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Paper 62
Date: April 18, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STRECK, INC. and STRECK LLC[1]
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*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Denying Petitioner's Motion to Exclude and Motion to Strike
37 C.F.R. §§ 42.23, 42.64

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[1] Original petitioner Streck, Inc. informed us that Streck LLC is a wholly-owned subsidiary of Streck, Inc. that recently acquired all rights of Streck, Inc. in this proceeding. Paper 58, 1. We have modified the caption to list both Streck entities as petitioners (collectively "Petitioner").

I. INTRODUCTION

Petitioner or "Streck," 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"). We instituted trial on April 22, 2022. Paper 20 ("Inst. Dec."). During trial, Ravgen, Inc. ("Patent Owner") filed a Patent Owner Response. Paper 31 ("PO Resp.").[2] Later filings include Petitioner's Reply (Paper 40 ("Pet. Reply")) and Patent Owner's Sur-Reply (Paper 46 ("PO Sur-Reply")). An oral hearing was held on January 24, 2023, and a transcript is of record. Paper 61 ("Tr.").

Petitioner also filed a motion to strike (Paper 50) and a motion to exclude (Paper 52; Paper 55 (reply in support of motion)). Patent Owner opposed both motions. Paper 53; Paper 54.

We have jurisdiction under 35 U.S.C. § 6(b). After considering the full record developed through trial, we determine that Petitioner has not proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a).

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,

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[2] Patent Owner identifies itself as the real party-in-interest. Paper 4, 1. Petitioner identifies Streck Laboratories, Inc. and Streck LLC as real parties-in-interest. Pet. 1; Paper 58, 1.

codes (21), (22), (45). The ’277 patent is a continuation-in-part (“CIP”) application of, *inter alia*, PCT/US03/27308, filed August 29, 2003. *Id.* at code (63), 1:7–25. The ’277 patent also claims priority, as a CIP, to several other applications, including other CIPs filed in February 2003; the earliest application listed in the ’277 patent’s priority chain is a provisional application filed on March 1, 2002. *Id.* at 1:7–25; *see also id.* at code (60).

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

The parties identify multiple lawsuits involving the ’277 patent. Pet. 1–2; Paper 7, 1; 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.); *Ravgen v. Quest Diagnostics*, No. 2:21-cv-09011-RGK-GJS (C.D. Cal.); and *Ravgen, Inc. v. Illumina, Inc.*, No. 1-20-cv-01644 (D. Del.). Paper 18, 1–2 (identifying other lawsuits).

The parties identify other matters involving the ’277 patent before the Patent Office. Pet. 2; Paper 18, 2. Claims of the ’277 patent have 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, and denied institution in IPR2021-00789 and IPR2021-00790. On November 5, 2021, we instituted trial in IPR2021-00902 and IPR2021-01054 (covering, collectively, claims 55–63, 66–69, 80–96, and 127–133). On January 26, 2022, we instituted trial in IPR2021-01272

(covering claims 55–63, 66–69, 80–91, 94–96, 126–130, 132, and 133). We terminated IPR2021-00788 due to settlement. IPR2021-00788, Paper 71. We entered final written decisions in IPR2021-00902 and -01054 on November 1, 2022 (finding Labcorp had not shown the challenged claims are unpatentable). *See* IPR2021-00902 (Paper 55); IPR2021-01054 (Paper 51). And, on January 25, 2023, we entered a final written decision in IPR2021-01272 (finding Illumina had not shown the challenged claims are unpatentable). *See* IPR2021-1272 (Paper 50). *Ex Parte* Reexamination Control No. 90/014,792 is also related to the ’277 patent. Paper 12, 11. That reexamination is stayed. *See* IPR2021-00902, Paper 24 (staying reexamination during pendency of the related IPRs).

The related ’720 patent has also been challenged in matters before the Office: IPR2021-00791 (terminated by settlement), IPR2021-01026 (final written decision entered Dec. 12, 2022), and IPR2021-01271 (final written decision entered Jan. 25, 2023); and *Ex Parte* Reexamination Control Nos. 90/014,703, and 90/014,869 (both stayed). IPR2021-00791, Paper 25; IPR2021-01026, Paper 17.

B. Asserted Grounds of Unpatentability

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

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
55–59, 61, 68, 69, 80–86, 89, 94, 126–130	102(a)[3]	Chiu[4]
55–59, 61, 68, 69, 80–86, 89, 94, 126–130	103(a)	Chiu, Lee[5]
55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, 133	103(a)	Pertl,[6] Granger[7]

Petitioner relies on the declarations of Bruce Patterson, M.D., among other evidence. Ex. 1009; Ex. 1029. Patent Owner relies on a declaration from Brian Van Ness, Ph.D. (Ex. 2239), among other evidence. The

[3] 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.
[4] 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. 1011, “Chiu”).
[5] 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”).
[6] 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”).
[7] Granger et al., WO 97/45729, published Dec. 4, 1997 (Ex. 1012, “Granger”).

deposition testimony of Drs. Patterson (Exs. 2299 and 2309; Ex. 1047) and Van Ness (Exs. 1031 and 1032[8]) is also of record.

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 2:52–57. 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).

A brief overview of blood and its components is helpful in understanding the asserted art and the challenge in this case. As explained by Dr. Van Ness, the majority of human blood is composed of plasma—the liquid portion of unclotted blood. Ex. 2239 ¶ 24. Suspended in plasma are various blood components, including white blood cells (“WBCs”), red blood cells (“RBCs”) and platelets. *Id.* The vast majority of nuclear DNA in blood is contained inside the cells (WBCs, in particular). However, DNA may also be found circulating freely outside the cells in plasma. *Id.* (explaining, for example, that cancer patients may have extracellular tumor DNA circulating in their blood and that transplant patients may have extracellular organ host DNA in their blood).

[8] Exhibit 1032 is deposition testimony taken in IPR2021-01272.

In the late 1990s, before the ’277 patent, researchers discovered that pregnant women have cell-free *fetal* DNA (“cffDNA”) along with maternal cell-free DNA (“cfDNA”) circulating in maternal blood plasma. Ex. 1001, 55:39–56; Ex. 1009 ¶¶ 44–46. 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 a cell-free form. Ex. 1011, 1612 (disclosing that “intact fetal cells contribute only a very small proportion of the quantifiable fetal DNA”).

To obtain and analyze cells or 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 blood samples. *Id.* ¶¶ 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 '277 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 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. The '277 patent reports that "the percentage of fetal DNA present in the sample that was treated with only EDTA was 1.56%" and the "percentage of fetal DNA present in the sample treated with formalin and EDTA was 25%." *Id.* at 91:14–20. The percent of total cffDNA in eighteen blood samples with and without formalin was then calculated, with the results (mean percentage cffDNA) provided in Table V.

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

Id. at 91:35–43 (reporting, *inter alia*, 19.47% with formalin and 7.71% without formalin), 219:38–226:26 (Example 15).

D. Challenged Claims

Independent claims 55 and 81, which are the only two independent claims challenged in this proceeding, 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.

To illustrate some of the challenged dependent claims, claim 59 depends from claim 55 and recites "wherein said agent is a cell lysis inhibitor," and claim 60 depends from claim 59 and adds that "said cell lysis inhibitor is selected from the group consisting of: glutaraldehyde, derivatives of glutaraldehyde, formaldehyde, derivatives of formaldehyde, and formalin." *Id.* at 473:13–18.

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. Applicant made 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 prosecution that

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[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.

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 combinations 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 (inhibit the lysis of) white blood cells. *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.

We also provide an overview of the prosecution of the related ’720 patent, which claims similar subject matter involving, at a high level, isolating and detecting free nucleic acid from a sample that “comprises an agent that impedes cell lysis, if cells are present.” *See* IPR2021-01271, Paper 1 (reproducing claim 1).

During prosecution of the ’720 patent, the Examiner initially rejected the pending claims over Kiessling (but in combination with different references than discussed above for the ’277 patent’s prosecution). *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’s use of formaldehyde to fix WBCs as meeting the “agent” limitation. *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.” *Id.* at 2527–2530. For the “agent” limitation, the Examiner again turned to Kiessling’s formaldehyde. *Id.* Amicucci disclosed that blood samples were collected in EDTA-containing tubes and Holodniy

disclosed that blood samples were collected in tubes containing acid citrate dextrose (i.e., "ACD"). Ex. 2046, 301; Ex. 2020, 3511 ("samples were collected in VACUTAINER . . . blood collection tubes that contained acid citrate dextrose").

Applicant further amended the claims, argued that there were no reasons to combine the references, and argued that the claimed methods produced unexpected results. Ex. 2041, 2608–2632. 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. ANALYSIS

A. Principles of Law

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)).

To show anticipation under 35 U.S.C. § 102, each and every claim element, arranged as in the claim, must be disclosed in a single piece of prior art. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). "An element may be inherently disclosed only if it is necessarily present, not merely probably or possibly present, in the prior art." *Guangdong Alison Hi-Tech Co. v. Int'l. Trade Comm'n*, 936 F.3d 1353, 1364 (Fed. Cir. 2019). "[A] limitation or the entire invention is inherent and in the public domain if

it is the natural result flowing from the explicit disclosure of the prior art." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (internal quotation omitted).

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).

When evaluating a combination of teachings, we must also "determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)); *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) ("[O]bviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.").

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 did not expressly contest this definition during trial, noting that "Dr. Van Ness meets [this] definition" and "confirms his opinions are the same under either party's definition." PO Resp. 9 (citing Ex. 2239 ¶¶ 18–23).

We applied Petitioner's definition at the institution stage, and we adopt and apply it again here.[11] To the extent there are differences in the

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[11] To clarify, we find it likely the POSA would also have some practical experience (1–2 years) working in a laboratory with the subject matter in Petitioner's definition (e.g., analysis of nucleic acids and processing of blood

parties' definitions, we find they are minor and not material to our analysis in this case. Further, the parties' technical declarants meet or exceed either definition and there is no indication that their opinions would change depending on which definition was applied. Ex. 1009 ¶¶ 4–21 (overview of qualifications and experience); Ex. 2239 ¶¶ 4–7 (same).

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). 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.*

A patent's specification may provide a special definition for a claim term, or the intrinsic evidence may reveal an inventor's disclaimer or disavowal of claim scope. *Phillips v. AWH Corp.*, 415 F.3d. 1303, 1316 (Fed. Cir. 2005). If the inventor acts as their own lexicographer to give a claim term a special definition, that definition must be set forth in the specification with reasonable clarity, deliberateness, and precision.

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samples) even where the POSA has an advanced degree. Without this clarification, Petitioner's definition might be read to encompass one without practical experience in that subject matter, which is otherwise relevant to the applied art and the problems noted therein. We adopted slightly differently phrased definitions for the POSA in the Labcorp and Illumina cases based on the parties' definitions there. *See* IPR2021-01054, Paper 11 at 13–15; IPR2021-01272, Paper 50 at 16–17. We do not see the differences as material or that the outcome here would change under the other definitions.

Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1249 (Fed. Cir. 1998). A disavowal, if any, can be made by language in the specification or the prosecution history. *Poly-America, L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1136 (Fed. Cir. 2016). "To disavow claim scope, the specification must contain 'expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.'" *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1306 (Fed. Cir. 2011) (quoting *Epistar Corp. v. Int'l Trade Comm'n*, 566 F.3d 1321, 1335 (Fed. Cir. 2009)). "[T]he standard for disavowal is exacting, requiring clear and unequivocal evidence that the claimed invention includes or does not include a particular feature." *Poly-America*, 839 F.3d at 1136.

Petitioner "proposes [that] no claim language requires express construction to resolve the grounds herein." Pet. 9. Patent Owner argues that the claims should be construed to exclude alleged "anticoagulant chelators," including EDTA and ACD, as satisfying the "agent" term. PO Resp. 9–19. We discuss in more detail below.

The two challenged independent claims (claims 55 and 81) both recite, among other limitations, that the sample comprises "an agent that inhibits lysis of cells, if cells are present." *See supra* Section I(D).[12] Patent Owner, citing a claim construction adopted by the district court in Patent Owner's litigation with a third-party, argues that this "agent" limitation

[12] The related '720 patent includes claims that require "an agent that impedes cell lysis, if cells are present." *See* IPR2021-01026, Ex. 1001, 535:17–18.

should be construed the same way by the Board. PO Resp. 10 (citing Ex. 2040, 1). The court interpreted the "agent" limitation to mean:

> [A] substance that inhibits the rupture of cells that is selected from the group consisting of membrane stabilizer, cross-linker and cell lysis inhibitor, and *does not include chelators used as anticoagulants* nor endogenous substances.

Ex. 2040, 1 (emphasis added);[13] *see also id.* at 4–6 ("[T]he Court holds that EDTA and other chelators used as anticoagulants are not within the scope of the 'agent' limitation.").

According to Patent Owner, this construction "is consistently and unambiguously supported by the specification, prosecution histories [of the '277 and '720 patents], and extrinsic evidence." PO Resp. 10; *see also id.* at 10–19 (citing intrinsic and extrinsic evidence in support). Because "chelators used as anticoagulants . . . encompasses both EDTA and ACD," Patent Owner argues, the Board should construe the agent term to exclude anticoagulant chelators, including EDTA and ACD. *Id.* at 10–11; *see also* PO Sur-Reply 1–4 (same).

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[13] We take this claim construction into account in construing the claims in this proceeding. 37 C.F.R. § 42.100. Although this construction excludes "endogenous substances," we need not further address that language because Petitioner does not argue that endogenous substances (e.g., chemicals already naturally present in the maternal sample) meet the "agent" term. *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.") (internal quotation marks omitted).

Patent Owner cites intrinsic evidence in support of its interpretation. PO Resp. 10–17. For example, Patent Owner contends the Specification distinguishes anticoagulant chelators from the claimed agent, including in a working example where a blood sample placed in a tube with *only EDTA* was considered a control and compared with a sample illustrating the invention, which included *EDTA in combination with formalin*. *Id.* at 10–11 (citing Ex. 1001, 89:11–13, 89:22–23, and 90:62–67). This example, the patent discloses, shows processing of samples "both in the absence and presence of cell lysis inhibitors," which Patent Owner contends should be unambiguously read as indicating that an agent that inhibits lysis of cells is "absent" in the EDTA-only sample. *Id.*[14]

Furthermore, Patent Owner cites portions of the prosecution history where the Applicant argued that disclosures about EDTA in the art did not meet the "agent" term. *Id.* at 11–17 (citing, as noted *supra* (Section I(E)), Applicant's argument that the Office was "simply incorrect" in finding Lo's EDTA was an agent that inhibits lysis of cells; "Rather, EDTA is a well-known chelator of calcium and magnesium . . . routinely added to blood . . . as an anticoagulant due to its ability to chelate calcium."). According to Patent Owner, the Examiner also found, and the Applicant similarly acknowledged, during the related '720 patent's prosecution that prior art

[14] As noted above, the '277 patent describes EDTA as a "magnesium chelator" and discusses EDTA separately from the listing of agents that inhibit cell lysis. *Compare* Ex. 1001, 31:52–56 (identifying EDTA), *with id.* at 31:57–32:12 (listing formaldehyde and glucose as, respectively, a cell lysis inhibitor and membrane stabilizer).

disclosing processing samples in EDTA and ACD tubes did not meet the "agent" term. *Id.* at 14–17 (citing, e.g., Ex. 2041, 1345 (Adams rejection), 2527 (Amicucci rejection), 2529 and 2625 (Holodniy rejection and response); Ex. 2023, 20:52–54 (Adams disclosing ACD); Ex. 2046, 301 (Amicucci disclosing EDTA); Ex. 2020, 3511 (Holodniy disclosing ACD)). Patent Owner argues that during reexamination of the '720 patent, it again disavowed any claim scope that would encompass ACD. PO Resp. 16 n.3 (citing Ex. 2238, 30–34; *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1361 (Fed. Cir. 2017)).[15]

Finally, Patent Owner cites extrinsic evidence, including several publications, as showing that EDTA and ACD are routinely characterized as

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[15] Although a patentee's statements to the Office may evidence a disclaimer, Patent Owner's statements in the cited reexamination do not weigh heavy here. There is no evidence the Examiner has acted on Patent Owner's statements of alleged disavowal in the reexamination. In *Aylus*, by contrast, the district court relied on patentee's earlier statements made in its preliminary response that contributed to the Board's *denial of inter partes review* for the relevant claims. *Aylus*, 856 F.3d at 1362–63. In that light, the patentee could not advance a narrow claim interpretation before the Office that secured IPR denial and later maintain a broader (and inconsistent) interpretation before the courts, which the courts in *Aylus* viewed as a prosecution disclaimer. Here, however, the reexamination of the '720 patent had just begun and we stayed it so the related IPRs could be completed first. We do not treat Patent Owner's argument *in the present IPR* about the claims not covering ACD or its components as a "disclaimer," and we decline to elevate similar argument made in the extant yet stayed reexam to such status. *Cf. Cupp Computing AS v. Trend Micro Inc.*, 53 F.4th 1376, 1383 (Fed. Cir. 2022) (holding "a disclaimer is not binding on the PTO in the very IPR proceeding in which it is made, just as a disclaimer in a district court proceeding would not bind the district court in that proceeding").

anticoagulants for blood-collection tubes, not as cell-lysis inhibitors, fixatives, or preservatives. PO Resp. 18–19. Patent Owner cites, for example, labeling for ACD classifying it as an anticoagulant and noting that ACD "acts as an anticoagulant by the action of the citrate ion chelating free ionized calcium." *Id.* at 17 (quoting Ex. 2036, 1). Patent Owner also cites, for example, one of Streck's patent applications that lists EDTA and ACD among the "anticoagulants," while listing preservatives and polysaccharides separately. *Id.* at 18–19 (citing Ex. 2037 ¶¶ 14 (listing formaldehyde as a preservative), 89 (listing anticoagulants), 90 (listing polysaccharides)).

The question that Patent Owner's proposed claim construction presents is whether a claimed agent that inhibits cell lysis may be a chelator used as an anticoagulant. The Specification and prosecution history make clear that at least one anticoagulant chelator—EDTA—is excluded from satisfying the claimed "agent" as recited in claims 55 and 81. As discussed above, the Specification includes an example where a sample processed in a tube with only EDTA is described as processing a sample in the "absence" of an agent that inhibits cell lysis. Ex. 1001, 89:11–34 (describing, in contrast, the EDTA + formalin sample as showing an example in the "presence of inhibitors of cell lysis"). If EDTA alone could be read as meeting the "agent" limitation, that example would make no sense. Petitioner provides no persuasive argument otherwise.

The prosecution history buttresses the exclusion of the anticoagulant chelator EDTA from being the claimed "agent." The Examiner at one point expressly identified the EDTA in Lo's tubes as satisfying the agent term, prompting Applicant's argument that the Office was "incorrect" in doing so,

and further distinguishing EDTA as merely "a well-known chelator of calcium and magnesium" that is added to blood "as an anticoagulant due to its ability to chelate calcium." Ex. 2223, 1192 (arguing "EDTA is clearly referred to as a chelator in Applicant's specification, not as a cell lysis inhibitor"); *supra* Section I(E); Ex. 1001, 31:52–56 (listing EDTA and EGTA as chelators). This, in turn, convinced the Examiner to withdraw the finding that EDTA was an "agent" as claimed and move on to art that disclosed formaldehyde as meeting that claim term. *See* s*upra* Section I(E); Ex. 2223, 1020 (Interview summary noting that "applicant pointed out [that] EDTA could not be defined as a cell lysis inhibitor but rather was simply an anticoagulant"). This colloquy during prosecution shows a clear and unmistakable disavowal of EDTA as being the claimed "agent."

Having determined that Patent Owner disavowed EDTA as the claimed "agent," we next consider whether the disavowal extends more broadly to other anticoagulant chelators and, specifically, to ACD. On this record, we find that it does as explained below. In distinguishing EDTA from being the "agent," Patent Owner relied not on properties that are unique to EDTA, but on the fact that it was a "well-known chelator" used as an anticoagulant in this technical field. Ex. 2223, 1192. Given Patent Owner's clear intent to exclude EDTA from the scope of the claimed "agent" on the basis that it was simply an anticoagulant chelator, we find that a POSA would also have understood other anticoagulant chelators as subject to Patent Owner's disavowal.

Consistent with this understanding, during later prosecution of the related '720 patent, the Examiner found that Holodniy (and at least one other

reference) did not disclose the "agent" term—notwithstanding that such references disclosed processing samples in ACD tubes. Ex. 2041, 2529 (finding that Holodniy "teach[es] a method of detecting free nucleic acid which comprises all of the limitations of Claim 1, except these authors do not teach that their samples comprise an agent that impedes cell lysis"); *see also id.* at 1345 (finding Adams "do[es] not teach adding an agent that impedes cell lysis to the sample"). Patent Owner confirmed the Examiner's finding on this point. *Id.* at 2625 (asserting that Holodniy fails to teach or suggest the claimed method "wherein an agent that impedes cell lysis has been added"). And Patent Owner argues persuasively, without dispute from Petitioner, that ACD is the only addition to the collection tubes of Holodniy and Adams besides the sample itself. PO Resp. 17; PO Sur-Reply 2–3; Ex. 2020, 3511; Ex. 2023, 20:52–54.[16] This lends further support that neither the Examiner nor Applicant/Patent Owner considered ACD as an anticoagulant chelator to be an "agent" as claimed.

In its Reply, Petitioner notes that ACD contains dextrose (i.e., glucose) as a subcomponent in solution, and points to the '277 patent's listing of glucose as a cell-stabilizing agent. Pet. Reply 1–3 (noting that ACD's citrate ion chelator component is the anticoagulant, not dextrose;

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[16] It appears to be the case, however, that ACD was never explicitly highlighted by the Examiner or Applicant during prosecution in relation to the agent term. As we discuss in more detail below, ACD is not a single chemical compound; instead it includes multiple compounds in aqueous solution, and some of those compounds are not chelators. Ex. 1009 ¶ 217; Ex. 1029 ¶ 4; Ex. 2036, 1; Ex. 1030, 4.

arguing that Applicant did not clearly disavow ACD's dextrose and that the court's claim construction did not address or exclude dextrose); Ex. 1001, 15:58–16:7 (listing glucose as a membrane stabilizer); Ex. 1009 ¶ 217 ("Dextrose is [the] name for the naturally occurring form of glucose.").[17] We address the dextrose component of ACD, and whether such dextrose may satisfy the claimed "agent" limitation, in Section II(F) below.

Petitioner dismisses the related '720 patent's prosecution as occurring *after* issuance of the '277 patent's claims. Pet. Reply 2 (arguing Patent Owner is improperly "attempting to *retroactively* disclaim ACD"). We agree with Patent Owner, however, that, where common terms in related patents are concerned, statements made in subsequent prosecution may be relevant to interpretation of claims in earlier-issued patents. PO Sur-Reply 2–3; *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1343 (Fed. Cir. 2015) (holding that, when construing claims, "statement[s] made during prosecution of related patents may be properly considered in construing a term common to those patents, regardless of whether the statement pre- or post-dates the issuance of the particular patent at issue"). As explained above, we determine that the Examiner's findings and the Applicant's remarks during the '720 patent's prosecution about the ACD-disclosing prior art may properly be considered in interpreting the substantially identical "agent" limitation of the '277 patent.

For the reasons above, we construe the phrase "an agent that inhibits lysis of cells" to exclude chelators used as anticoagulants. Although the

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[17] Like the parties, we may use dextrose and glucose interchangeably herein.

"agent" cannot itself be an anticoagulant chelator, the sample, as a whole, in the claimed methods may *include* chelators used as anticoagulants. The claims use the phrase "said sample *comprises*" indicating that the claims are open ended, and that the sample may include other unrecited components. *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."). Indeed, the Specification includes examples that purport to represent the invention where maternal blood samples are processed in tubes that combine EDTA (an anticoagulant chelator) with formalin/formaldehyde (the cell-lysis inhibitor), which samples are contrasted with a control where the maternal blood is processed in EDTA-only tubes.

Because we find that the intrinsic evidence is sufficiently clear, we need not rely on extrinsic evidence to construe the claims. *Seabed Geosolutions (US) Inc. v. Magseis FF LLC*, 8 F.4th 1285, 1290 (Fed. Cir. 2021) ("Given the clarity of the intrinsic evidence, resort to extrinsic evidence is unnecessary."); *Wi-Lan, Inc. v. Apple Inc.*, 811 F.3d 455, 462 (Fed. Cir. 2016) (extrinsic evidence "is generally of less significance than the intrinsic record" in matters of claim construction). That said, on this record, consistent with Patent Owner's argument, ACD is commonly characterized as an anticoagulant (and not as a cell preservative) in many extrinsic publications. PO Resp. 17–19 (citing publications).

D. Overview of the Asserted Prior Art

1. 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, and filtration, 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 amount 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 [(centrifugation at 16000g)]." *Id.* at 1610, 1613 ("We recommend the use of the latter approach [(microcentrifugation)] because it is both simpler and less costly to implement than filtration").

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"). 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 processing protocols] needs to be agreed on." *Id.* ("By highlighting the importance of centrifugation protocols for plasma processing, our data have obvious bearing on this type of analysis [(i.e., research on circulating nucleic acid for diagnostic purposes)].").

2. Lee (Exhibit 1015)

Lee is a February 2001 article about quantitating cell-free genomic DNA in serum and in plasma. Ex. 1015, 276. Lee discloses that "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").

3. 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 teaches detection of fetal DNA using nine highly polymorphic short tandem repeat ("STR") markers[18] and fluorescent multiplex PCR. *Id.* at 45–46 ("Multiplex fluorescent PCR was used to detect fetus-specific alleles in the corresponding maternal plasma samples."), 48 ("The results of this study show that we can now confirm the presence of fetal DNA in maternal plasma independent of gender.").

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.* Maternal blood samples were collected prior to delivery in tubes containing EDTA. *Id.* (disclosing that paternal blood was also collected where available); *see also id.* (disclosing that maternal blood samples were centrifuged at 2,000 g, the plasma then transferred to fresh tubes and recentrifuged at 3,000 g, after which the

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[18] Pertl explains that it used STR markers outside the Y chromosome (which chromosome would be present with a male, but not female, fetus). Ex. 1010, 45. Pertl further explains that the polymorphism is due to the variation in tandemly repeated units between alleles and, because of the high degree of polymorphism, most individuals will be heterozygous for the markers with two amplified products in most normal samples, each of which is inherited from one parent. *Id.*

supernatant was collected in fresh tubes and stored at -20°C until further processing (i.e., DNA extraction, selection of primers, PCR amplification, and allele detection by fluorescence analysis of amplification products)).

In the article's Discussion, Pertl discloses that "[o]ur results demonstrate the feasibility of detection of male and female fetal DNA in maternal plasma with the use of highly polymorphic STR markers and fluorescent multiplex PCR." *Id.* at 48. Pertl teaches that, "[i]n the present study, [Pertl] used PCR amplification of nine STRs to detect fetal-specific alleles in maternal plasma samples." *Id.* 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 et al. (1998, 1999)" that analyzed sequences on the Y chromosome). 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 (Lo et al. 1998), our proposed technique was sensitive enough to detect fetal-specific alleles in all mother/child pairs studied." *Id.*

Pertl suggests further studies applying its method earlier in fetal gestation. Pertl discloses that "[w]e intentionally performed this study using samples at term to maximize the amount of fetal DNA present," and "[f]uture studies need to be performed earlier in gestation at a time when

noninvasive prenatal diagnostic information may be more clinically useful." *Id.* According to Pertl, "[a]lthough more studies are needed to determine the sensitivity and specificity of this method at various gestational ages, multiplex PCR amplification of STRs may be an important technique for a wide range of clinical applications." *Id.*

4. Granger (Exhibit 1012)

Granger is 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., 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 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 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 blood specimen containing paraformaldehyde is comparatively stabilized. *Id.* at 11:1–27.

E. Anticipation by Chiu[19]

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 from 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 cffDNA from the blood sample as claimed. *Id.* (citing Ex. 1011, 1608–1609 (disclosure about centrifuging samples to prepare and further process plasma portions, and

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[19] For consistency, this Decision addresses the grounds in the order addressed by the parties in their post-institution briefing: anticipation by Chiu (Ground 2); obviousness over Chiu and Lo (Ground 3); and obviousness over Pertl and Granger (Ground 1).

extracting fetal DNA using a Qiagen 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" limitation, Petitioner cites Chiu's collection tubes that contain EDTA. Pet. 44–45; Ex. 1011, 1609; Ex. 1009 ¶ 179. And, according to Petitioner, the Lee reference shows 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 similar, cross-referencing Petitioner's analysis on claim 55. Pet. 48 ("Chiu anticipates Claim 81 for the same reasons as Claim 55.").

Patent Owner makes two points in rebuttal. According to Patent Owner, Chiu discloses the use of EDTA only as an anticoagulant, not as an "agent" as claimed. PO Resp. 19–20 (citing Chiu's disclosure (Ex. 1011, 1608) about using EDTA tubes to prepare *plasma* (as opposed to serum derived from samples that have undergone coagulation)). Moreover, Patent Owner argues, "EDTA is not the claimed 'agent that inhibits lysis of cells'" as that limitation is properly construed. *Id.* (cross-referencing argument about interpretation of the "agent" limitation).

We agree with Patent Owner that EDTA is not the claimed "agent." We conclude that the claimed "agent that inhibits lysis of cells, if cells are present" does not encompass EDTA. *See supra* Section III(C). We thus

find that Petitioner has not shown by a preponderance of the evidence that Chiu anticipates claims 55–59, 61, 68, 69, 80–86, 89, 94, and 126–130.[20]

F. 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; Pet. Reply 4–6. Chiu and Lee are summarized above. *See supra* Section II(D).

We focus on Petitioner's contentions against independent claim 55 as representative. Pet. 49–52, 54 (cross-referencing, for independent claim 81, the analysis of claim 55). We then proceed to Patent Owner's arguments, which are directed to the challenged claims as a group. PO Resp. 20–35.

Petitioner argues that Chiu discloses collecting blood samples from pregnant women in tubes that contain EDTA, centrifuging the samples to prepare and separate plasma, isolating fetal DNA from the plasma samples, and determining the sequence of a loci of interest on fetal DNA as claimed. Pet. 50 (cross-referencing Petitioner's anticipation challenge); Ex. 1009 ¶¶ 206–209. Except for the "agent that inhibits lysis of cells, if cells are present" limitation, Patent Owner does not contest that Chiu teaches the other limitations of claim 55's method. PO Resp. 20–35; PO Sur-Reply 5–9.

For the "agent" limitation, Petitioner cites to Lee's disclosure of ACD. Pet. 50. According to Petitioner, Chiu discloses collecting blood samples in

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[20] Petitioner presented no further argument on its anticipation challenge post-institution (*see generally* Pet. Reply) and Dr. Patterson confirmed that he is no longer opining that EDTA is an "agent" as claimed. Ex. 2309, 30:20–24 (agreeing he is "not offering the opinion that the scope of the agent term should include EDTA").

tubes containing EDTA, and Lee discloses that ACD can be used in place of EDTA to when collecting blood samples to prepare plasma; and Petitioner contends ACD, particularly its dextrose component, is an agent that inhibits the lysis of cells as claimed. *Id.* at 49–52 (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 that Lee reported that male 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 cites evidence that ACD includes dextrose (i.e., glucose (Ex. 1009 ¶ 217)), and contends that the '277 patent identifies glucose as a membrane stabilizer and 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 it would have been obvious to combine the relevant disclosures in Chiu and Lee. Pet. 51. More specifically, Petitioner argues that "[t]he anticoagulant ACD is a common alternative to EDTA" and "[i]t would have been obvious to a POSA to substitute ACD for EDTA in the samples employed by Chiu." *Id.* 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.

Patent Owner argues that Petitioner's challenge fails because ACD in the combination of Chiu/Lee is not an "agent" as recited in the method of claim 55. PO Resp. 23–27 (repeating, *inter alia*, Patent Owner's claim construction argument that the claimed "agent" does not include chelators used as anticoagulants). Properly construed, according to Patent Owner, "Lee provides no disclosure that ACD (or its dextrose component) is a membrane stabilizer, cell lysis inhibitor, or crosslinker ***that inhibits lysis of cells***" as claimed. *Id.* at 23–24 (citing Ex. 2239 ¶¶ 161–162).

Even if ACD and its dextrose component is not excluded as a matter of claim interpretation, Patent Owner argues that Petitioner fails to show that dextrose introduced via ACD in the proposed Chiu/Lee combination meets the "agent" term. *Id.* at 27–35. Patent Owner contends that Lee's disclosure is limited to the use of ACD as an anticoagulant and, to the extent Lee includes any suggestion about lysis-inhibition in its samples, it attributes that to EDTA's and ACD's anticoagulant/anticlotting function—not to the presence or any function of dextrose. *Id.* at 27–28 (citing Ex. 1015, 276 ("Most cell-free DNA in serum samples is generated during the process of clotting," whereas "cell free . . . DNA in fresh plasma is probably the same as that in circulation.")). According to Patent Owner, "a POSA reading Lee would have understood the differences in cell-free DNA levels between plasma and serum were due to ***clotting***—i.e., blood collection ***with or without an anticoagulant*** such as ACD, and not any effect of dextrose on sample cells." *Id.* at 28 (citing Ex. 2239 ¶ 163). As between the

anticoagulants used in Lee, Patent Owner contends that "at all times measured, the ACD [(with dextrose)] plasma samples behaved just like the EDTA [(no dextrose)] plasma sample." *Id.* at 30–32 (citing data and tables in Lee (e.g., Ex. 1015, Fig. 2A, Fig. 4) and related testimony of Dr. Van Ness (e.g., Ex. 2239 ¶¶ 164–169)); Ex. 2299, 98:11–99:2 (Patterson testimony that Lee discloses no significant difference between EDTA and ACD plasma samples, and does not report any different effect or mechanism of EDTA versus ACD). From this, Patent Owner contends that Petitioner has not shown that ACD's dextrose component in a hypothetical Chiu/Lee modification necessarily inhibits lysis of cells as claimed.[21] *Id.* at 33–35. Lastly, Patent Owner acknowledges the '277 patent's identification of dextrose as a membrane stabilizer, but Patent Owner contends the patent never states that glucose (especially as a dextrose component of ACD) inhibits lysis of cells under any and all conditions. *Id.* at 34–35 (citing precedents on the showing needed to establish inherency).

The undisputed evidence shows that ACD includes dextrose, which is a species of glucose. Ex. 1009 ¶ 217 (Patterson testimony that ACD's dextrose is a form of glucose); Ex. 1029 ¶ 20 (Patterson testimony that ACD is a multi-component solution and includes dextrose in aqueous solution);

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[21] Patent Owner also cites evidence that rapid separation and cooling, like in Lee, would render cells nonfunctional, stopping them from, for example, metabolizing glucose. PO Resp. 34 (citing, e.g., Ex. 2299, 102:4–21 (testimony of Dr. Patterson that chilling slows all the cellular processes down); Ex. 1015, 278 (Lee's teaching that WBCs become nonfunctional after storage at 4° C); Ex. 2239 ¶¶ 170–172 (Van Ness testimony about the inability of cells to metabolize glucose at low temperatures, citing support).

Ex. 2036, 1 (data sheet listing ACD's components, including dextrose monohydrate (0.245g per 10 mL of solution)); Ex. 1030, 4 (FDA prescribing information for ACD A). Nor is there any dispute that the '277 patent identifies glucose as among several cell-stabilizing agents that may be added to a sample to inhibit maternal cell lysis. Ex. 1001, 32:4–21. The dispute here centers on two questions: 1) whether the exclusion of anticoagulant chelators from meeting the claimed "agent" excludes dextrose introduced to a sample through ACD, and 2) whether Petitioner has established, by a preponderance of the evidence, that the dextrose in ACD inhibits lysis of cells sufficient to satisfy the claimed "agent" limitation in Petitioner's combination of Chiu and Lee. We address these questions in turn below.

1. Whether exclusion of anticoagulant chelators as the claimed "agent" also excludes glucose introduced to a blood sample in an ACD tube?

As discussed above (Section II(C)), the claims exclude anticoagulant chelators from being the claimed "agent that inhibits lysis of cells, if cells are present." We now consider whether that exclusion extends to the individual components of ACD—dextrose, in particular. First, we provide an overview of ACD.

ACD comprises three main components in water: (1) citric acid, (2) sodium citrate, and (3) dextrose. Ex. 1030, 4; Ex. 2036, 1. As described in FDA information, ACD Solution A "acts as an extracorporeal anticoagulant by binding the free calcium in the blood," which "[c]alcium is a necessary co-factor to several steps in the clotting cascade." Ex. 1030, 4. It is the sodium citrate component, specifically the citrate ion, that provides

this chelation and anticoagulant function in ACD. Ex. 2036, 1 ("ACD-A acts as an anticoagulant by the action of the citrate ion chelating free ionized calcium, thus making calcium unavailable to the coagulation system."); Ex. 1030, 4 (disclosing that "[s]odium [c]itrate anticoagulates"). As for the other components of ACD, the "[c]itric acid [is] for pH regulation" and "[d]extrose [is] for isotonicity." Ex. 1030, 4. In short, ACD has three components in aqueous solution—a chelator (sodium citrate), a pH buffer (citric acid), and glucose (for isotonicity[22]).

The '277 patent identifies glucose as a cell membrane stabilizer that may be added to maternal samples to reduce lysis. Ex. 1001, 32:4–21 ("[A]n agent that stabilizes cell membranes may be added to the maternal blood samples to reduce maternal cell lysis including . . . glucose."). This presents the question whether glucose is nonetheless excluded from satisfying the claimed "agent" limitation because it was introduced into the blood sample as a component of ACD in a solution that also includes a chelator (sodium citrate) and a pH buffer (citric acid). We find that glucose is not so excluded. As discussed above, the claims are open-ended and may cover combinations that include an anticoagulant chelator (e.g., the compound EDTA) along with a lysis-inhibiting agent, such as formaldehyde.

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[22] As explained by Dr. Patterson, isotonicity, hypertonicity, and hypotonicity are related concepts that concern the relative proportion of solutes and liquid in a solution, and can influence the manner in which liquid moves in the system (e.g., as across a cellular membrane into or out of cells). Ex. 2309, 15:11–16:25, 18:16–19 (testifying that a cell placed in a hypotonic solution can swell, while a cell placed in a hypertonic solution can shrink).

The claims place no apparent limitation on how the "agent" comes to be in the sample. The claims simply require that the "sample comprises" an "agent that inhibits lysis of cells, if cells are present." It would seem odd that a sample to which is added a substance listed as membrane stabilizer in the Specification would be excluded from meeting the "agent" term simply because that substance (glucose) was introduced to the sample as one component of a solution also comprising an anticoagulant chelator (sodium citrate). This is particularly true where there is no indication on this record that glucose (in ACD or otherwise) plays any specific role in anticoagulation or chelation. *See, e.g.*, Ex. 2036, 1; Ex. 1030, 1.

For Patent Owner's disavowal of claim scope to extend to an individual chemical component of the ACD solution that itself plays no apparent role in anticoagulation or chelation, Patent Owner's disavowal needed to make that unambiguously clear. *Poly-America*, 839 F.3d at 1136. As discussed above, the sodium citrate component of ACD is that solution's anticoagulant chelator—glucose, which provides a different function, is not.[23]

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[23] As support for the notion that the claims exclude ACD's dextrose component, Patent Owner also cites the district court's order granting summary judgment of no anticipation in a related litigation. PO Sur-Reply 3; Ex. 2306, 1 ("[A]cid citrate dextrose (ACD) in . . . Lee . . . do[es] not disclose the claimed 'agent' . . . as a matter of law."). Beyond noting that the motion was "GRANTED," the order includes one sentence on this point (quoted in relevant part in the parenthetical above) without further explanation of the court's reasoning. Petitioner is not a party to that case, the records are different, and the court applies a higher standard of proof

Patent Owner excluded anticoagulant chelators from being the claimed "agent." *See supra* Section II(C). It is not, however, clear that the exclusion extends to all of the individual components of a multi-part "anticoagulant" solution—at least one of which is explicitly identified in the '277 patent as being among the agents that can inhibit cell lysis. As discussed already, during prosecution the Examiner considered at least two references that each collected blood in ACD tubes, and found that those references lacked a teaching of the claimed agent. But there is no indication that, in doing so, the Examiner considered the position urged here by Petitioner, i.e., that the glucose sub-component within ACD meets the "agent" limitation. Pet. 52; Pet. Reply 1–3. Patent Owner's disavowal does not unambiguously extend to glucose as relevant here. Even short of disavowal, we are also not persuaded that the POSA would interpret glucose as excluded from possibly satisfying the "agent" limitation when other parts of the intrinsic evidence list it as a membrane stabilizer and lysis inhibitor.[24]

2. <u>Has Petitioner established that the dextrose in ACD inhibits lysis of cells in the combined Chiu/Lee method?</u>

Chiu describes collecting maternal blood in EDTA-containing tubes and Lee describes collecting donor blood in tubes with ACD, EDTA, or no

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than is required in this IPR. Pet. Reply 3–4. For these reasons, the court's order is of limited persuasive value and plays no role in our Decision.

[24] In the remarks where Applicant clearly disclaimed EDTA, explaining that it was merely a "well-known chelator," Applicant then contrasted EDTA with examples of inhibitors of cell lysis listed in the patent, including glucose. Ex. 2223, 1192 (arguing that "EDTA is clearly referred to as a

anticoagulant. Ex. 1011, 1608 ("Antecubital venous blood samples . . . were collected into EDTA tubes . . . [and] processed within 2 h of sample collection"); Ex. 1015, 277 (Materials and Methods, disclosing blood is collected in "tubes with ACD (yellow top)"). Lee teaches that, compared to coagulated serum samples, lysis was inhibited in both the EDTA and ACD tubes, but nowhere does Lee disclose that such lysis inhibition resulted from the dextrose component of ACD introduced to the blood samples. To the contrary, as noted by Patent Owner, Lee explains the difference in higher DNA content released in serum versus plasma is due to "clotting." PO Resp. 28 (citing Ex. 1015, 276, 279 ("The most likely explanation for the higher levels of [cell-free] DNA in serum than in plasma is that the ***process of clotting*** lyses" WBCs)). Lee further explains that "cell-free . . . DNA in fresh plasma is probably the same as that in circulation." *Id.* (quoting Ex. 1015, 276). In other words, as reported in Lee, ACD inhibited lysis by its anticlotting function (i.e., ACD's sodium citrate acted as an anticoagulant chelator to impede clotting, as discussed above) in plasma compared to serum (no anticoagulant). And we credit Dr. Van Ness's testimony that a POSA would understand from Lee that any observed differences in DNA levels between plasma and serum were due to clotting, "not any effect of dextrose on sample cells." Ex. 2239 ¶ 163.

In the Petition, to satisfy claim 55's "agent" limitation through substitution of Lee's ACD for Chiu's EDTA, Petitioner emphasized two

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chelator in Applicant's specification, . . . whereas multiple examples of agents that inhibit cell lysis are provided separately (*see, e.g.*, paragraphs [0166] to [0167])"); *id.* at 1377 (paragraph 167, listing "glucose").

points. First, Petitioner cited Lee's teachings about relative lysis inhibition in anticoagulated EDTA and ACD blood samples compared to coagulated serum. Pet. 50–51 (citing Lee's teachings and arguing 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"). As discussed immediately above, even crediting that the POSA would have been motivated to substitute ACD for EDTA on the basis that they are interchangeable, Lee's teachings about avoiding lysis caused by clotting with ACD blood samples does not address the key question—what, if any, effect does ACD's *dextrose* component have in inhibiting lysis of cells in the blood sample. On that question, Chiu and Lee are silent. Ex. 2309, 54:15–55:2 (admission of Dr. Patterson that Lee does not disclose any mechanism by which ACD's dextrose inhibits lysis).

The second point emphasized by Petitioner is that the '277 patent states that glucose is a membrane stabilizer that may be added to reduce maternal cell lysis. Pet. 52 (citing Ex. 1001, 15:58–16:7). That statement is entitled to weight. But, as pointed out by Patent Owner, the patent "never states that ACD (or its components used in combination) is a membrane stabilizer that inhibits cell lysis" under all conditions including conditions relevant here. PO Resp. 34–35 (citing precedents and arguing that a mere possibility of glucose inhibiting lysis under certain conditions is not sufficient to support inherency in Petitioner's Chiu/Lee combination); PO Sur-Reply 7–9 ("The mere ***potential*** to prevent lysis is not enough to show that dextrose ***necessarily*** inhibits lysis"; "[w]hether ACD's dextrose could have inhibited lysis in other conditions does not cure the deficiencies of the

prior art mapped in the Petition."). In short, the patent's identification of glucose as a membrane stabilizer does not mean that glucose will necessarily inhibit lysis of cells under any and all circumstances—particularly those posited in the Chiu/Lee combination.

The key issue is whether ACD's dextrose component, when added to a blood sample by substituting ACD for EDTA in the modified Chiu/Lee method, necessarily satisfies the claimed agent limitation. In route to deciding this issue, we reject the notion that mere presence of dextrose is all that must be shown for Petitioner to prevail. *See* Pet. Reply 5–6 (arguing dextrose would be present in solution, and that Patent Owner "does not show that dextrose would be inert").[25] By the plain language of claim 55 (and equally claim 81), the method requires the blood sample include an "agent that inhibits lysis of cells, *if cells are present*," and at least some cells would be present in blood samples taken according to the modified Chiu/Lee method.[26] Petitioner does not carry its burden simply by showing that dextrose is added to the samples via ACD. Rather, Petitioner must show that

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[25] Petitioner cites testimony of Dr. Van Ness in a related proceeding that, "if you add an agent that is covered in the claims, you immediately have infringed the patent." Pet. Reply 5 (citing Ex. 1032, 86:25–87:5). Whether Dr. Van Ness may have misinterpreted or applied the claims too broadly in another proceeding is not decisive because the intrinsic evidence and plain meaning of the claims is controlling.

[26] Although Chiu teaches that, by some further physical processing methods, it is possible to generate "virtually cell-free plasma" (Ex. 1011, 1613), we are unprepared to say on this record that no cells whatsoever remain after such further processing. Moreover, Petitioner never argued in this case that it need not establish any lysis inhibition by dextrose on account of Chiu's samples being further processed to wholly eliminate any residual cells.

dextrose in the Chiu/Lee samples inhibits at least some cell lysis, although we agree with Petitioner that the claims do not recite any specific amount of inhibition. *Id.* at 5.

In its Reply, Petitioner urges three theories to support that the dextrose in ACD will stabilize membranes and inhibit lysis of cells. *Id.* at 5–6. Petitioner compares lysis inhibition provided by EDTA versus ACD in Lee, with ACD allegedly showing superior inhibition; Petitioner cites dextrose's "impact on isotonicity"; and Petitioner states that "[s]ugars, like glucose and dextrose" can stabilize cells by "feeding" them. *Id.* On this record, none of these theories persuasively establishes that Petitioner has met its burden to show that the agent limitation is met in the Chiu/Lee combination.

First, Petitioner contends that "Lee indicates that ACD performed measurably better than EDTA, contradicting PO's theory that non-chelator dextrose plays no added role in preventing lysis." *Id.* As noted by Patent Owner, however, Petitioner's assertion hinges on unsupported extrapolation from a poorly-printed figure in Lee that even Dr. Patterson concedes is "a really bad graph."[27] PO Sur-Reply 6–7; Ex. 2309, 50:7–15 (Patterson

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[27] Patent Owner also highlights Petitioner's assertion that, if Lee shows cfDNA levels "were ***higher*** in 5 of 6 donors in ACD compared to EDTA in Lee's Fig. 2A," that would undermine Petitioner's argument about the dextrose in ACD providing a lysis-inhibiting effect. PO Sur-Reply 6 (quoting Pet. Reply 5 (with Patent Owner's emphasis), and arguing that "***higher*** cfDNA levels in ACD could only be attributed to increased lysis"). Patent Owner is correct as the position is literally stated in Petitioner's Reply. But, in Dr. Patterson's rebuttal declaration, he opines that "[f]ive of six donors had ***lower*** levels of cell-free DNA in ACD tubes compared to

testifying that, "[i]f I was a reviewer, I'd ask for a better graph"). As also pointed out by Patent Owner, Lee expressly reported "***no significant differences*** [in free nucleic acid concentration] between EDTA and ACD plasma" samples, which aligns with other reporting in the literature. PO Resp. 29–33; PO Sur-Reply 6; Ex. 2239 ¶¶ 164–169 (testimony of Van Ness citing a study (Ex. 2237, 2) reporting "no statistically significant difference between $\log_{10}$ copy numbers [of circulating nucleic acids] in samples collected in ACD tubes and those samples collected in EDTA tubes").

Ultimately, the argument on comparing results with EDTA and ACD in Lee is neutral in our analysis. We have not been directed to evidence that calls out any specific effect of dextrose in Lee. As discussed above, EDTA is a chelator that prevents coagulation of the blood. Ex. 1001, 31:52–54 ('277 patent describing EDTA as a "magnesium chelator"). ACD is also an anticoagulant, but includes a different chelator compound (sodium citrate; citrate ion as a calcium chelator). The comparisons here between EDTA and ACD, which provide substantially the same anticlotting effects using different chelators, sheds little light on whether and to what extent any lysis inhibition is attributable to dextrose in Lee's ACD, much less whether dextrose would have such effect in a modified Chiu/Lee method. Put differently, Petitioner's argument fails to show specific effects of dextrose in ACD samples distinct from ACD's anticoagulation function generally.

EDTA." Ex. 1029 ¶ 18 (emphasis added). It thus appears that Petitioner mistakenly used the word "higher" in its briefing.

Petitioner's second theory relates to ACD's dextrose component as being a "key component . . . for isotonicity." Pet. Reply 6 (quoting Ex. 1030, 4). Petitioner contends that Dr. Van Ness agreed that, "[i]n the absence of an isotonic solution cells have the potential to rupture." *Id.* (quoting Ex. 1032, 59:5–20). And, Dr. Patterson opines that "[d]extrose's impact on isotonicity prevents rupture (lysis) of cell membranes." *Id.* (citing Ex. 1029 ¶ 22). Petitioner does not meet its burden by identifying a mere "potential" for increased lysis of cells without ACD's dextrose component. *Guangdong Alison Hi-Tech*, 936 F.3d at 1364. Although Dr. Patterson's declaration suggests a POSA would understand that ACD's dextrose necessarily prevents rupture and lysis, he later admitted that such result is uncertain—cells *may or may not* lyse if the solution in which cells were placed is hypertonic or hypotonic. Ex. 2309, 17:20–19:25 (admitting that, in "[h]ypertonic solutions, the cells tend to shrink" and "[t]hey're not so prone to lysis"; for hypotonic, whether cells lyse "depends on how hypotonic the solution is" and admitting cells "might swell a little bit and not lyse"). And, further undercutting Petitioner's theory, Dr. Patterson could not explain whether the samples would become hypotonic or hypertonic in the absence of ACD's dextrose. *Id.* at 45:15–19 (Q. "[Y]ou don't know, if you took dextrose out of a blood sample that had ACD in it, whether that sample would become hypo or hypertonic; true? A. No. Never done it.").

Petitioner's third theory that ACD's dextrose feeds the cells, and therein inhibits lysis, fares no better. Pet. Reply 6. Petitioner contends that whether cells become nonfunctional and feeding (via glycolysis) stops at low temperatures (e.g., 4°C as in Lee) is irrelevant because, in Petitioner's

combination, cells would be exposed for at least some time to dextrose at room temperature after the blood draw. *Id.* (citing Ex. 1029 ¶¶ 23–24 (noting Chiu's processing of samples within two hours of blood collection and opining "even if Lee's lower temperatures were employed, a POSA would understand that glycolysis is still occurring in despite those temperatures")[28]). Petitioner and Dr. Patterson fail to provide any data, testing, or other persuasive evidence to support the notion that less lysis would necessarily occur by reason of ACD's dextrose acting as a nutrient source for cells in the Chiu/Lee modified method than without such dextrose. 37 C.F.R. § 42.65(a) (testimony that does not disclose underlying facts or data is entitled to little weight). That glycolysis (i.e., metabolism of sugar) might continue for some short time in Chiu's samples[29] before samples are frozen (at -20°C; Ex. 1011, 1608) does not address the salient question whether that ***necessarily*** results in reduced cell lysis. Petitioner cites testimony from Dr. Van Ness (Pet. Reply 6 (citing Ex. 1031, 134:3–13)), but that testimony simply remarked that some lysis would likely occur within the two-hour initial processing window depending on how the

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[28] Dr. Patterson provides no support for the opinion that glycolysis will continue even at Lee's low temperatures. The preponderance of the evidence suggests the opposite. *See, e.g.*, Ex. 1015, 279 ("WBC's become nonfunctional after storage at 4°C, [while] the cell membrane's integrity remains intact."); Ex. 2299, 102:4–21 (Dr. Patterson admitting that chilling blood decreases cellular metabolism: "That's why they do it.").
[29] Chiu does not specify the temperature at which the sample collection and initial processing occurs, but for purposes of this analysis, we will assume the sample is handled at room temperature for at least some time.

samples are "handled." Dr. Van Ness was not asked about, and did not admit to, any lysis being inhibited by reason of cells purportedly feeding on ACD's dextrose in Petitioner's Chiu/Lee combination.[30] Petitioner provides insufficient evidence to establish that ACD's dextrose necessarily inhibits lysis of cells by acting as a food source in the modified Chiu/Lee method.

Altogether, considering the argument and evidence of record, Petitioner has shown, at best, that it is *possible* that ACD's dextrose component might inhibit lysis of cells. But such possibilities are not enough for Petitioner to prevail. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient."); *Guangdong Alison Hi-Tech*, 936 F.3d at 1364 (same); *see also Par Pharm., Inc. v. TWI Pharm.*, Inc., 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (noting the "high standard" for inherency in an obviousness analysis, as "the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed in the art"). Petitioner has not, on this record, met its burden to show that ACD's dextrose in the modified method of Chiu/Lee is an "agent that inhibits lysis of cells" as claimed.[31]

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[30] Another confounding issue, which Petitioner never addresses, is how we might parse glycolysis and any alleged inhibition of cell lysis resulting from the cells' metabolism of dextrose added via ACD versus glucose that would naturally be present in a blood sample.

[31] We do not reach Patent Owner's argument on objective indicia of nonobviousness. *See Hamilton Beach Brands, Inc. v. f'real Foods, LLC*,

3. Conclusion

For the reasons above, we find Petitioner has not established by a preponderance of the evidence that the combination of Chiu/Lee discloses "an agent that inhibits cell lysis, if cells are present" as recited in independent claims 55 and 81, and the claims depending therefrom. Accordingly, Petitioner has not established that claims 55–59, 61, 68, 69, 80–86, 89, 94, and 126–130 would have been obvious over Chiu and Lee.

G. 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 II(D). As discussed below, the challenge in this case turns on whether Petitioner met its burden to demonstrate, by a preponderance of the evidence, that an ordinarily skilled person would have been motivated to modify Pertl in view of Granger and would have done so with a reasonable expectation of success.

We start with Petitioner's contentions against independent claim 55 as representative. Pet. 22–31 (claim 55 analysis); Pet. 37 ("Claim 81 would have been obvious to a POSA for the same reasons Claim 55 would have been obvious"). We then outline Patent Owner's counterarguments before moving to our analysis.

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908 F.3d 1328, 1343 (Fed. Cir. 2018) (holding there is no need to reach objective indicia of nonobviousness where the petitioner has not made a showing necessary to prevail on a threshold issue).

1. Petitioner's Contentions

Petitioner argues that "Pertl discloses all but one feature" of claim 55. Pet. 22–31. Petitioner cites Pertl's teachings about taking blood samples from pregnant human females, centrifuging that blood to prepare plasma samples to isolate cell-free fetal DNA, further isolating the DNA by extracting it with a QIAamp kit, and using multiplex fluorescent PCR to determine the sequence of a locus of interest on free fetal DNA in the sample. *Id.* at 22–24 (citing Ex. 1010, 46; Ex. 1009 ¶¶ 76–79, 89–93 (declaration of Dr. Patterson that, *inter alia*, Pertl's selection of highly polymorphic STRs can be used for multiplex PCR assays and to detect fetal DNA following PCR amplification, wherein intensities of fluorescence signals are analyzed)). According to Petitioner, Pertl's method meets each limitation of the method of claim 55 except the requirement that the sample comprises "an agent that inhibits lysis of cells" (i.e., the "agent" limitation).[32] *Id.*

For the "agent" limitation, because "Pertl does not otherwise expressly disclose its samples included an agent that inhibits lysis of cells," Petitioner turns to Granger. *Id.* at 24–25. Petitioner cites Granger's specimen (e.g., blood) collection fluid that comprises formaldehyde or paraformaldehyde. *Id.* at 25 (citing Ex. 1012, 4:16–27, 5:14–17 (disclosing that formaldehyde and paraformaldehyde as preferred)). Petitioner asserts that a POSA would have known formaldehyde is a cross-linker. *Id.* (citing

[32] Petitioner, in a footnote, contends that Pertl uses EDTA blood collection tubes and "EDTA is an agent that inhibits cell lysis." Pet. 22 n.1. We disagree that EDTA is the claimed "agent." *See supra* Section II(C).

Ex. 1009 ¶ 126). And Petitioner contends that the ’277 patent acknowledges that “formaldehyde is encompassed within the lysis inhibitors” of claim 55. *Id.* (citing Ex. 1001, 473:15–18).

Petitioner argues that a POSA would have been motivated to combine the teachings of Pertl and Granger, with a reasonable expectation of success in arriving at the subject matter of claim 55. Pet. 25–31 (arguing it would have been obvious “to employ an agent, such as disclosed in Granger, in methods described in Pertl, to inhibit cell lysis”). According to Petitioner, Pertl describes “varying success” detecting the STRs because markers for fetal specific DNA were found on certain chromosomes but “[o]ther markers were less successfully amplified.” *Id.* at 25. Petitioner cites Pertl’s disclosure about the non-selective nature of its PCR amplification in that both fetal (target) and maternal (background) DNA sequences are amplified together. *Id.* at 25–26 (citing Ex. 1010, 46, 48). Petitioner asserts that “Pertl cautioned an excess of maternal background sequences could out-compete rare target sequences for amplification.” *Id.* Petitioner notes Pertl’s use of blood from pregnant women “at term” to “maximize” fetal DNA amounts; however, for more clinically useful information, Petitioner asserts that a POSA would have known that samples needed to be secured earlier in fetal gestation (i.e., earlier in pregnancy), when less fetal DNA is present. *Id.* at 26 (citing Ex. 1010, 45, 48). Petitioner argues that “[t]hese observations would motivate POSAs to look for ways to reduce increases in maternal background sequences.” *Id.* (citing Ex. 1010, 45, 48; Ex. 1009 ¶¶ 96–98).

Petitioner cites Chiu as disclosing that additional maternal DNA may be released into blood samples through lysis of maternal white blood cells if

such cells are not removed effectively, increasing the amount of maternal background DNA in comparison to cffDNA. *Id.* ("Chiu observed total cell-free DNA increased less the more effectively intact cells were removed.") (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).

Petitioner argues that "[b]oth Pertl and Chiu reported increases in background DNA despite centrifugation." *Id.* (citing Ex. 1011, 1609–1610; Ex. 1010, 46). Although "Chiu ultimately reduced background DNA through precise filtration and ultra-high speed centrifugation," Petitioner contends that "these treatments are beyond more modest capabilities of most doctors' offices and clinics where blood collection for prenatal testing would occur." *Id.* at 27–28. Petitioner asserts that samples taken at doctors' offices or clinics are generally shipped to regional labs. *Id.* ("Gene sequencing needed to assess free fetal DNA is generally performed by laboratories distant from blood collection points."). Petitioner contends that a "POSA would have appreciated shipment delays to laboratories capable of this processing would result in lysis of maternal blood cells and sample contamination." *Id.* (citing Ex. 1009 ¶¶ 121–122); *see also id.* at 28 ("Later filtration or centrifugation would not remedy cell lysis occasioned by such delays.") (citing Ex. 1009 ¶ 123)).

According to Petitioner, Granger teaches that delayed analysis of blood samples might compromise sample integrity due to the buildup of debris from lysed WBCs. *Id.* at 28–29 (citing, for example, Ex. 1012, 1:25–2:2, 11:23–27, 13:15–19; Ex. 1009 ¶¶ 125–127). Petitioner contends that Granger teaches a specimen collection fluid that preferably includes formaldehyde and that, by using this fluid, it is possible to reduce cellular deterioration. *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 ("[S]tablised specimens . . . have minimal haemolysis over a 7 day period."). Petitioner argues a POSA would "have been motivated to add formaldehyde or paraformaldehyde to maternal blood samples to prevent premature lysis of maternal cells and reduce a further release of free maternal DNA before samples could be further processed." *Id.* at 30 (citing Ex. 1009 ¶¶ 130–131).

Petitioner contends that a POSA would have reasonably expected success combining Pertl and Granger because adding formaldehyde or paraformaldehyde[33] would have been expected to inhibit lysis of maternal WBCs in blood samples. Pet. 30–31 (arguing this would have been expected to stabilize samples for the time needed for processing, preventing cell lysis and introduction of background maternal DNA sequences).

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[33] Petitioner's declarant, Dr. Patterson, testified that formaldehyde and paraformaldehyde share the same mechanism of action and effectively are interchangeable. *See* PO Resp. 47 n.7 (citing Ex. 2299, 25:23–26:6). Like the parties, we focus on the addition of formaldehyde but on this record our analysis also applies to paraformaldehyde.

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.")); 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").

2. Patent Owner's Counterarguments

Patent Owner raises several arguments against Petitioner's asserted motivation to combine Pertl and Granger and the alleged reasonable expectation of success in doing so. PO Resp. 35–50 (argument on "All Claims"). We summarize those arguments and then turn to our analysis.

First, Patent Owner contends that a POSA would not have been motivated to modify Pertl to address alleged problems with maternal cell lysis and background DNA. PO Resp. 35–39. According to Patent Owner, Pertl's method already addressed the "purported problem" advanced by Petitioner and "already achieved the goal that Petitioner presents as the foundation to its motivation to combine." *Id.* at 35–36. Patent Owner argues that Pertl used a two-step physical processing protocol involving two centrifugation steps to prepare fresh plasma, remove cells that might lyse, and therein addressed the potential release of additional background maternal DNA to the extent such DNA was allegedly a concern. *Id.* (citing, e.g., Ex. 1010, 46, 48 (describing Pertl's successive centrifugations at 2000g and 3000g and careful removal of the supernatant); Ex. 2239 ¶¶ 112–113).

Patent Owner also contends that, contrary to Petitioner's arguments, Pertl's method "was sensitive enough to ***detect fetal-specific alleles in all mother/child pairs studied***" despite any background maternal DNA in its samples. *Id.* at 37 (quoting Ex. 1010, 48); *see also id.* (noting Pertl's reporting (like Lo (Ex. 2016, 771–772)), of mean cffDNA available in plasma of 3.4% and 6.2% in early and late pregnancy, respectively). According to Patent Owner, because Pertl showed the sensitivity of its method and the feasibility of detecting cffDNA sequences in plasma (regardless of the sex of the fetus) in samples taken later in pregnancy, Pertl suggested applying *its* method to samples taken earlier in pregnancy—not some other method. *Id.* at 38–39 (citing Ex. 1010, 46–48; Ex. 2239 ¶ 116). And, Patent Owner argues that Pertl "does not give any hint the *compositions in the tube itself* could or should be adjusted to improve its plasma processing." *Id.*

Patent Owner argues that Pertl, like others at the time, believed that fetal DNA in maternal circulating blood was ~3–6% over the course of pregnancy and that such recovery could be obtained by physical processing steps to obtain plasma substantially free of cells. PO Resp. 37–38. Patent Owner contends that this 3–6% figure "was widely accepted," including by prior art authors like Chiu and Lo. *Id.* (citing Ex. 1011, 1607–1608; Ex. 2016, 771–772; Ex. 2271, 10762). According to Patent Owner, based on "accepted research at the time, a POSA would have thought, like Pertl, Chiu, and Lo, that using plasma prepared with Pertl's careful physical processing already achieved the recovery of the fetal DNA percentages occurring *in vivo*," obviating the need to change Pertl's method. *Id.* (citing Ex. 2239

¶ 114). Patent Owner contends that it was only years later, after the claimed invention, that those in the field, including Drs. Chiu and Lo, realized concentrations of cffDNA in circulation were much higher. *Id.* at 38 (citing, e.g., Ex. 2271, 10762 (2004 paper reporting "fetal DNA amounts to ≈3-6% of the total DNA in maternal plasma"); Ex. 2114, 1670 (reporting, in 2008, concentrations "approximately 2-fold higher than previously reported"), Fig. 4 (~10–20%); Ex. 2124, 286–287 (reporting, in 2012, "fractional fetal concentrations in maternal plasma . . . some two- to threefold higher" than the "mean of 3–6%")).

Second, Patent Owner contends that Petitioner's rationale based on the supposed absence of processing capabilities (e.g., centrifuges) at doctors' offices and clinics (where blood collection allegedly would occur) sufficient to perform initial blood processing steps (like in Chiu) lacks evidentiary support and is fueled with hindsight. PO Resp. 39–41 ("Petitioner's unsupported assertions regarding nonexistent doctors' offices and clinics in the prior art have no connection to the studies and methods reported in the prior art."). According to Patent Owner, Petitioner's declarant "merely parrots" the argument with no independent factual support. *Id.* at 39 (citing Ex. 1009 ¶ 121). Patent Owner describes this "unsupported argument" as an "egregious" example of hindsight because Petitioner deploys the argument to bypass Chiu's solution (processing by filtration or centrifugation at higher speeds) while simultaneously relying on the problem Chiu solves (lysis and background DNA). *Id.* at 40. Contrary to Petitioner's arguments, Patent Owner contends Chiu urged "standardization" of physical blood processing steps with no suggestion that blood samples for prenatal testing were being,

or should be, collected remotely at clinics or doctors' offices and then shipped away, much less with additional chemical reagents added. *Id.* (citing Ex. 2239 ¶¶ 117–119; Ex. 1011, 1607). Patent Owner also contends, with supporting evidence, that centrifuges and filters like those used in Chiu were readily available and easy to use. *Id.* at 40–41 (citing, e.g., Ex. 2303 (instruction manual for Eppendorf centrifuge), 6 (describing as "user-friendly" and "ideal for everyday routine tasks"); Ex. 2239 ¶ 118).

Third, Patent Owner argues that the POSA would not have been motivated to use formaldehyde in a modified method of Pertl, or expected success in doing so. PO Resp. 42–50. Patent Owner notes that "[e]vidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine" even if such evidence is found to not "rise to the level of teaching away." *Id.* at 46 (quoting *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017)). Among other things, Patent Owner contends that there was no evidence suggesting formaldehyde's use in connection with cell-free DNA, much less cffDNA, which was a newly discovered analyte in the late 1990s and, until work by the likes of Lo, Pertl, and Chiu, this analyte had been simply discarded with the non-cellular fraction of samples. *Id.* at 42–50. Patent Owner also contends that, while there was no data before the '277 patent showing how formaldehyde affects cell-free DNA or cffDNA, evidence of negative perceptions about formaldehyde in the art, including that it was known to damage even cellular nucleic acids, would have discouraged its use in the manner proposed by Petitioner. *Id.* We review Patent Owner's argument in greater detail below.

Even if a POSA had sought to address Petitioner's "purported problem" by combining Pertl and Granger, Patent Owner contends that Granger's use of formaldehyde "was ***not*** in the context of ***cell-free*** nucleic acid." *Id.* at 42–44 (citing, e.g., Ex. 2299, 58:24–59:2 (admission by Dr. Patterson that Granger is "***silent on cell-free nucleic acids***")); Ex. 2239 ¶¶ 121–123 (explaining that Granger concerns cellular analysis and flow cytometry and, to the extent RNA is disclosed, this is not cell-free nucleic acid but RNA extracted from within stabilized cells). Patent Owner contends this is significant because, before Dr. Lo's discovery of cffDNA in the late 1990s, the plasma where this cell-free material exists was "routinely discarded by investigators." PO Resp. 49 (quoting Ex. 2038, 4 (emphasis omitted)). And, before the '277 patent, how formaldehyde might affect cffDNA and its downstream analysis was, according to Patent Owner, not specifically known. Ex. 2239 ¶¶ 128–131 (testifying a POSA would, considering the state of the art (citing technical publications), have held concerns about formaldehyde and its potential effects that would have led a POSA away from its use for cffDNA analysis); PO Sur-Reply 16 (citing Dr. Patterson's testimony (Ex. 1029 ¶ 42) agreeing that cell-free DNA was routinely discarded up to 1998, and a POSA would know "there was no data on the use of formaldehyde with cell free DNA").

Patent Owner contends that cellular DNA and cell-free nucleic acids are not the same, and approaches that might be suitable for stabilizing cells outside the context of cell-free DNA are not necessarily suitable for cell-free DNA or its analysis. PO Resp. 44–46. According to Patent Owner, Petitioner Streck conceded these points during prosecution of Streck's own

patent application in this field. *Id.* (citing, e.g., Ex. 2298, 33 and *Ex parte Fernando*, Appeal No. 2021-003268, 2022 WL 855866, at *12 (PTAB Mar. 21, 2022) (where Streck argued successfully that it was not obvious to combine an approach for stabilizing cells that did not involve cell-free nucleic acids (as taught in Streck's own patent) with an approach related to cffDNA analysis)).

Further, Patent Owner cites patents and other sources in the technical literature reporting on formaldehyde's known problems, including its toxicity and capacity to damage DNA. *Id.* at 46–50. For example, Patent Owner cites Streck's own patent on a cell-stabilizing composition and method that "warned formaldehyde is 'toxic, flammable, and carcinogenic,'" among other problems. *Id.* at 50 (quoting Ex. 2230,[34] 2:36–38; *id.* at 2:40–43 (teaching that formaldehyde is "a danger to laboratory workers and health-care professionals")). And, although formaldehyde's specific effects on cffDNA were unknown at the time, Patent Owner contends that "there were significant concerns regarding its detrimental effects on nucleic acids." *Id.* at 47; Ex. 2239 ¶¶ 128–129. Patent Owner cites, for example, reports on formaldehyde's harmful effects even in the context of tissues/cells and cellular DNA. PO Resp. 47–48 (citing, e.g., Ex. 2139 (Swenberg), 945 (noting "DNA breaks" and "chromosome aberrations . . . and mutations");

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[34] Ryan, U.S. 5,849,517, issued Dec. 15, 1998 (assigned to "Streck Laboratories, Inc."). Ex. 2230, codes (45), (73); Pet. 1 (listing Streck Laboratories, Inc. as Petitioner's RPI). This patent is also referred to as the "Ryan" patent in briefing and evidence herein. PO Resp. 44; Ex. 2298, 10, 31 (Streck appeal brief addressing a rejection over Ryan and other art).

Ex. 2150 (Srinivasan), 1964 ("considerable evidence suggests that formaldehyde induces DNA degradation"), 1966 ("A method to overcome the problems of formaldehyde is to use an alternative fixative that is better suited for the preservation of nucleic acids and proteins."); Ex. 2158 (Heinmoller), 443 ("Crosslinking of DNA in tissues fixed with . . . formalin, limits the efficiency of PCR amplification")). Patent Owner, thus, argues that "significant evidence of negative perceptions of formaldehyde" would have dissuaded use of Granger's formaldehyde in a modified method of Pertl. PO Resp. 50; PO Sur-Reply 13–18.[35]

3. Analysis

Based on the record through trial, we agree with Patent Owner and determine that Petitioner has not carried its burden to establish by a preponderance of the evidence that it would have been obvious to modify Pertl's plasma processing and cffDNA detection method to include Granger's formaldehyde. More particularly, we find that Petitioner has not shown persuasively that a POSA would have been motivated to modify Pertl's method to add formaldehyde in the manner proposed by Petitioner. We explain below.

Patent Owner does not contest that, in the combined disclosures of Pertl and Granger, each limitation of claim 55 can be found. *See generally*

[35] Patent Owner also argues Petitioner invokes hindsight analysis for some dependent claims (PO Resp. 51–52) and that objective evidence of non-obviousness (e.g., praise and commercial success) supports patentability (*id.* at 52–64). We need not reach these arguments because Petitioner's challenge fails for other reasons discussed herein.

PO Resp. 35–50. Instead, as discussed above, Patent Owner challenges Petitioner's proffered motivation for combining the asserted art and the alleged reasonable expectation of success in doing so to arrive at the method recited in the claims. *See supra* Section II(G)(2).

As an initial matter, we find that Petitioner overstates Pertl's alleged concerns with "background" maternal DNA and misstates the purported "increases" in background DNA from cell lysis in Pertl's method. Pet. 26–27. Petitioner's rationale for modifying the method of Pertl is weakened as a result. We discuss below.

According to Petitioner, "Pertl cautioned an excess of maternal background sequences could out-compete rare target fetal sequences for amplification." *Id.* (citing Ex. 1010, 46, 48). In context, however, this alleged caution related, not to any concerns with maternal cell lysis, but to the lower detection sensitivity of Pertl's method compared to a prior study by Lo because, unlike Lo, Pertl's method used STRs and was analyzing fetal DNA independent of fetal gender. Ex. 1010, 45–46, 48 ("Hence, the described [STR] technique has a lower sensitivity for detecting fetal DNA in maternal plasma than the SRY system described by Lo et al. (1998, 1999)."). Continuing, Pertl discloses:

> 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 (Lo et al. 1996). Under these conditions, the excess of the maternal background sequences could out-compete the rare target sequences for amplification.

Id. at 48. The hypothesis that background DNA could out-compete the fetal

sequences beyond the capabilities of Pertl's assay did not, however, prevent Pertl from achieving its objective of detecting fetal-specific alleles in maternal plasma, as Pertl makes plain. Indeed, citing a "high concentration" of free fetal DNA present in maternal plasma (i.e., ~3–6%), Pertl concluded: "our proposed technique was sensitive enough to detect fetal-specific alleles in all mother/child pairs studied." *Id.*; *see also id.* at 45 (describing cffDNA concentration in maternal blood as a mean of 3.4–6.2% in early and late pregnancy, respectively); PO Resp. 36–37; Ex. 2239 ¶¶ 113–114 (testimony of Dr. Van Ness on Pertl's method and successful results).

Pertl does not mention cell lysis or convey that potential lysis would remain a concern with its method. We are also unpersuaded that Pertl supports that background DNA is a problem when its method is used to amplify target DNA, or indicate that its method could be improved by reducing background DNA by some further reduction of lysis. Given Pertl's success with samples taken later in pregnancy, Pertl suggests future study using *its method* "earlier in gestation at a time when noninvasive prenatal diagnostic information may be more clinically useful," i.e., at a time when the ratio of target to background DNA would be tilted more heavily in favor of background DNA.[36] Ex. 1010, 48 (teaching that "more studies are needed to determine the sensitivity and specificity ***of this method*** at various

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[36] Petitioner states that a POSA would know that less fetal DNA would be present earlier in fetal gestation. Pet. 26. We agree. The art, including Pertl, repeatedly reported that cell-free fetal DNA circulating in maternal blood varied from about 3–6% in early and late pregnancy, respectively. Ex. 1010, 45; Ex. 2016, 772; Ex. 1011, 1607.

gestational ages") (emphasis added); PO Sur-Reply 9 (citing Ex. 2239 ¶¶ 112–117, 144–148). We credit Dr. Van Ness's opinion that "[a] POSA reading Pertl would have understood that it did not recognize the issue of maternal cell lysis" as presenting a concern in applications using Pertl's method, and that a POSA would have understood that Pertl's plasma processing techniques, including "double-centrifugation" were sufficient to reduce background interference by, for example, removing cells that might lyse. Ex. 2239 ¶ 113 (discussing Pertl's centrifugation at 2000g and 3000g with careful transfer of plasma to fresh tubes at each step); PO Resp. 35–36.

Petitioner argues that Pertl "reported increases in background DNA despite centrifugation," and "POSAs would have understood increased background maternal cell-free DNA in samples described in Pertl was caused by lysis of intact maternal cells and consequent release of their DNA into the sample's *extra*cellular component." Pet. 27 (citing Ex. 1010, 46). We disagree. Pertl ***does not*** report ***increases*** in background DNA in its samples. Pertl remarked that, with a less sensitive assay, "the excess of the maternal background sequences could out-compete the rare target sequences." Ex. 1010, 48. But an "excess" is not an "increase," and certainly not an observed "increase" in maternal DNA despite centrifugation due to cell lysis in Pertl's samples. The most natural reading of "excess" here is simply Pertl's recognition that *most* circulating cell-free DNA in maternal blood is maternal DNA (i.e., the percentage beyond the ~3–6% of fetal origin). *Id.*

In its Reply, Petitioner charges Patent Owner with "blatantly misquot[ing]" Pertl in an effort to suggest "Pertl had achieved perfection."

Pet. Reply 7. Petitioner takes issue with Patent Owner quoting only a portion of Pertl's disclosure related to whether Pertl's method "maximize[d] the amount of fetal DNA present," allegedly obviating a need for further changes. *Id.*; *see* PO Resp. 35–38. Patent Owner's use of a partial quote here is off base in comparison to Petitioner's actual challenge. In full, as Petitioner notes, the relevant disclosure is that Pertl "***intentionally performed this study using samples obtained at term*** to maximize the amount of fetal DNA present." Pet. Reply 7 (quoting with Petitioner's emphasis the portion omitted by Patent Owner). Petitioner is not relying solely on this disclosure regarding samples taken later in pregnancy. Instead, Petitioner points to Pertl's recommendation for future studies on samples taken at earlier gestational ages—when less fetal DNA would be present. *Id.*; Pet. 26 (arguing that Pertl's teaching about a need to take samples earlier in pregnancy "would motivate POSAs to look for ways to reduce increases in maternal background sequences"). Notwithstanding the above, as we explained already, Pertl does not express concerns that cell lysis would interfere with its method or report increased background DNA released due to lysis (contrary to Petitioner's assertion); and, as for Pertl's call for further study on samples taken earlier in pregnancy, Pertl suggests that *its own* method be used. PO Resp. 35–38; PO Sur-Reply 9; Ex. 2239 ¶¶ 113–116.

Petitioner's overstatements about Pertl aside, this is not the end of the inquiry because Petitioner also cited Chiu for a disclosure of potential cell-lysis in maternal blood samples depending on how they are processed. Pet. 26–27. As argued by Petitioner, "Chiu observed total cell-free DNA

increased less the more effectively intact cells were removed." *Id.* (citing Ex. 1011, 1608, 1612–1613; Ex. 1009 ¶¶ 58–63); *see* Ex. 1009 ¶¶ 110–112, 120–121 (explaining that Chiu disclosed that total cell-free DNA increased in samples undergoing a single initial centrifugation step (at 800g or 1600g) compared to samples subjected to treatments (e.g., centrifugation at 800g + filtration, or centrifugation at 1600g + centrifugation at 16000g) that produced essentially cell-free plasma). And, for the first time in Reply, Petitioner argues a POSA would have known that the available percentage of cffDNA in maternal plasma was much greater than 3–6% because Chiu allegedly recovered 25% by preventing cell lysis. Pet. Reply 7 (citing, e.g., Ex. 1029 ¶¶ 31–36 (Patterson rebuttal testimony)).

Chiu discloses that blood processing protocols can affect the quantification of total DNA in maternal blood samples. Ex. 1011, 1607. Indeed, Chiu discloses that, "despite centrifugation, some of the maternal cells could remain in plasma, leading to an increase in the total DNA in plasma." *Id.* at 1612. Conversely, Chiu reports that "[v]irtually cell-free plasma can be obtained by centrifugation of blood samples, followed by filtration or microcentrifugation." *Id.* at 1613. Chiu's study compares a single slower-speed centrifugation step at 800g or 1600g, versus an initial slower-speed centrifugation combined with a second higher-speed centrifugation (at 16000g ("microcentrifugation")) or filtration. *Id.* at 1608–1609.[37]

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[37] As Chiu explains, the disclosed filtration involves use of a 0.2µm filter, and microcentrifugation involves use of an Eppendorf Centrifuge (5415D) at full speed (16000g). Ex. 1011, 1608.

Pertl's protocol—a first centrifugation at 2000g, careful removal of plasma, and a second centrifugation of the removed plasma at 3000g where the supernatant was again carefully removed and transferred to fresh tubes—differs from Chiu's. Ex. 1010, 46. This begs the question: would a POSA, in light of Chiu, believe that a significant cellular component, subject to possible lysis, remained in Pertl's plasma samples? The parties and their declarants disagree. Dr. Van Ness, citing Pertl's double-centrifugation protocol and reporting on maternal plasma containing ~3–6% cffDNA (alleged to be the prevailing view about *in vivo* concentrations and amounts available for analysis at the time), opines that a POSA would have believed Pertl's method sufficient to remove cells that might lyse and address background interference. Ex. 2239 ¶¶ 113–114. On the other hand, Petitioner and Dr. Patterson contend that a POSA would have understood that far greater proportional cffDNA amounts were achievable by preventing maternal cell lysis based on Chiu's alleged teaching of 25% cffDNA in samples, thus supplying "[a]mple motivation" to modify Pertl's method by adding formaldehyde. Pet. Reply 7–8 (citing Ex. 1029 ¶¶ 26–38). Petitioner bears the ultimate burden of persuasion here and, for reasons explained below, we are not persuaded the POSA would have understood from Chiu that up to 25% cffDNA was available in maternal blood for analysis.

As Patent Owner argues, the prevailing view at the time of Chiu's publication, and for years afterward, was that circulating cell-free fetal DNA in maternal plasma varied from between about 3–6%. PO Resp. 36–38; PO Sur-Reply 10–11. This was the range *actually* and *repeatedly* reported by Lo, Pertl, and even Chiu. Ex. 2271, 10762; Ex. 1010, 45, 46, 48; Ex. 1011,

1607 ("[I]t has been shown that fetal DNA represents a substantial portion of the total DNA in maternal plasma, contributing ~3.4% and ~6.4% of total plasma DNA in early and late pregnancy, respectively.").

Petitioner's declarant, Dr. Patterson, for the first time in support of Petitioner's Reply, derives the 25% amount from some of the box plot images in Chiu and calculations from gene products allegedly depicted in those plots. Ex. 1029 ¶¶ 31–34. Chiu does not, however, disclose these calculations or report that 25% cffDNA was available—an amount at least four times greater then the 3–6% range that was widely disclosed and accepted in the art at the time, including in Chiu.[38] Had the Chiu authors discovered such a marked increase in cffDNA, it stands to reason that they would have announced it then specifically and clearly. They did not. And, tellingly, Dr. Patterson's initial declaration is silent on any recognition in the art of amounts greater than 3–6%, much less Chiu's alleged 25%. *See, e.g.*, Ex. 1009 ¶ 97 (testifying that "mean concentration of such fetal DNA in early pregnancy is only 3.4%") (citing studies by Pertl and Lo); Ex. 2299, 39:20–40:4 (cross-examination of Dr. Patterson agreeing that "what Chiu and Lo reported in the early 2000's is that fetal DNA was 3 or 6 percent").

The evidence shows that it was not until years after Chiu's 2001 publication that those in the art, including Drs. Lo and Chiu among others,

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[38] Petitioner's counsel agreed that Chiu does not recite recovery of 25%, but asserted that such a percentage can be derived from some of Chiu's figures and applying Petitioner's calculations. Tr. 11:11–17 (asserting further that Patent Owner's expert agreed with the calculations).

recognized and reported on greater amounts of cffDNA being available, and for reasons distinct from Chiu's physical processing techniques from 2001. Ex. 2114,[39] 1670 (paper by Chiu and Lo in 2008 reporting concentrations "approximately 2-fold higher than previously reported"), Fig. 4 (~10–20%); Ex. 2124, 286–287 (paper by Chiu and Lo in 2012 reporting "fractional fetal concentrations in maternal plasma . . . some two- to threefold higher" with advances in digital PCR and sequencing technology)). Even three years after Chiu's 2001 publication, Drs. Chiu and Lo continued to maintain in their writings that "[d]uring pregnancy, fetal DNA amounts to ≈3–6% of the total DNA in maternal plasma" without remarking on greater amounts being available, much less the 25% Petitioner argues would have been understood or expected by the POSA. Ex. 2271,[40] 10762. If Dr. Chiu and Dr. Lo (who, according to Streck, "can easily be considered the foremost expert in the field of cell-free fetal DNA") did not understand from Chiu's work in 2001

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[39] Fiona M. F. Lun and Rossa W. K. Chiu, et al., 54:10 *Microfluidics Digital PCR Reveals a Higher than Expected Fraction of Fetal DNA in Maternal Plasma*, CLINICAL CHEMISTRY, 1664–1672 (2008). The title of this paper is itself telling, and this paper is authored by Dr. Lo, and Dr. Chiu and Tze Kin Lau, who were both authors of Chiu (Ex. 1011).

[40] This 2004 paper and study by Drs. Chiu and Lo is notable because it follows the Chiu 2001 centrifuge protocol of "centrifugation at 1,600 x g" followed by "centrifugation at 16,000 x g" (explicitly citing Chiu's 2001 paper for it), yet the 2004 paper continues to report 3–6%. *See* Ex. 2271, 10763, 10766–10767 (Discussion: "Because the paternal specific allele exists at ≈3–6% in total maternal plasma DNA, its corresponding peak in the mass spectrum is often dwarfed by the background peak."; Bibliography: citing reference 21 (i.e., Chiu 2001)).

that 25% cffDNA was available in maternal plasma for recovery, we are unpersuaded that the ordinarily skilled person would have had held that understanding. Ex. 2086[41] ¶ 3. Again, as argued by Patent Owner and based on the record here, the widely reported and prevailing view in the art at the time was that about 3–6% cffDNA was available in maternal plasma.

Looking past the unpersuasive 25% assertion, we also note that the Petition simultaneously highlights the asserted benefits of Chiu's processing method while turning away from Chiu's techniques concerning Petitioner's proposed modification of Pertl. Pet. 27–28. Petitioner maintains that, although a POSA would understand Chiu's processing techniques could be used to produce essentially cell-free plasma and address cell lysis (inasmuch as Pertl's method had an alleged lysis and background DNA problem in need of a solution), Petitioner suggests Pertl's method *would not* have been modified according to Chiu's teachings. *Id.* Instead, Petitioner argues filtration or centrifugation techniques as in Chiu are beyond the capabilities of doctors' offices and clinics where maternal blood collection for prenatal testing would occur. *Id.* So, the POSA allegedly would have thought maternal blood samples needed to be shipped to distant labs for processing and prenatal DNA analysis and, accounting for shipment delays, would have

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[41] Exhibit 2086 is a declaration of Brad Hunsley, Streck's long-time employee and Director of Research and Development, submitted to the Office under 37 C.F.R. § 1.132 in connection with a Streck patent application on methods for stabilizing samples and analyzing cell-free fetal nucleic acids. Ex. 2086 ¶¶ 1–3.

believed that a stabilizing chemical—formaldehyde—should first be added to the samples before they are shipped away. *Id.*

As discussed above (*supra* Section II(G)(2)), Patent Owner argues this reasoning about capabilities of clinics and a need for shipment lacks support and suffers from hindsight bias. We agree. The evidentiary basis for Petitioner's rationale on this point is rather weak, relying on the verbatim, and otherwise unsupported, *ipse dixit* opinion of Dr. Patterson. Pet. 27–28 (citing Ex. 1009 ¶¶ 121–122); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (Aug. 24, 2022) (precedential) (holding that conclusory declaration testimony that repeats conclusory assertions in the petition is entitled to little weight). Petitioner's contention that offices or clinics would not have been capable of carrying out filtration or centrifugation of samples is questionable.[42] Patent Owner cites evidence that the filtration and centrifugation materials (like used in Chiu) were, in fact, available, inexpensive, and easy to use. Ex. 2303, 6 (instruction manual for the same model centrifuge as used in Chiu, describing as "user-friendly," "ideal for everyday routine tasks," and recommended for use by "clinics"); *see also* Ex. 2299 (Patterson cross-examination) 43:11–44:7 (admitting filtration was in standard use in the 1990s and "inexpensive"), 45:2–12 (admitting the centrifuge "vendor didn't matter" and its operation involves only "two dials,

[42] This is assuming that remotely located doctors' offices or clinics are where blood samples for prenatal testing were being collected or were suggested as would-be sites for such collection prior to the '277 patent, a point on which there is no persuasive evidence of record cited.

speed and time"); Ex. 2239 ¶ 118 (Dr. Van Ness testimony on the accessibility of centrifugation protocols).

In rebuttal, Petitioner contends that adopting Chiu's centrifugation or filtration would "require doctors' offices to function as blood processing labs, necessitating trained personnel." Pet. Reply 8 n.2. And, in support, Petitioner cites solely to Dr. Patterson's "personal experience" with typical offices. *Id.* (citing Ex. 1029 ¶ 38 (pointing to "personal knowledge")). We do not doubt Dr. Patterson's experience as a physician but independent support for Petitioner's rationale on this point is still wanting. Moreover, although Petitioner argues adding a centrifuge would turn offices into blood processing labs and require trained staff, Petitioner never explains persuasively why (or why that would be unacceptable given the alleged benefits of the processing techniques described in Chiu (e.g., production of virtually cell-free plasma)).[43]

If, as Petitioner contends, the POSA would have seen cell lysis as a problem in Pertl, and assuming cells were not removed sufficiently, Chiu

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[43] While Petitioner presents this blood processing and training as an obstacle to use of Chiu's techniques, Petitioner does not persuasively explain why adding formaldehyde—a "toxic" and "danger[ous]" chemical—to maternal blood samples in doctors' offices or clinics where the blood would be collected (per Petitioner's rationale) would not itself have required careful blood processing and training. *See, e.g.*, Ex. 2230, 2:34–46 (Streck's patent on cellular fixatives disclosing, in Background, that formaldehyde in its commonly-used form is a "noxious gas which is also toxic, flammable, and carcinogenic" and, despite efforts to protect personnel when used, "formaldehyde still presents a danger to laboratory workers and health care professionals").

would appear to provide a readily available and documented solution. *See* Ex. 1011, 1613 (urging "standardization" and recommending its centrifugation protocol to produce virtually cell-free plasma because it is even "simpler and less costly to implement than filtration"). But Petitioner sidesteps that and urges instead that adding formaldehyde would have been the obvious answer.[44] To be clear, we are not suggesting that a POSA must choose only the "best" solution to prove obviousness. *Par Pharm.*, 77 F.3d at 1197–98 (holding that the motivation need not be the best option, but it must at least be proved "*suitable*" based on the evidentiary record). Petitioner's theory does, however, highlight the question why the POSA would have been motivated to choose a technique (adding formaldehyde to maternal blood samples) with unpredictable consequences when applied in an entirely new way (analysis of circulating cell-free fetal DNA in maternal plasma)—even Dr. Patterson concedes there was "no data" on use of formaldehyde with cell-free DNA. Ex. 1029 ¶ 42; Ex. 1047, 81:15–82:18. We explore that question, taking account of the known problems with

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[44] At oral argument, Petitioner's counsel stated that the mention of Chiu's centrifugation protocols (and the alleged inability to perform at offices or clinics) was simply to head off argument that a POSA would have adopted "those rather cumbersome and costly procedures [of Chiu] in lieu of the more simple and straightforward solution that Granger proposed." Tr. 15:24–16:15. On this record, as explained, we are not persuaded that those procedures are comparatively cumbersome and costly. Petitioner, in a footnote, also asserts that use of preservatives and Chiu's techniques "are not mutually exclusive." Pet. Reply 8 n.2. This assertion was not meaningfully developed in Petitioner's briefing and it does not persuasively counter Patent Owner's charge of hindsight bias with the theory expressed in the Petition, as discussed above. PO Resp. 39–41.

formaldehyde and why that would have discouraged its use in the manner proposed, in further analysis below. Altogether, however, Petitioner's reasoning insofar as it cites some need to ship samples away because of an alleged inability to centrifuge them locally, does suggest hindsight bias is at work and deployed to justify Petitioner's turn to formaldehyde.

The parties dispute whether formaldehyde's problems would have dissuaded the POSA from modifying Pertl's methods to add it. Petitioner argues that formaldehyde was a well-known cross-linker used to stabilize blood cells. Pet. 25, 28–29 (citing Ex. 1009 ¶¶ 126–127; Ex. 1012, 9:18–10:20). On the other hand, Patent Owner presents evidence, such as the Srinivasan reference, showing that a POSA would have been aware of and concerned about formaldehyde's detrimental effects, including damage to nucleic acids and toxicity, among other problems. PO Resp. 47–50 (citing, e.g., Srinivasan (Ex. 2150), Swenberg (Ex. 2139), and Heinmoller (Ex. 2158)).[45]

We find that Srinivasan provides strong evidence that formaldehyde was known to have detrimental effects on nucleic acids. *See, e.g.*, Ex. 2150, 1964 (reporting, e.g., that formaldehyde is a widely used tissue (cellular) fixative, "[h]owever, attempts to extract usable DNA from formalin-fixed tissue for molecular biological studies have been variably successful").

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[45] Patent Owner cites numerous references as evidencing the problems with formaldehyde's use. Some of the references post-date the filing date of the '277 patent by years. *See, e.g.*, PO Resp. 48–49 (citing Ex. 2155, published in 2005; Ex. 2156, published in 2014). Unless otherwise noted, for purposes of this decision, we do not rely on these later references as probative of the POSA's understanding before the '277 patent.

Srinivasan reports that "considerable evidence suggests that formaldehyde induces DNA degradation" and that "formalin-fixed tissues exhibit a high frequency of nonreproducible sequence alteration." *Id.* (disclosing, e.g., that only "few" studies reported yield of high-molecular weight DNA; noting "hydrolysis of phosphodiester bonds" in DNA and induced artificial mutations). Srinivasan ultimately suggests that other fixatives should be used: "A method to overcome the problems of formaldehyde is to use an alternative fixative that is better suited for the preservation of nucleic acids and proteins." *Id.* at 1966 (discussing other fixatives). We also credit Dr. Van Ness's testimony that concerns about formaldehyde's problems, including known damage to DNA (even in cellular applications with cellular DNA) and unknowns about how formaldehyde would affect downstream cffDNA analysis, would have discouraged its use in a modified Pertl method as argued by Petitioner here. *See, e.g.*, Ex. 2239 ¶¶ 128, 131.

Petitioner argues in Reply that Srinivasan "post-date[s] the earliest claimed priority date of the '277 Patent" and does not "evidence a POSA's understandings as of the claimed priority date." Pet. Reply 8–9 (citing *Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus.*, 145 F.3d 1303, 1313 (Fed. Cir. 1998)). We disagree.

Petitioner assumes that the challenged claims are entitled to priority earlier than Srinivasan's December 2002 publication date. Ex. 2150, 1961. Patent Owner does not argue that the challenged claims have any priority date earlier than Srinivasan's publication. Tr. 33:2–18. Neither party sought to make any evidentiary showing on this record that the claims are entitled to priority earlier than the filing of the September 11, 2003, application that

matured into the ’277 patent.[46] *See supra* Section I(A) (identifying related applications). And, for argument’s sake, if the claims were entitled to priority to earlier ancestral applications listed in the patent’s ancestral chain, the earliest of which is a provisional application filed in March 2002, Srinivasan is explicitly a “Review” article. Ex. 2150, 1961. All of Srinivasan’s seventy-four citations, including those cited in passages discussing damage to DNA caused by formaldehyde, are to articles that published in 2001 or earlier. *Id.* at 1970–1971; PO Sur-Reply 18–19. On this record, we find that Srinivasan is informative on the POSA’s perspective of the concerns with formaldehyde’s use at the time of the invention, whether that be September 2003 or the filing of the aforementioned provisional application in March 2002.[47]

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[46] We will not presume on this record that the ’277 patent’s claims are entitled to the earlier priority date of other applications listed in its ancestral chain. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008) (explaining that “there is simply no reason to presume that claims in a [CIP] application are entitled to the effective filing date of an earlier filed application”). Such a presumption is especially unjustified here given the ’277 patent’s complex priority chain involving numerous CIPs and provisional applications. Ex. 1001, 1:7–5.

[47] *Chiuminatta*, cited by Petitioner (Pet. Reply 8), is distinguishable. There, the Federal Circuit discussed a district court’s finding that a Department of Transportation report (published many years after the patent at issue) “was not relevant” because “the report describes a study performed after the filing date of the patent and did not purport to be a survey of methods used in the prior art.” *Chiuminatta*, 145 F.3d at 1313. Srinivasan, as a “Review” article, does survey and summarize prior studies (from 2001 and earlier) on formaldehyde and, thus, is probative of its known problems before the earliest applications in the ’277 patent’s ancestral chain (even if the claims were entitled to priority earlier than Srinivasan’s publication in late 2002).

Moreover, inasmuch as Petitioner is suggesting generally with its argument that it was not known in the prior art that formaldehyde can damage DNA, such a suggestion is undermined by Petitioner's own declarant. Although Dr. Patterson pushes back on whether damage to DNA would have discouraged formaldehyde's use, he admits, "[a]bsolutely," to being "aware of concerns expressed in the prior art about formaldehyde's ability to damage nucleic acids" when he prepared his declaration. *See* Ex. 2299, 28:11–17; *id.* at 27:23–28:5 (conceding on cross examination that his declaration submitted with the Petition did not address concerns in the art about formaldehyde damaging nucleic acids).

We also consider Swenberg's teachings about formaldehyde inducing "DNA breaks" and Heinmoller's teachings about formaldehyde limiting PCR efficiency. Ex. 2139, 945 (disclosing, e.g., DNA breaks and mutations); Ex. 2158, 443 (disclosing formaldehyde-induced cross-linking can limit efficiency of PCR amplification). Petitioner dismisses Swenberg on the basis that it allegedly concerns only formaldehyde's harms to living organisms. Pet. Reply 9 n.5 (Ex. 1029 ¶ 44 ("This publication does not discuss cell-free DNA")). The fact remains, however, Swenberg indicates that formaldehyde was known to be genotoxic and to have detrimental effects on DNA (including cellular DNA and in organisms), consistent with Patent Owner's argument. Ex. 2139, 945 (disclosing harms to DNA of cultured cells, including human cells); Ex. 2239 ¶ 128 (testifying, citing Swenberg, that "[s]everal studies at the time of the claimed invention demonstrated that formaldehyde degraded human DNA"). That Swenberg does not describe those harms specifically as against cell-free DNA or

cffDNA analysis is unremarkable because there is no evidence of record—and "no data"—specific to formaldehyde's use in that context before the '277 patent. Ex. 1029 ¶ 42; Ex. 2239 ¶ 131 (testifying that cell-free fetal DNA had only been recently discovered and, before then, was simply discarded with the non-cellular plasma fraction). Heinmoller does not weigh significantly in Patent Owner's favor here because Dr. Patterson testified persuasively that, if cross-linking and its impact on PCR amplification was a concern, it could be addressed in Pertl's DNA isolation steps before amplification. Ex. 1047, 15:5–21, 20:14–21:9 (testifying on reversing cross-links by enzymatic digestion with reagents in the Qiagen kit used in Pertl).

Even Streck's own patent cautions against formaldehyde's use for stabilizing blood cells despite it being a "common fixative." PO Resp. 50; Ex. 2230, 2:33–44. Indeed, Streck warned that "toxicity associated with known formulations for stabilization of cells also renders their use *less than satisfactory*" and the specific example given is "formaldehyde." Ex. 2230, 2:33–44. (emphasis added). Streck explained that formaldehyde in its commonly-used form is "toxic, flammable, carcinogenic" and "a danger" to those working with it. *Id.* (disclosing that formaldehyde's use is also "expensive" and "inconvenient").[48] The Petition neither mentions nor

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[48] Streck's "Ryan" patent purports to address toxicity by avoiding direct use of formaldehyde in its stabilizer compositions. *See* Ex. 2230, 5:1–29. Petitioner cited the Ryan patent in support argument that Streck avoids formaldehyde in its products. Pet. Reply 18–19; *see also* Ex. 2086 (Hunsley Decl.) ¶ 7 (testifying that a product called "Streck Cell Preserve" sold since the 1990s is the subject of the Ryan patent). Streck echoed formaldehyde's

addresses these known concerns. And Dr. Van Ness testifies persuasively that they would have led a POSA away from selecting formaldehyde for an entirely new application to analysis of cell-free fetal DNA in maternal plasma. Ex. 2239 ¶ 133. In response, Petitioner contends that scientists were aware of safety measures allowing formaldehyde's use. Pet. Reply 9 (citing Ex. 1029 ¶ 43). Yet Streck's patent includes its warnings against formaldehyde's use "despite" the "efforts . . . made when this chemical is used to protect workers." Ex. 2230, 2:38–44 ("[D]espite such efforts . . . formaldehyde still present[s] a danger to laboratory workers and health care professionals.").

Petitioner argues that none of Patent Owner's "critiques" would have discouraged adding formaldehyde to Pertl's method. Pet. Reply 9–12. According to Petitioner, concerns about formaldehyde's use related to longer DNA fragments, tissue samples unrelated to cell-free DNA, or DNA sequence analysis that differs from Pertl's—Petitioner argues, cell-free fetal DNA in maternal blood is "plentiful" and if some of it is damaged, what is left could still be amplified and detected. *Id.* (citing, e.g., Ex. 2150, 1963, 1965; Ex. 1029 ¶¶ 46, 49).

Petitioner's argument is unavailing. Srinivasan's disclosure on amplification products being generally "500bp [(base pair)] or less" in some formalin-fixed tissues was an indicator of failure, not success, and we are unpersuaded this would have suggested that formaldehyde should be used

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toxicity problems even more than a decade after the Ryan patent. Ex. 2247 ¶ 9 (Streck patent application on stabilizers for cffDNA analysis describing, as background, "toxicity considerations" with formaldehyde).

where shorter sequences (allegedly, as in Pertl) are the desired target. Ex. 2150, 1965 ("The low-molecular weight DNA may be the *result of scission of phosphodiester backbone* of DNA.") (emphasis added); PO Sur-Reply 17–18.[49] That Srinivasan or other art cited by Patent Owner focused on formaldehyde's harms to DNA from tissues or cells only underscores that even less was actually known at the time about formaldehyde's effects on cell-free DNA.[50] We also disagree with Petitioner's assertion in reply that damaging some of Pertl's cffDNA would not have been a concern because cffDNA is "plentiful." Pet. Reply 11. Streck's R&D Director, Mr. Hunsley, declares that cell-free DNA "quantities were limited" and this was an

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[49] Petitioner also cites Exhibit 2302 (a Streck-sponsored study from 2014) as relating to use of formaldehyde with a 787 bp fragment. This study published over a decade after the '277 patent was filed, and we decline to consider it as fairly evidencing the POSA's perspective at the relevant time. If it somehow did, it likely would not, on balance, help Petitioner. *See* Ex. 2302, 55 ("formaldehyde and glutaraldehyde are known to cause damage to DNA in clinical samples"), 58 ("In our experiments formaldehyde . . . treated DNA showed a time dependent decrease in DNA amplification indicating . . . damage to DNA that adversely affect the DNA amplification by PCR" compared to "DNA treated with [Streck's] BCT reagent [that] showed no change in amplification . . . [and] did not cause any damage to DNA."). This exhibit does not show that formaldehyde could be used without damaging shorter fragments.
[50] Petitioner's suggestion that Srinivasan's disclosure is inapplicable or irrelevant to cell-free DNA analysis is also undermined by a 2012 research paper funded by Streck and co-authored by a Streck scientist that specifically related to Streck's cell-free DNA blood collection reagents and cites Srinivasan. Ex. 1034, 481 ("Research has shown that formaldehyde fixed tissues exhibit non-reproducible DNA sequence alteration or loss of PCR products (Srinivasan et al., 2002)"); PO Sur-Reply 15.

"obstacle" to recovery. Ex. 2086 ¶ 4 (citing Lo's seminal work in 1998). Pertl describes the cffDNA it is trying to target and analyze as "rare." Ex. 1010, 48; Ex. 1009 ¶¶ 95–98 (testimony of Dr. Patterson discussing "rare" cffDNA sequences). PO Sur-Reply 13 (noting inconsistencies in Petitioner's positions). As discussed above, Pertl sought to "maximize" the amount of cffDNA available for testing, which Petitioner flagged previously as important for its obviousness theory and revealing concerns a POSA would have about the scarcity of cffDNA, especially if testing were carried out earlier in gestation when lower amounts of the cffDNA analyte would be present. Ex. 1010, 48; Pet. 26. Petitioner's argument *now* that a POSA would not have been overly concerned with damaging the same analyte that Pertl was trying to detect—limited and rare cell-free fetal DNA sequences—is unpersuasive.

Petitioner also argues that Granger expresses no concerns about formaldehyde damaging nucleic acids. Pet. Reply 12 (asserting that Granger used formaldehyde in its collection fluid yet this was not incompatible with PCR analysis of RNA). We have accounted for what Granger discloses (and does not disclose) in our analysis. Granger does not discuss DNA damage from formaldehyde. But, as discussed above, other evidence of record demonstrates that formaldehyde's downsides were known in the prior art. Granger also does not teach or suggest that formaldehyde could be used successfully for the analysis of cell-free fetal DNA in maternal plasma—Patterson admits that Granger describes "*intra*cellular nucleic acids," that Granger "does not disclose any interactions between its stabilizers and nucleic acids," and that Granger is "*silent* on cell-free nucleic acids."

Ex. 1029 ¶ 55; Ex. 2299, 54:10–13, 58:24–59:22 (emphases added); Ex. 2239 ¶¶ 103, 122–126 (Dr. Van Ness similarly testifying that Granger does not discuss or concern cell-free nucleic acids); PO Sur-Reply 18.[51] It is true that Granger discloses that RNA can be extracted from formaldehyde-treated samples and amplified via PCR. Ex. 1012, 10:6–8, Fig. 11. This is, however, RNA extracted from cells in whole blood samples, where a substantial cell volume is present, and it is not apparent that Granger was amplifying and detecting a scarce analyte—rare nucleic acid sequences in limited quantity—against a background of excess sequences being concurrently amplified like Pertl. *Id.* at 14:14–24; *see also id.* at 13:27–14:8, Figs. 9–10 (cell counts and differential); Ex. 2239 ¶¶ 102, 124–126 (discussing Granger's extraction of cellular RNA for PCR and testifying this would not have suggested success with cffDNA analysis).[52] Accordingly,

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[51] In its Reply, Petitioner argues the POSA would understand from Granger that formaldehyde was compatible with PCR of "free fetal nucleic acids" because formaldehyde could penetrate the cells and interact with nucleic acids or the nucleic acids could be exposed formaldehyde when cells are lysed to expose their nuclear contents. Pet. Reply 12 (citing Ex. 1029 ¶¶ 54–56). This is unpersuasive, especially in view of Dr. Patterson's earlier concessions, including that Granger is silent on any cell-free nucleic acids and that a POSA would know there was "no data" in the art on any use of formaldehyde with cell-free DNA. Ex. 2299, 58:24–59:22; Ex. 1029 ¶ 44.

[52] Granger discloses that, over the course of days, RNA content in its samples decreased more in stabilized versus unstabilized whole blood samples. Ex. 2239 ¶ 125 (discussing reduction of 29.4% versus 56.6% in stabilized and control, respectively); Ex. 1012, 14:17–25. This would appear uncontroversial given Granger's focus on stabilizing cells because, with cells stabilized over many days, more cells would be available later from which to extra nucleic acids.

considering the overall record, we are unpersuaded that Granger's RNA amplification would have suggested success with amplification and detection of rare cell-free fetal DNA isolated from maternal plasma in Pertl.

Lastly, Petitioner asserts that formaldehyde's alleged problems are not alluded to in the '277 patent. Pet. Reply 13; PO Sur-Reply 18 (arguing no authority is cited by Petitioner that would require the patent to provide such disclosures). We are unpersuaded on this record that this evidences that the addition of formaldehyde in Pertl's modified method would have been obvious. The point of novelty for the challenged claims was the addition of a lysis-inhibiting agent, formaldehyde, in particular, to methods for cffDNA processing and analysis. *See supra* Section I(E). And the '277 patent includes detailed working examples showing how that can be done, with accompanying results. *See, e.g.*, Ex. 1001, 89:1–91:50 (Example 4).

Patent Owner also cited Streck's arguments to the Board concerning claims in Streck's own, later-filed, patent application on methods of stabilizing maternal blood samples for cell-free fetal analysis as allegedly undermining positions advanced by Petitioner here. *Supra* Section II(G)(2); PO Resp. 44–46 ("Petitioner itself has argued—and the Board has already acknowledged—that differences regarding cell-free nucleic acids would frustrate application of general cell stabilizers to cell-free nucleic acids.") (citing, e.g., Ex. 2298 (Streck's Nov. 4, 2020, Appeal Brief during prosecution of U.S. Application No. 12/689,370 (filed Jan. 19, 2010)), 33 (argument against certain § 103 rejections); *Ex parte Fernando*, 2022 WL

855866, at *12[53]). At a high level, there does appear to be some tension, if not inconsistency, between Streck's prosecution arguments and the obviousness theory that Streck seeks to persuade us with here. Streck argued *against* the obviousness of modifying a method for analyzing cell-free fetal DNA (Li reference) by adding a cell-stabilizer composition as disclosed in Streck's Ryan patent, which Streck emphasized is *unrelated* to cell-free fetal DNA. Ex. 2298, 33–34 (arguing "[u]pon performing a word search of the Ryan 1 specification, the Appellant cannot locate any recitation of 'cell-free', 'fetal', or even 'maternal'"). On the other hand, Petitioner contends that arguments made during prosecution of its own application reflect matters learned after the '277 patent, including some issues arising from the '277 patent inventor's later work; there appears to be some support for that view of the prosecution record as well. Pet. Reply 13–14 (citing Ex. 2298, 34 (citing a 2005 paper by Chung (Ex. 1016, 3–4 (discussing Dr. Dhallan's experiments with formaldehyde)). Ultimately, Streck's prosecution arguments and the related *Fernando* decision were based on different claims, different art, and a different record developed in that appeal

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[53] Streck's arguments evidently persuaded the Board, which reversed the rejections for obviousness, crediting, *inter alia*, the argument that the examiner "provides no reasoning why a skilled artisan would modify the teachings of Li, which employs cell-free ***fetal*** nucleic acid, with the teachings of Ryan ['517], which ***does not*** employ cell-free ***fetal*** nucleic acid." *Ex parte Fernando*, 2022 WL 855866 at *12, 21–22 (quoting Streck's Appeal brief); *see also id.* at *1–2 (reproducing illustrative claims).

proceeding, and those arguments and appeal decision do not factor into our Decision here.

Altogether, we find that the evidence of record supports that formaldehyde was known to be dangerously toxic and to have detrimental effects on nucleic acids. We also find that, notwithstanding the known use of formaldehyde as a stabilizer for cells, a POSA would have had significant and unresolved concerns about expanding formaldehyde's use to applications involving rare circulating cell-free fetal DNA in maternal plasma as such use could damage the cffDNA analyte in the sample itself, frustrating its detection and analysis. And we credit Dr. Van Ness's testimony that such concerns would have dissuaded a POSA from modifying Pertl's method with Granger' formaldehyde as proposed by Petitioner.

For the above reasons, considering the argument and evidence presented through trial, Petitioner does not persuade us by a preponderance of the evidence that a POSA would have been motivated to combine Pertl and Granger to arrive at the subject matter of claims 55 and 81. Petitioner's challenge to the dependent claims relies on its analysis for claims 55 and 81 analysis (Pet. 32–42), and Petitioner does not argue or show that its challenge to the dependent claims makes up for deficiencies we have noted above. Pet. Reply 6–15 (same responsive argument for all claims). Thus, we conclude that Petitioner has not proved that claims 56–61, 68, 69, 80, 82–86, 89–90, 94, 126–130, 132, and 133 are unpatentable as obvious over Pertl and Granger. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.").

III. MOTIONS

A. Motion to Strike (Paper 50)

Petitioner filed a motion to strike portions of Patent Owner's Sur-Reply. Paper 50. Patent Owner opposes the motion. Paper 53. Petitioner contends Patent Owner raised new argument about Exhibit 1014 (a paper authored by Dr. Patterson), which was submitted with the filing of the Petition but only cited by Patent Owner for the first time in its Sur-Reply. Paper 50, 1–3; PO Sur-Reply 14 (citing Ex. 1014). According to Petitioner, Patent Owner presents new argument about the reversibility of certain cross-links caused by formaldehyde, cites new experimental data (in Ex. 1014, Fig. 2.1), and argues such matters would have been known before any possible priority date of the '277 patent. Paper 50, 1–3. Moreover, Petitioner argues, the untimeliness of Patent Owner's arguments about Exhibit 1014 prevented the exhibit's author, Dr. Patterson, from addressing them to provide explanation or context. *Id.* at 2–3.

For the reasons given below, we deny Petitioner's motion to strike.

First, we find that Patent Owner's arguments on Exhibit 1014 are, on balance, responsive to issues raised by Petitioner in its Reply. It is true that Petitioner submitted Exhibit 1014 with its Petition and that Patent Owner did not cite it until its Sur-Reply. However, the points raised by Patent Owner about Exhibit 1014 respond to certain of Petitioner's arguments raised for the first time in its Reply. For example, Petitioner argued a POSA would not have been concerned about formaldehyde's use (such as cross-linking disclosed in Heinmoller that Patent Owner cited in its Response) and that those concerns arose only after the supposed priority date of the '277 patent.

Pet. Reply 8–9. Patent Owner's citation of Exhibit 1014 is responsive on such points (e.g., it discusses cross-linking with formaldehyde's use), it published in 2000 and is thus earlier than some references Petitioner argued were too late to evidence a POSA's knowledge, and, lastly, it was authored by Dr. Patterson and arguably called into question the credibility of rebuttal opinions he offered about the state of a POSA's knowledge on such issues.

Second, Exhibit 1014 does not, ultimately, help Patent Owner as we do not rely on the portions of Exhibit 1014 cited by Patent Owner or Patent Owner's argument about them. As discussed in our analysis, if cross-linking (as reported in Heinmoller or, for that matter, Exhibit 1014) was a perceived problem, Dr. Patterson provides a credible explanation how it could be and likely was addressed by Pertl.[54] *Supra* Section II(G)(3) (citing Ex. 1047).

Third, there is no prejudice to Petitioner here because, with our authorization, Petitioner submitted additional direct testimony from Dr. Patterson addressing Exhibit 1014 and Patent Owner's arguments about it. Ex. 3003 (authorizing the deposition and explaining its scope); Ex. 1047 (deposition transcript); Paper 60 (Petitioner's designations and Patent Owner's cross designations).[55]

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[54] Patent Owner also cited Figure 2.1 of Exhibit 1014 (PO Sur-Reply 14), but, when given an opportunity to explain, Dr. Patterson indicated that the data was an extreme example and involved extraction reagents that Pertl does not use. Ex. 1047, 25:8–26:9, 28:6–29:11.

[55] Consistent with the narrow authorization given, we expected that the parties' deposition designations from the additional Patterson transcript would be limited in number and scope, yet the parties designated nearly all of the eighty-plus page transcript, with nearly all of designations objected to

B. Motion to Exclude (Paper 52)

Petitioner moves to exclude the following: (1) the jury verdict in Patent Owner's litigation against Laboratory Corporation; (2) portions of Exhibit 1014 relied on by Patent Owner in Sur-Reply; (3) trial testimony of Dr. Van Ness from the litigation against Laboratory Corporation relied on by Patent Owner; (4) "new arguments" about Srinivasan (Ex. 2150) used in Patent Owner's Sur-Reply; and (5) paragraphs 202 and 211–236 of Dr. Van Ness's Declaration (Ex. 2239) related to commercial success. Paper 52, 1–12. Patent Owner opposes the motion (Paper 54) and Petitioner filed a reply in support of the motion (Paper 55).

We do not, in this Final Written Decision, rely on any of the above-numbered items (1)–(3) or (5). Accordingly, Petitioner's motion as to those items is denied as moot.

Regarding (4), Petitioner argues that Patent Owner "makes new arguments in its Sur-Reply" with respect to statements on pages 10–11 of Srinivasan (Ex. 2150). Paper 52, 9 (citing Patent Owner's assertion that Srinivasan is a "Review" paper that summarizes the state of the art and its cited references pre-date the claimed invention). Petitioner contends that Patent Owner is relying on Exhibit 2150 for the truth of the matter asserted

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by the non-designating party. *See generally* Paper 60. We nevertheless reviewed the designated testimony. The objections are overruled, but were also considered during review.

(i.e., dates of the cited references in Srinivasan) and, thus, Patent Owner's reliance on those citations should be excluded as hearsay. *Id.* at 9–10.

For the reasons below, Petitioner's motion is denied as to item (4). First, if Petitioner's concern was "new arguments" about Srinivasan, the way to raise is a motion to strike, not a motion to exclude. *See* PTAB Consolidated Trial Practice Guide (Nov. 2019), 79 ("A motion to exclude is not a vehicle . . . to address arguments or evidence that a party believes exceeds proper scope of a reply or sur-reply."). Second, with respect to the alleged new argument and citations in Srinivasan in the Sur-Reply, Petitioner did not sufficiently preserve an objection under our rules. 37 C.F.R. § 42.64(b)(1) (requiring "any objection must be filed within five business days of service of evidence to which the objection is directed" and that such "objection must identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence"). The Sur-Reply with the alleged new arguments and evidence about Srinivasan was served November 30, 2022. Petitioner filed an objection on December 7, 2022, with no objection to Srinivasan or any alleged new arguments or evidence from it. *See generally* Paper 47. Petitioner contends it objected earlier (Paper 32, filed July 26, 2022) when it objected to evidence submitted with Patent Owner's Response. Even if we considered that to be a timely objection, the objection in Paper 32 lacks sufficient particularity as to its basis to put Patent Owner on notice of the content in Srinivasan that Petitioner now complains about in its motion such that Patent Owner might have cured the objection. The earlier objection buries Exhibit 2150 in a string listing roughly forty exhibits with vague

assertions about the exhibits allegedly lacking authentication, foundation, being hearsay, and not qualifying as summaries. Paper 32, 5.[56]

Moreover, assuming Srinivasan did fall under the definition of hearsay according to the Federal Rules of Evidence, we would find that Petitioner waived that objection (for not raising in a timely and specific manner as discussed above), but also because Petitioner itself cites Srinivasan for the truth of matters asserted within. *See, e.g.*, Pet. Reply 9 (citing Srinivasan's disclosure that formaldehyde is the most widely used universal fixative). Srinivasan is also plainly the sort of reference that persons of ordinary skill in the art would rely upon—both Dr. Van Ness and Dr. Patterson do here. *See, e.g.*, Ex. 2239 ¶ 128; Ex. 1029 ¶ 39. Indeed, even independent of this proceeding, Streck scientists have cited and relied on Srinivasan in Streck funded research papers. Ex. 1034, 481, 485–486. Under such circumstances, we are not persuaded that Petitioner should be allowed to pick only so much of Srinivasan as allegedly supports its position, while excluding what is unhelpful to Petitioner.

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[56] On page 4 of Paper 32, Petitioner provides a slightly more specific objection, listing Exhibit 2150 among three other exhibits, but that objection is only to the alleged irrelevance of those exhibits, which Petitioner objected have no connection to secondary considerations or to any nexus between the claims and the asserted secondary considerations. Paper 32, 4. That is not a basis on which Petitioner seeks exclusion now.

IV. CONCLUSION

On this record, Petitioner has not shown by a preponderance of the evidence that any of the challenged claims are unpatentable based on grounds advanced in the Petition.

In Summary:

Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not shown Unpatentable**
55–59, 61, 68, 69, 80–86, 89, 94, 126–130	102(a)	Chiu		55–59, 61, 68, 69, 80–86, 89, 94, 126–130
55–59, 61, 68, 69, 80–86, 89, 94, 126–130	103(a)	Chiu, Lee		55–59, 61, 68, 69, 80–86, 89, 94, 126–130
55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, 133	103(a)	Pertl, Granger		55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, 133
Overall Outcome				55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, 133

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petitioner has not proved by a preponderance of the evidence that claims 55–61, 68, 69, 80–86, 89–92, 94, 126–130, 132, and 133 are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Strike (Paper 50) is denied;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 52) is denied;

and

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

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