and then unequivocally stated that "EDTA is not an 'agent that inhibits cell lysis.'" Ex. 2223, 1192. That argument was an explicit and unambiguous disclaimer confirming that EDTA does not satisfy the "agent" limitation. *Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 798 (Fed. Cir 2019) ("[T]o operate as a disclaimer, the statement in the prosecution history must be clear and unambiguous, and constitute a clear disavowal of scope."). Based on the totality of the intrinsic evidence, we thus agree with Patent Owner and the district court that EDTA is not within the scope of the "agent" limitation of claims 55 or 81. Ex. 2040, 6 (finding that applicant's "use of quotations around the relevant claim language unambiguously shows the applicant distinguished EDTA from the claim term 'agent that inhibits cell lysis'").

Patent Owner's proposed claim interpretation goes farther—excluding not just EDTA, but all other "anticoagulant chelators," allegedly including ACD, from the scope of the "agent" limitation. Prelim. Resp. 19–29

(arguing the evidence "consistently and unambiguously establish[es] that the claimed 'agent that inhibits lysis' does ***not*** include anticoagulant chelators, such as EDTA and ACD"). We focus here on ACD and the components that make up ACD, and need not, for purposes of determining if institution is warranted, decide whether all other compounds or compositions that might be characterized as "anticoagulant chelators" are excluded from the scope of the claimed "agent." *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))).

Some basic information about ACD is necessary to understand the present dispute. ACD is a solution that includes citric acid, sodium citrate, and dextrose (i.e., glucose) in water. Ex. 2036, 1 (listing components of ACD, and disclosing that it "acts as an anticoagulant by the action of the citrate ion chelating free ionized calcium"); Ex. 1009 ¶ 217 (testifying that "[d]extrose is [the] name for the naturally occurring form of glucose" as included in ACD). ACD, thus, includes a chelator compound (sodium citrate/citrate ion) but also a glucose component, which the '277 patent expressly lists as a membrane stabilizing agent that may be added to reduce cell lysis. Ex. 1001, 32:4–12 ("In another embodiment, an agent that stabilizes cell membranes may be added to the maternal blood samples to reduce maternal cell lysis including but not limited to aldehydes . . . sucrose, astaxanthin, *glucose* . . . ."") (emphasis added). Petitioner cites to ACD and

its inclusion of a glucose component when mapping the "agent" limitation to the prior art. Pet. 51–52.

During the '277 patent's prosecution, the Examiner did not expressly address whether ACD (or its glucose component) is the claimed "agent." The only compounds the Examiner cited as meeting the "agent" limitation were EDTA and formaldehyde. The applicant disclaimed EDTA as discussed above. In so doing, applicant explained that EDTA is a chelator compound used as an anticoagulant based on the compound's ability to chelate calcium. Ex. 2223, 1192. There is evidence here that ACD, like EDTA, is commonly used as an anticoagulant for preparing plasma samples from whole blood. *See, e.g.*, Ex. 2017, 4 (extrinsic publication disclosing that "[m]any different anticoagulants can be used in the preparation of plasma, such as heparin, acid citrate dextrose (ACD) and ethylenediaminetetraacetic acid (EDTA)"). We are not persuaded, however, that applicant disavowed all anticoagulants and all of the components of such anticoagulants. Indeed, in the same remarks where EDTA was disclaimed, applicant distinguished EDTA from examples of lysis-inhibiting agents identified in the patent—among them, glucose, an undisputed component of ACD. *Id.* (arguing that "EDTA is clearly referred to as a chelator in Applicant's specification, . . . whereas multiple examples of agents that inhibit cell lysis are provided separately (see, e.g., paragraphs [166] to [167])"); *see id.* at 1376–1377 (paragraph 167, listing "glucose"). On such a record, we are not persuaded that applicant clearly and unambiguously disavowed ACD and all the compounds that make up ACD, especially glucose, from meeting the "agent" limitation.

Patent Owner also points out that, during prosecution of the later-issued '720 patent, some of the cited prior art disclosed ACD yet the Examiner determined that such art did not disclose an "agent that impedes cell lysis." Prelim. Resp. 25. That is an accurate account of the prosecution history, but there is no evidence the Examiner actually considered the disclosure about ACD (much less ACD's glucose component) as meeting the "agent" limitation—that specific issue was simply never raised by Examiner or by applicant in any responsive remarks. *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325–26 (Fed. Cir. 2003) ("[F]or prosecution disclaimer to attach, . . . the alleged disavowing actions or statements made during prosecution to be both clear and unmistakable."). Instead, by that time in the prosecution of the '277 and '720 patents, the Examiner had already moved from EDTA to reliance on formaldehyde, as disclosed in Kiessling, to satisfy the "agent" limitation. Ex. 2223, 569–70; Ex. 2041, 1380–1381, 2618–2619.

Based on the intrinsic record, the claimed "agent" encompasses glucose. Ex. 1001, 15:53–65, 32:4–12; Ex. 2223, 1192, 1376–1377. We find no clear and unmistakable disclaimer of glucose in that record, whether glucose is used alone or with other compounds in solution as in ACD. The claims, as a whole, are open-ended and do not exclude compounds or compositions that comprise chelators or anticoagulants. *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1319 (Fed. Cir. 2009) ("The claim uses the term 'comprising,' which is well understood in patent law to mean 'including but not limited to.'"). Nothing in Patent Owner's cited extrinsic evidence, allegedly classifying ACD as an anticoagulant only, changes the

breadth of the claims as defined by the patent itself and its prosecution history. Prelim. Resp. 26–27.

Inasmuch as Petitioner's position and our discussion above interprets the claimed "agent" to encompass the glucose component of ACD, we do not agree that such interpretation "conflicts" with the interpretation adopted by the district court. Prelim. Resp. 19. The district court's interpretation is silent on whether glucose within ACD is within the scope of the "agent" limitation. *See generally* Ex. 2040 (including no discussion specific to ACD or glucose).

D. Overview of the Asserted Prior Art

1. Pertl (Exhibit 1010)

Pertl is an article that published in 2000 and relates to detection of male and female fetal DNA in maternal plasma. Ex. 1010, 45–46 ("The goal of our study was to develop a fetal DNA detection method that can be used independently of the fetal gender."). Pertl discloses the detection of fetal DNA using highly polymorphic STR markers and fluorescent multiplex PCR. *Id.* at 45–46, 48.

Pertl teaches collecting blood samples from pregnant women at term. *Id.* at 46. According to Pertl, "[p]regnant women at term were selected because of prior data suggesting an increased concentration of fetal DNA in maternal plasma at term . . . and because of the ease of obtaining confirmatory material from the newborn." *Id.* The maternal blood samples were collected prior to delivery in tubes containing EDTA. *Id.* (disclosing that paternal blood was also collected where available).

Pertl teaches that, "[i]n the present study, [Pertl] used PCR amplification of nine STRs to detect fetal-specific alleles in maternal plasma samples." *Id.* at 48. Pertl reports that "[t]he sensitivity of PCR amplification of different STRs was estimated to be 0.01-2.5%." *Id.* (disclosing that "the described technique has a lower sensitivity for detecting fetal DNA in maternal plasma than the SRY system described by Lo"). Pertl discloses that this "lower level of sensitivity may be due to the nonselective nature of PCR amplification of STRs in that both the target (i.e., the fetus') and the background (i.e., the mother's) sequences are amplified together." *Id.* According to Pertl, "[u]nder these conditions, the excess of the background sequences could out-compete the rare target sequences for amplification," yet "because of the high concentration of fetal DNA present in maternal plasma . . . , our proposed technique was sensitive enough to detect fetal-specific alleles in all mother/child pairs studied." *Id.*

2. Chiu (Exhibit 1011)

Chiu is an article published in 2001. *See generally* Ex. 1011. 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 "the discovery of fetal DNA in maternal plasma and serum in 1997 . . . [and] numerous reports have confirmed its potential application for noninvasive prenatal diagnosis." *Id.* at 1607. 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.* Chiu addresses "whether fetal DNA circulates predominately in a cellular or cell-free form in maternal plasma." *Id.* at 1608.

Chiu discloses the use of different protocols to process blood samples and separate maternal plasma, including centrifugation, microcentrifugation, filtration, and Percoll density-gradient separation, and the effects of such processing protocols on the amounts of fetal and maternal DNA in plasma samples. *Id.* at 1608–1609. In Chiu's study, the blood samples were initially drawn and collected into EDTA tubes and processed within two hours. *Id.* at 1608.

As described in Chiu, certain genes (β-globin and *SRY*) in the separated plasma were isolated and amplified via PCR for determination of the levels of fetal and total DNA in the samples. *Id.* These genes could be used as proxies for determining the percentage of fetal compared to total DNA because the β-globin gene is present in maternal and fetal DNA, and the *SRY* gene only in the fetal DNA. *Id.* at 1608, 1612.

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 discloses 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 further teaches that "[v]irtually cell-free plasma can be obtained by centrifugation of blood samples, followed by filtration or microcentrifugation." *Id.* at 1613.

Chiu teaches that the "lack of difference in fetal DNA concentration among the different [sample-processing] treatment groups . . . suggests that most of the fetal DNA circulates in an extracellular form." *Id.* at 1612 ("[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. Moreover, Chiu concludes that "[a]s research in the field of circulating nucleic acids is growing rapidly[,] for findings to be easily compared across studies, some form of standardization [on blood processing protocols] needs to be agreed on." *Id.*

3. Granger (Exhibit 1012)

Granger an international patent application that published in 1997. Ex. 1012, code (43). Granger relates to a specimen collection fluid that comprises an aliphatic aldehyde. *Id.* at Abstr.; *see also id.* at 1:6–9 ("This invention relates to specimen collection fluids . . . for the treatment of blood

and/or bone marrow specimens to be used for immunohaematological analysis.").

Granger discloses that sample integrity may be negatively affected due to delays in processing or analysis. *Id.* at 1:17–2:2 ("If analysis is delayed, for example . . . [if] a specimen is transported from one country to another, it may not be in a suitable condition when finally submitted to analysis, and a further specimen may need to be taken.").

Granger teaches that a specimen collection fluid may be used, which fluid includes a sterile aqueous solution comprising an aliphatic aldehyde and, preferably, an anticoagulant. *Id.* at 3:19–25. Granger further teaches that "any suitable aliphatic aldehyde" can be used, but the aldehyde "is preferably formaldehyde, and most preferably paraformaldehyde." *Id.* at 5:14–17. According to Granger, with use of Granger's specimen collection fluid, "immunohaematological analysis can be performed upon peripheral blood after more than 5 days and up to 7 days following collection without substantial deterioration in the antigen or cellular integrity." *Id.* at 9:18–10:3 (disclosing that "white cell count . . . can remain substantially stable during this period"). Granger further discloses that "RNA can be extracted from specimens for up to 5 days after collection, for example, for PCR analytical techniques." *Id.* at 10:6–8; *see also id.* at 10:12–16 ("The peripheral blood parameters remain substantially stable, facilitating the transportation of specimens over long distances or allowing retention of specimens until times which are convenient for analysis."). In an example, Granger discloses that "non-lymphocytes and debris have built up in the control specimen to the

extent that the measurements are regarded as unreliable," while the specimen containing the aliphatic aldehyde is comparatively stabilized. *Id.* at 11:1–27.

4. Lee (Exhibit 1015)

Lee is an article about quantitating cell-free genomic DNA in serum and in plasma, which article indicates a publication date of February 2001. Ex. 1015, 276. Lee discloses "a protocol to process serum and plasma samples for genomic DNA PCR amplification has been optimized, and baseline concentrations of cell-free DNA in serum and plasma have been evaluated for the study of posttransfusion chimerism." *Id.* at 277.

As part of Lee's study, "[f]resh blood from healthy donors was collected into tubes with ACD (yellow-top), EDTA (purple-top), or no anticoagulant (red-top)." *Id.* Lee discloses that the samples were then centrifuged at 3000 rpm to prepare plasma (yellow-top and purple-top) and serum (red-top) samples, and aliquots from the samples were prepared within two hours of blood draw and frozen at -80º C. (i.e., at Day 0). *Id.* The original plasma and serum collection tubes were placed at 4°C and the process for preparing additional aliquots (discussed above) was repeated each day, on days 1–7. *Id.* (noting that the tubes were re-centrifuged for fifteen minutes each day before the preparation of the additional aliquots). Subsequently, the aliquots were thawed and DNA was extracted and quantified using a PCR. *Id.* at 277–278.

Lee describes the differences in cell-free DNA concentrations between serum and plasma samples. *Id.* at 276. According to Lee, "[f]resh serum samples had concentrations of cell-free DNA that were about 20-fold higher than the concentrations in fresh plasma samples." *Id.* Lee discloses

that cell-free genomic DNA increased daily in serum samples upon storage (e.g., to a level more than 100 times baseline) compared to the plasma samples, which exhibited "a small increase in cell-free plasma DNA in stored ACD whole blood samples." *Id.* In comparing the samples, Lee teaches that, "[o]n Day 0, serum samples . . . contain much more cell-free genomic DNA than EDTA . . . or ACD . . . plasma samples (range, 6–24 times plasma)" and, with respect to the serum samples, Lee notes that cell-free DNA concentration increased 3-fold from day 0 to day 1 and increased 42-fold from day 1 to day 4. *Id.* at 280, Figs. 2A, 2B; *see also id.* at 280, Fig. 4 (disclosing that, "for most corresponding [ACD] plasma samples, no significant changes in concentration of cell-free genomic DNA were seen during storage at 4°C").

Lee concludes that "[m]ost cell-free DNA in serum samples is generated during the process of clotting in the original collection tube" and, thus, "serum samples should not be used to monitor the concentration of cell-free DNA in a patient's circulation." *Id.* at 276; *see also id.* at 279–281 (disclosing that the most likely explanation for higher levels of genomic DNA in serum than plasma is that "the process of clotting lyses WBCs, which release nuclear fragments into the serum").

E. Ground 1: Obviousness over Pertl and Granger

Petitioner asserts that claims 55–61, 68, 69, 80–86, 89–90, 94, 126–130, 132, and 133 are unpatentable as obvious over the combination of Pertl and Granger. Pet. 22–42. Pertl and Granger are summarized above. *See supra* Section III(D). Our discussion focuses on claim 55 and we note that

Patent Owner, at this time, does not argue the patentability of the challenged claims separately. *See generally* Prelim. Resp. 38–44.

According to Petitioner, "Pertl discloses all but one feature" of claim 55. Pet. 22–31.[15] Petitioner cites, *inter alia*, disclosure in Pertl about using blood samples collected from pregnant human females, centrifuging blood samples to isolate and cell-free fetal DNA in plasma, and determining the sequence of a locus of interest on free fetal DNA using multiplex fluorescent PCR. *Id.* at 22–24 (citing Ex. 1010, 46; Ex. 1009 ¶¶ 76–79, 89–93). For the "agent" limitation, if EDTA is not the claimed agent, Petitioner contends that "Pertl does not otherwise expressly disclose its samples included an agent that inhibits lysis of cells," and Petitioner turns to Granger. *Id.* at 24–25. Petitioner cites Granger's specimen collection fluid that comprises an aliphatic aldehyde, preferably formaldehyde. *Id.* at 25 (citing Ex. 1012, 4:16–27, 5:14–17). Petitioner asserts that formaldehyde was a known cross-linker compound, and is a cell lysis inhibitor in the '277 patent. *Id.* (citing Ex. 1009 ¶¶ 126–127; Ex. 1001, 473:15–18).

Patent Owner's response does not identify any limitation of claim 55 that is not taught or suggested in the combined disclosures of Pertl and Granger. *See generally* Prelim. Resp. 38–44. Based on the preliminary record, we find that Petitioner has established a reasonable likelihood that Pertl and Granger teach or suggest all the limitations of claim 55.

[15] Petitioner, in a footnote, contends that Pertl uses EDTA and "EDTA is an agent that inhibits cell lysis." Pet. 22 n.1. We disagree that EDTA is the claimed "agent" as already explained. *See supra* Section III(C).

Petitioner argues that a POSA would have been motivated to combine the teachings in Pertl and Granger, with a reasonable expectation of success in arriving at the subject matter of claim 55. Pet. 25–31. According to Petitioner, Pertl describes varying levels of success in detecting free fetal-specific DNA; and Pertl noted the non-selective nature of PCR and the potential for excess maternal background DNA to out-compete rare target (i.e., fetal) sequences as a possible explanation. *Id.* at 25–26 (citing Ex. 1010, 46, 48). Petitioner also notes that Pertl sought to maximize fetal DNA amounts and, thus, employed samples from pregnant women at term. *Id.* at 26 (citing Ex. 1010, 45, 48). Petitioner contends that "[t]hese observations [in Pertl] would motivate POSAs to look for ways to reduce increases in maternal background sequences," and Petitioner's interpretation of the art on these points is supported by Dr. Patterson's testimony. *Id.* (citing Ex. 1009 ¶¶ 94–98).

In further support, Petitioner cites Chiu as evidence that POSAs were aware that maternal background DNA may be released into blood samples through cell lysis to the extent maternal cells are not removed, impacting the analysis of free fetal DNA in such samples. *Id.* (citing Ex. 1011, 1612–13). Thus, Petitioner contends, "POSAs would have understood increased background maternal cell-free DNA in samples described in Pertl was caused by lysis of intact maternal cells," and that "[a]dverse consequences of background maternal cell-free DNA would have motivated POSAs to include an agent known to inhibit lysis." *Id.* at 27 (citing, *e.g.*, Ex. 1009 ¶¶ 62–63, 98–103, 111–113).

According to Petitioner, "Pertl and Chiu [both] reported increases in background DNA despite centrifugation." *Id.* (citing Ex. 1011, 1609–1610; Ex. 1010, 46). Petitioner argues that, although Chiu teaches that reductions in background DNA may be possible through precise filtration and ultra-highspeed centrifugation, those processing means are "beyond more modest capabilities of most doctors' offices and clinics where blood collection for prenatal testing would occur." *Id.* at 27–28. Moreover, Petitioner asserts, samples taken at doctors' offices and clinics are usually shipped to regional labs for analysis and a "POSA would have appreciated shipment delays" would result in WBC lysis and contamination of the sample with maternal background DNA. *Id.* ("Once lysed, a maternal cell's background DNA cannot be removed effectively by filtration, microcentrifugation, or a combination of both.") (citing Ex. 1009 ¶¶ 119–123)).

Petitioner contends a POSA would have known that cross-linking aldehydes can inhibit cell lysis and would have looked to Granger's specimen collection fluid. Pet. 28–29. According to Petitioner, Granger describes problems with delayed specimen processing, including the buildup of debris from lysed WBCs in blood samples absent further sample treatment. *Id.* (citing, for example, Ex. 1012, 1:25–2:2, 11:23–27, 13:15–19; Ex. 1009 ¶¶ 125–127). Petitioner contends that Granger describes a specimen collection fluid that preferably includes an aliphatic aldehyde, like formaldehyde or paraformaldehyde, and that, by using such a fluid it is possible to reduce deterioration of cellular integrity in the samples for up to several days. *Id.* at 29–30 (citing, for example, Ex. 1012, 3:19–27, 9:18–23, 10:3–6, 10:12–16, 14:2–8; Ex. 1009 ¶¶ 128–129); *see also* Ex. 1012, 14:10–

12 ("It is also found that stablised specimens in accordance with the invention have minimal haemolysis over a 7 day period."). Petitioner argues a POSA would, thus, have been motivated to add formaldehyde or paraformaldehyde to prevent premature lysis of maternal cells and reduce the release of free maternal DNA before samples could be further processed. *Id.* at 30; Ex. 1009 ¶¶ 130–131.

Petitioner contends that a POSA would have reasonably expected success in combining Pertl and Granger because the addition of, for example, formaldehyde would have been expected to inhibit lysis of maternal WBCs in blood samples from pregnant human females. Pet. 30–31 (asserting this would have been expected to stabilize samples for the time needed for processing, and reduce addition of background maternal DNA sequences). Moreover, Petitioner contends, Granger's specimen collection fluid is compatible with analysis of free nucleic acids. Petitioner argues that "Granger specifically contemplated use of its specimen collection fluid in blood samples from which nucleic acids were extracted for PCR analysis." *Id.* at 31 (citing Ex. 1012, 10:6–8 ("RNA can be extracted from specimens for up to 5 days after collection, for example, for PCR analytical techniques.")); *see also* Ex. 1009 ¶ 134 (testifying that Granger "announced that its specimen collection fluid was compatible with the use of PCR analysis of free nucleic acids, such as free fetal DNA, in the sample").

Patent Owner responds, challenging Petitioner's position that a POSA would have been motivated to combine Pertl and Granger with a reasonable expectation of success. Prelim. Resp. 39–42. According to Patent Owner, Petitioner fails to recognize that Granger's addition of aliphatic aldehydes to

blood samples "is ***not*** in the context of ***cell-free*** RNA." *Id.* at 39 (citing Ex. 1012, 9:18–10:8 (disclosing "cell count[s]" remain stable). Indeed, Patent Owner argues, Petitioner misinterprets Granger's disclosure about extracting RNA for further analysis because that disclosure relates to extracting RNA from intact cells, not extracting RNA from a cell-free portion of the sample. *Id.* at 40 ("Granger's only mention of nucleic acids refers to extracting RNA from fixed cells."); *see also id.* at 18 (Patent Owner's overview of Granger).

Although Patent Owner provides no testimony to support its interpretation of Granger on these points (responsive to Dr. Patterson's testimony and apparent contrary interpretation), Patent Owner's position may have merit. We note, in what appears to be a more detailed discussion of extracted RNA, Granger discloses that, between day zero to day five, the RNA content in the unstabilized (i.e., control) sample dropped from 495 μg/ml to 215 μg/ml. Ex. 1012, 14:10–24. Comparatively, in the stabilized sample, the RNA content dropped to a lesser extent from 340 to 240 μg/ml over days zero to five. *Id.* The Board could benefit, and the parties should consider further addressing, whether this (or other) relevant disclosure supports their competing interpretations of Granger. At this stage, we determine that the dispute about Granger's disclosures specific to extracted RNA raises material questions best resolved on a full evidentiary record.

Continuing from Patent Owner's position that Petitioner misinterprets Granger's teachings about using formaldehyde and extracted RNA, Patent Owner contends that other studies recognized that formaldehyde could have a negative effect on nucleic acids. Prelim. Resp. 40. According to Patent

Owner, "[s]tudies warned against using formaldehyde and recommended alternative fixatives due to potential effects on nucleic acids." *Id.* In support, Patent Owner cites three exhibits—an article from 1983, an article from late 2002, and a 2005 article co-authored by Lo and Chiu. *Id.* at 40–41 (citing Exs. 2139, 2150, and 2155). The 1983 article relates to carcinogenic risks and a review of formaldehyde's genotoxicity and notes, for example, "reports that formaldehyde could induce genetic alterations . . . [and] can induce single-stranded DNA breaks." Ex. 2139, 945. Whether such a disclosure may or may not have discouraged the addition of formaldehyde as proposed by Petitioner is a matter best resolved on a full record, weighing the potential benefits and alleged drawbacks of adding formaldehyde. The other two articles post-date the putative earliest effective filing date of the '277 patent. Thus, as those articles do not appear to have been available at the time of such filing, the extent to which they might inform the POSA's expectations or detract from the reasons for combining the art at the time of invention is unclear. Patent Owner is free to raise this issue at trial and we will revisit as necessary on a fully-developed record.[16]

Patent Owner argues the "only plausible explanation for Petitioner's proposed combination is hindsight analysis based on Dr. Dhallan's [(i.e., the named inventor's)] own invention." Prelim. Resp. 42–43. We do not, at this stage, agree with Patent Owner. Petitioner's challenge invokes the teachings

[16] The 2005 article (Ex. 2155) "conclude[s] that formaldehyde has a detrimental effect on plasma RNA detection." The parties may wish to consider briefing whether this reflects, for example, industry skepticism, provided a sufficient nexus with the claims is shown as discussed *infra*.

of Pertl (and Chiu) for the isolation and analysis of cell-free fetal DNA in maternal blood samples, and as recognizing that release of maternal background DNA from lysis of maternal WBCs poses potential problems for such analysis. Pet. 22–27. To address the problematic lysis, Petitioner contends, with documentary and testimonial support, that a POSA would have considered well-known WBC lysis inhibiting agents—cross-linker aliphatic aldehydes, as disclosed in Granger. *Id.* at 24–25. That subject matter has an evidentiary basis rooted in the cited prior art, not solely the '277 patent. And, on this preliminary record, Petitioner provides persuasive reasoning to support the allegedly obvious addition of paraformaldehyde or formaldehyde to reduce the undesired maternal cell lysis especially where samples cannot undergo immediate processing but require shipment and associated delays. *Id.* at 27–28.

Patent Owner argues that Petitioner's hindsight bias is also revealed because the claimed invention allegedly met a long-felt need, produced surprising results, and garnered praise from peers in the field. Prelim. Resp. 43–44. We decline to attribute significant weight to those considerations at this stage. As discussed below, the challenged claims are broad compared to Patent Owner's comparatively narrow evidence about alleged unexpected results, etc. Patent Owner has not, on this preliminary record, established a sufficient nexus between that evidence and the broad claims. We thus find unavailing at present the argument that such evidence shows that Petitioner's challenge is based on hindsight.

Patent Owner argues that we should deny institution of Ground 1 (and Ground 3) because Petitioner does not address secondary considerations of

nonobviousness. Prelim. Resp. 44–49 (citing argument about an alleged long-felt need and unexpected results raised during prosecution). Patent Owner also cites several decisions of the Board that Patent Owner contends support its argument in favor of denial. *Id.*

It would have been prudent for Petitioner to provide some discussion (even if brief) about the alleged secondary considerations in the Petition itself. Discussion about secondary considerations is absent in Petitioner's overview of the prosecution history (Pet. 4–8) and merits analysis.[17] Under the unique circumstances here, however, we conclude it is not appropriate to deny the Petition on this basis.

The Board rarely denies a petition for failure to preemptively address alleged secondary considerations of nonobviousness. As we explained to Patent Owner in related matters, where the Board has done so, it is usually reserved for cases where the secondary considerations are known, and clearly relied upon as being persuasive in prior proceedings before the courts or the Patent Office. IPR2021-00902, Paper 13, 51 (citing cases and distinguishing cases cited by Patent Owner). Patent Owner disagrees with that assessment, citing the same cases we distinguished previously. Prelim. Resp. 44–49. According to Patent Owner, the Examiner's reliance on secondary considerations here was no less decisive than in past Board

[17] The only apparent reference to secondary considerations by Petitioner or its declarant, Dr. Patterson, is a generic listing of categories and the need to establish a nexus between such considerations and the claims, along with an assertion by Dr. Patterson that he is "unaware of any such secondary considerations in relation to the challenged claims." Ex. 1009 ¶¶ 27–28.

decisions that denied institution. *Id.* at 48–49 (arguing the Examiner allowed the '277 patent's claims based on "persuasive argument(s)" made in applicant's remarks, which included argument on secondary considerations). Patent Owner's disagreement with our reading of the cases aside (which distinctions we do not repeat), each of those cases was decided on their unique facts and none of them is binding on this panel.

Moreover, there are two key considerations here that weigh against denying the Petition on the basis that it did not preemptively grapple with secondary considerations. First, the extent to which the Examiner relied on the alleged secondary considerations in allowing the challenged claims is hardly clear. And second, even if the Examiner had relied on the alleged secondary considerations, without a nexus between the evidence and the claims, those considerations are entitled to little or no weight. The absence of a sufficient nexus is self-evident—with no attempt by patentee to make a nexus showing during prosecution or even now in its preliminary papers. We further discuss these two points below.

During prosecution of the '277 patent, the Examiner never referenced the applicant's evidence of long-felt need or unexpected results as the basis for allowing the claims. In allowing the claims, the Examiner referred to claim amendments and vaguely to "argument(s)" made by applicant—of which there were several, some of which were based on alleged secondary considerations. *See* Ex. 2223, 521; *supra* Section I(E). During prosecution of the later issued '720 patent, the same Examiner, at one point, did appear to find applicant's argument about long-felt need and unexpected results to be "[t]he most persuasive," withdrawing the pending rejections as a result.

See IPR2021-00788, Paper 23, 16–17 (summarizing portions of the '720 prosecution history); Ex. 2041, 2459. Shortly afterward, however, the Examiner withdrew the prior action (where the Examiner made the comment about secondary considerations) and reinstated rejections of the claims for obviousness. Ex. 2041, 2527–2532. This suggests, if anything, that the Examiner changed their mind about what weight (if any) the alleged secondary considerations should be given. When the '720 patent's claims were allowed later, there was no mention of secondary considerations. *Id.* at 2661 (stating that the art did not teach the limitations of the claims). On such a record, whether the Examiner relied on any alleged secondary considerations as a basis for allowing the claims of the '277 and '720 patents is ambiguous at best.

The absence of a nexus between Patent Owner's alleged secondary considerations and the challenged claims is also clear on its face. For example, Patent Owner's argument and evidence about unexpected results are specific to the addition of formaldehyde/formalin as the lysis-inhibiting agent, yet independent claims 55 and 81 do not require formaldehyde, or even recite any specific agent. Prelim. Resp. 46–48. Secondary considerations are only relevant to the obviousness inquiry if there is a nexus between the claimed invention and that evidence. *In re Affinity Labs of Tex., LLC*, 856 F.3d 883, 901 (Fed. Cir. 2017); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). It is Patent Owner's threshold burden to establish this nexus. *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999) ("The patentee bears the burden of showing that a nexus exists."). Patent Owner does not attempt to address the nexus issue

here despite the Board noting this deficiency several times in related proceedings.[18] *See* IPR2021-00788, Paper 23 at 55–62; IPR2021-00902, Paper 13 at 52–53; IPR2021-01272, Paper 14, 58–59.

For the above reasons, we decline to deny the Petition on the basis that it does not address the alleged secondary considerations and we also, at this stage, give little weight to Patent Owner's argument and evidence on such secondary considerations. As appropriate, we will further address secondary considerations of nonobviousness on a full record.

Altogether, we determine that Petitioner has met its threshold burden and established to a reasonable likelihood that at least claim 55 would have been obvious over Pertl and Granger. Petitioner cites evidence to support its assertions on the other challenged claims, none of which are separately argued by Patent Owner at this stage. Pet. 32–42. Considering Petitioner's argument and evidence, Petitioner is reasonably likely to prevail in establishing that one or more of those additional claims are unpatentable over Pertl and Granger.

F. Ground 2: Anticipation by Chiu

Petitioner asserts that claims 55–59, 61, 68, 69, 80–86, 89, 94, and 126–130 are anticipated by Chiu. Pet. 42–49. For independent claim 55, Petitioner contends that Chiu discloses all of the limitations of the claimed method. According to Petitioner, Chiu discloses collecting blood samples

[18] For future guidance, the parties may consider developing argument and evidence on alleged secondary considerations as discussed in our institution decision in Quest's case (IPR2021-00788, Paper 23 at 55–62).

from healthy pregnant women, meeting the claim element of "[a] sample obtained from a pregnant female." *Id.* at 43 (citing Ex. 1011, 1607–1608; Ex. 1009 ¶ 170). Petitioner contends that Chiu teaches isolating cell-free fetal DNA from the blood sample as claimed. *Id.* (citing Ex. 1011, 1608–1609 (disclosure about centrifuging samples to prepare and further process plasma portions, and extracting fetal DNA using a Qiagen blood kit)); Ex. 1009 ¶¶ 170–172. Petitioner further contends that Chiu discloses determining the sequence of a locus of interest on free fetal DNA as claimed. Pet. 43–44 (citing Chiu's disclosure on determining sequences using quantitative PCR for the *SRY* and *β-globin* genes); Ex. 1011, 1609, 1612; Ex. 1009 ¶¶ 173–178.

For claim 55's "agent that inhibits lysis of cells" limitation, Petitioner cites Chiu's disclosure of collecting samples in tubes that contain EDTA. Pet. 44–45; Ex. 1011, 1609; Ex. 1009 ¶ 179. According to Petitioner, Lee evidences that EDTA "reduce[s] the lysis of white blood cells and prevent[s] the release of cellular DNA into the sample." Ex. 1009 ¶¶ 179–182; Pet. 45–46; Ex. 1015, 277–280.

Petitioner's challenge to independent claim 81 as anticipated by Chiu is no different, cross-referencing Petitioner's analysis on claim 55. Pet. 48 ("Chiu anticipates Claim 81 for the same reasons as Claim 55.").

Patent Owner raises a single counterargument. According to Patent Owner, "EDTA is not the claimed 'agent that inhibits lysis of cells.'" Prelim. Resp. 28–30 (cross-referencing Patent Owner's argument about interpretation of the "agent" limitation). We focus on Patent Owner's argument because, on this preliminary record, it is decisive.

We agree with Patent Owner that EDTA is not the claimed "agent" of claims 55 or 81 (or the challenged dependent claims). Based on the intrinsic evidence, we conclude that the claimed "agent that inhibits lysis of cells" does not encompass EDTA. *See supra* Section III(C). For at least that reason, we determine on this record that Petitioner is not reasonably likely to prevail in showing that claims 55–59, 61, 68, 69, 80–86, 89, 94, and 126–130 are anticipated by Chiu. If trial is instituted it must, however, be instituted on all challenged claims and grounds. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1354 (2018).

G. Ground 3: Obviousness over Chiu and Lee

Petitioner asserts that claims 55–59, 61, 68, 69, 80–86, 89, 94, and 126–130 would have been obvious over Chiu and Lee. Pet. 49–55. Chiu and Lee are summarized above. *See supra* Section I(D).

We focus on Petitioner's contentions against claim 55 as representative. Pet. 49–52. We then proceed to Patent Owner's arguments, which are directed to the challenged claims as a group. Prelim. Resp. 30–38.

Petitioner argues, persuasively on this record, that Chiu discloses collecting blood samples from pregnant women, isolating fetal DNA from the sample, and determining the sequence of a loci of interest on fetal DNA as claimed. Pet. 50 (cross-referencing Petitioner's Ground 2 contentions as to these limitations); Ex. 1009 ¶¶ 206–209. Patent Owner provides no argument otherwise at this stage.

For the "agent" limitation, Petitioner cites to Lee's disclosure of ACD. Pet. 50. According to Petitioner, Chiu disclosed preparing plasma samples

in tubes containing EDTA, and Lee discloses that ACD can be used in place of EDTA to prepare plasma samples, and that ACD is an agent that inhibits the lysis of cells. *Id.* at 49–50 (asserting that "a POSA would have been motivated to substitute Lee's acid citrate dextrose ('ACD') in place of Chiu's EDTA, with reasonable expectations of success"); Ex. 1009 ¶¶ 211, 216. Petitioner argues, with no Patent Owner rebuttal, that Lee reported that significant portions of WBCs were lysed and DNA sequences released from the cells into the sample in the absence of ACD. Pet. 51 ("Lee counsels POSAs [that] plasma, rather than serum, samples should be employed . . . [and] advocates the addition of an anticoagulant, such as ACD, to blood samples intended for the analysis of cell-free DNA" to limit coagulation and the release of genomic material "as a result [of] white blood cell lysis"); Ex. 1015; Ex. 1009 ¶ 214. Petitioner also cites evidence that ACD includes dextrose (i.e., glucose (Ex. 1009 ¶ 217)), and notes that the '277 patent specifically identifies glucose as an agent that inhibits lysis of cells as claimed. Pet. 52 (citing Ex. 1001, 15:58–16:7, 32:4–21); Ex. 1009 ¶ 218.

Petitioner argues that "[t]he anticoagulant ACD is a common alternative to EDTA" and that "[i]t would have been obvious to a POSA to substitute ACD for EDTA in the samples employed by Chiu." Pet. 51. Indeed, Petitioner contends a "POSA would have been motivated to add ACD to Chiu's blood sample in place of EDTA because it would prevent cell lysis and because it is interchangeable with EDTA for the purposes of the processes described in the Chiu Article." *Id.*; Ex. 1009 ¶¶ 216, 219.

Petitioner persuades us, at this stage, that it is reasonably likely to prevail in establishing that claim 55 is unpatentable as obvious over the

combination of Chiu and Lee. Petitioner provides evidentiary support for its contentions, including citations to the prior art and Dr. Patterson's unrebutted testimony.

Patent Owner contends that Lee fails to disclose the claimed "agent." Prelim. Resp. 30–32. Patent Owner repeats its argument that the claimed "agent" does not encompass alleged anticoagulant chelators including ACD and EDTA. With respect to ACD and its glucose component, we do not agree with Patent Owner's argument for the reasons provided above. *See supra* Section III(C).

Patent Owner further contends that Petitioner's argument fails insofar as it invokes inherency. Prelim. Resp. 32. According to Patent Owner, Petitioner's cited evidence does not establish that ACD and its glucose component necessarily inhibits cell lysis. *Id.* at 32–34.

Patent Owner's argument is unavailing on this record. Patent Owner contends that the '277 patent "merely states that ***glucose*** may serve as a membrane stabilizer." *Id.* at 32. Patent Owner apparently reads the '277 patent as suggesting that glucose *may or may not* be a cell membrane stabilizer, but we do not agree with that reading of the patent. The patent discloses, *inter alia*, that glucose ***is*** a membrane stabilizing agent that "may be added to the maternal blood samples to reduce maternal cell lysis." *See, e.g.*, Ex. 1001, 32:4–12; *see also id.* at 15:58–65 ("An agent that stabilizes cell membranes may be added to the sample including but not limited to aldehydes . . . [and] glucose."). It appears that the word "may" in the phrase above modifies the *addition* of the listed membrane stabilizing agents; such an agent "may" be added but is not strictly required. The phrase continues,

however, stating that such agent may be added "***to reduce*** maternal cell lysis." *Id.* at 32:4–12 (emphasis added). It does not state that the listed agents "may reduce" lysis. The '277 patent identifies glucose as a membrane stabilizer, it is undisputed that ACD is a solution that includes glucose,[19] and the claimed *Markush* group lists "membrane stabilizer[s]" as one of three categories of "agent[s] that inhibits lysis of cells." *Id.* at 472:66–473:5. Moreover, claim 55 does not require any particular degree of membrane stabilization or cell-lysis inhibition. Claim 55 instead requires a sample that "comprises . . . an agent that inhibits lysis of cells, if cells are present." *Id.*

Patent Owner argues that ACD is known and used as an anticoagulant and includes more than just dextrose/glucose, including compounds that act to chelate calcium and magnesium ions. Prelim. Resp. 31–32. We do not disagree. But, as explained above (*supra*, Section III(C)), the claims are open ended and do not exclude anticoagulants or chelator compounds. Again, on this record, we are not persuaded that the claimed "agent" excludes ACD and its glucose component. Patent Owner further argues that there is "no evidence that dextrose, when present along with other components of acid citrate dextrose, must necessarily function as the claimed agent." *Id.* at 33. Patent Owner's argument does not, however, account for Lee's teaching that more free DNA was released into samples without ACD compared to samples with ACD—supporting Petitioner's

[19] *See, e.g.*, Ex. 1009 ¶ 217; Ex. 2036, 4 (disclosing that ACD includes 0.245g of dextrose per 10 mL of solution).

position that ACD provides that function and that it would have been obvious that it does so. *See, e.g.*, Ex. 1015, Figs. 2A, 4.

Patent Owner argues that, "to the extent Petitioner's position is not based on inherency, it is improper to use the patented invention as a blueprint . . . to perform a hindsight reconstruction of the invention." Prelim. Resp. 34. We do not agree on this record that hindsight is the basis of Petitioner's challenge. Petitioner is proposing substitution of known prior art elements for their known uses as taught in the art—substitution of ACD for EDTA as alternative anticoagulants. Pet. 51–52. This is supported by the prior art, including at least Lee, and Dr. Patterson's testimony, and is a rationale with a well-established history. *See KSR*, 550 U.S. at 416 (discussing substitution of well-known prior art alternatives for their disclosed functions); Ex. 1015, 277, 280, Fig. 2A (identifying EDTA and ACD as alternatives); Ex. 1009 ¶¶ 211–216. For similar reasons, we disagree with Patent Owner's argument that Petitioner has provided no rationale for its modification of Chiu's EDTA with Lee's ACD. Prelim. Resp. 35.

Continuing, Patent Owner argues that "a POSA would ***not*** have been motivated to substitute Chiu's EDTA with Lee's ACD" because Chiu is "focused on utilizing ***physical processing protocols***." *Id.* at 35–36; *see also id.* at 37–38 (arguing a POSA would not have modified Chiu's methods "because a POSA would have understood that the 3–6% fetal DNA . . . using those methods were as good as one could expect"). Even if we agreed that Chiu's focus is on physical processing, such as centrifugation and microcentrifugation, when obviousness is the issue, the prior art is not

limited to what the art is "focused on." The prior art must instead be considered for all that it teaches and suggests.

In any event, Patent Owner's argument is a red herring. Petitioner's combination of Chiu and Lee is not based on doing away with physical processing protocols or potential improvements thereto like disclosed in Chiu. And Chiu, despite the alleged focus on physical processing, does not appear to teach that anticoagulants, such as EDTA, are unnecessary when preparing plasma samples for analysis of cell-free DNA. Petitioner's modification is merely based on substituting EDTA for ACD because they are known alternatives and Petitioner points to Lee as evidence that ACD will inhibit clotting and cell lysis. Petitioner's substitutable-alternatives rationale under Ground 3 is not, as we read it, based on the POSA expecting some significant increase in the proportion of measurable free fetal DNA compared to the methods already taught or suggested in Chiu. The reasons for modifying the prior art need not be the same as what motivated the patentee, nor does obviousness hinge on making only those modifications that purport to be the most beneficial. *KSR*, 550 U.S. at 419–420; *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012).

Petitioner cites documentary and testimonial support for the remaining claims challenged under Ground 3. Pet. 52–55. Patent Owner, at this time, does not provide any argument (separate from that addressed above) for these other claims. Considering the argument and cited evidence, we determine on this preliminary record that Petitioner is reasonably likely to prevail in establishing that one or more of those additional claims are unpatentable over the combination of Chiu and Lee.

IV. TIME BAR

Patent Owner's final argument is that Streck's petition is time barred. Prelim. Resp. 60–63. According to Patent Owner, Natera is an unnamed real party-in-interest ("RPI") or a privy of Streck and, because Natera was sued for infringement of the '277 patent over one year before this Petition was filed, this Petition is time barred under 35 U.S.C. § 315(b). *Id.* at 60–61 (listing considerations that inform whether parties are RPIs or privies).

Whether a party is an RPI or privy is highly dependent on the facts of each case, taking account of equitable and practical considerations. CTPG 13; *RPX Corp. v. Applications in Internet Time, LLC*, IPR2015-01750, Paper 128 at 7–8 (PTAB Oct. 2, 2020) (precedential) (hereafter "*RPX*") (asking "whether the non-party is a clear beneficiary that has a preexisting, established relationship with the petitioner") (quoting *Applications in Internet Time, LLC v. RPX Corp.*, 897 F.3d 1336, 1351 (Fed. Cir. 2018)). Two questions are at the heart of the RPI inquiry: whether the non-party desires review of the patent and whether the petition has been filed at the non-party's behest. *RPX* at 7–8; *see also* CTPG at 16 (explaining that a "common consideration" is "whether the non-party exercised or could have exercised control over a party's participation in proceeding"). Privity is a more expansive concept because a privy need not be an RPI. *RPX* at 37; CTPG at 13.

We do not agree on this record that Natera is an RPI or privy of Streck. Natera and its supplier Streck both seek to invalidate claims of the '277 patent. As discussed above, Natera filed an *ex parte* reexamination request, and Streck has filed this Petition. In that respect, the interests of

Streck and Natera are partly aligned. But beyond that, for many of the same reasons discussed above (*supra* Section II(B)(1)), we determine on this record that Natera is not an RPI or privy of Streck in this case.

The ongoing relationship between Natera and Streck is that of customer and supplier—not significantly more than that, on this record. Streck sells blood collection tubes to Natera (and many other customers). Prelim. Resp. 61–62 (noting a supply agreement disclosed in Natera's Form 10-K). Patent Owner has cited the use of Streck's tubes as including an alleged lysis-inhibiting "agent" in infringement allegations against many of Streck's customers, including Natera. *Supra* Section II(B)(1). But, there is no evidence that Streck is controlling Natera or its defense against the patent. To the contrary, Streck's representative testifies that Streck sells its tubes in "arms-length commercial transactions," that Streck "does not control the actions of these [customer] companies or their counsel in the respective litigations," and that "[i]n no such [customer] agreements, nor in its terms and conditions, did Streck agree to indemnify these companies in connection with the allegations made by [Patent Owner] against them." Ex. 1013 ¶¶ 5–7 (testifying that any indemnity demands have been denied). Despite having taken discovery from Streck and Natera in the Natera lawsuit on precisely these topics, Patent Owner provides no evidence to the contrary. *See, e.g.*, Ex. 2229 (subpoena for documents); Ex. 2021 (subpoena for deposition); *see generally* Paper 14 (describing other discovery taken).

Streck's role in the testing of its tubes in a likely effort to help its customer does not evidence control by Streck over the Natera litigation. Streck conducted some apparently limited experimental testing related to the

use of Streck's tubes for its customer Natera, which Natera's expert relied upon to support a noninfringement position. Prelim. Resp. 62–63 (citing Ex. 2066). A supplier providing limited technical or experimental support about its own products to a customer responsive to third-party infringement allegations does not indicate that the supplier is controlling the customer, or vice-versa. *Cf. Broadcom Corp. v. Telefonaktiebolaget L.M. Ericsson*, IPR2013-00601, Paper 23 at 13–14 (PTAB Jan. 24, 2014). Patent Owner states that Streck might have the "opportunity" to control Natera or the litigation even if the record shows that Streck is not, in fact, exercising control. There is no evidence to support Patent Owner's speculation. As explained above, Streck has denied all indemnity demands and, despite having already taken discovery from Streck and Natera about, *inter alia*, any relevant agreements, and any communications between Streck and Natera about the '277 patent or the lawsuit, Patent Owner provides no evidence to suggest that Streck is controlling (or has the opportunity to control) Natera in its litigation with Patent Owner. Ex. 2229, 13–14.

Nor is there evidence that Streck filed this Petition at Natera's behest or that Streck is otherwise acting as Natera's proxy related to this proceeding. Patent Owner moved in this case for additional pre-institution discovery on RPI and privy issues, which motion was granted-in-part on February 11, 2022. *See generally* Paper 14. We granted Patent Owner's motion for discovery related to any agreements that Natera may assist in, control, or fund this proceeding, and documents sufficient to show what role (if any) Natera had in approving, filing, controlling, or funding this Petition. *Id.* at 12–13. Patent Owner's preliminary response cited its then-pending

motion and reserved its right to seek additional briefing should "additional evidence be discovered" to support its arguments that Natera is an RPI or privy of Streck. Prelim. Resp. 61 n.6. Patent Owner did not, however, seek additional briefing or submit additional evidence on this issue. As we also explained in our discovery order, evidence suggests Streck and Natera did not coordinate their attacks insofar as Streck is not challenging claims and patents on which Natera may have infringement liability. Paper 14 at 10–11 (noting that Streck is not challenging some claims of the '277 patent, or any claims of the related '720 patent, that remain asserted against Natera).[20]

For the above reasons, we find on this record that Natera is not an RPI or privy of Streck and, thus, the Petition is not time barred.

V. CONCLUSION

Petitioner has established on this preliminary record a reasonable likelihood of prevailing in showing that at least one of the challenged claims is unpatentable. We will make a final determination on the patentability of the challenged claims, as necessary and applying the preponderance of the evidence standard, based on a fully developed record through trial.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an

[20] Patent Owner references an alleged admission by Streck's counsel related to privileged documents. Prelim. Resp. 62. Patent Owner misconstrues the alleged admission as we explained in our discovery order, which explanation we adopt again here. Paper 14, 8–9.

argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *granted*, and we institute *inter partes* review of claims 55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, and 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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