

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner

v.

RAVGEN, INC.,
Patent Owner

Patent No. 7,332,277

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 7,332,277**

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LIST OF EXHIBITS

Ex.1001	U.S. Patent No. 7,332,277 to Dhallan (“the ’277 patent”)
Ex.1002	Assignment record of the ’277 patent from USPTO assignment database
Ex.1003	International Publication No. WO 03/062441 to Landes et al. (“ <i>Landes</i> ”)
Ex.1004	U.S. Provisional Application No. 60/360,232 (“the ’232 provisional”)
Ex.1005	U.S. Provisional Application No. 60/378,354 (“the ’354 provisional”)
Ex.1006	U.S. Provisional Application No. 60/349,877 (“the ’877 provisional”)
Ex.1007	U.S. Patent No. 5,667,963 to Smith et al.
Ex.1008	Schlenke, et al., <i>Evaluation of a Novel Mononuclear Cell Isolation Procedure for Serological HLA Typing</i> , Clinical and Diagnostic Laboratory Immunology, 5(6):808-813 (1998)
Ex.1009	BD Vacutainer Systems, Preanalytical Solutions - Tube Additive/Application Guide, available at: https://web.archive.org/web/20020805142012/http://www.bd.com:80/vacutainer/products/venous/tube_guide.asp
Ex.1010	Bush, et al., <i>Advancements in Blood Collection Devices</i> , Laboratory Medicine, 29(10), 616-622 (1998)
Ex.1011	Mollison, P.L., <i>Historical Review: The Introduction of Citrate as an Anticoagulant for Transfusion and of Glucose as a Red Cell Preservative</i> , British J. of Haematology, 108:13-18 (2000)
Ex.1012	File History of the ’277 patent (U.S. Patent Application No. 10/661,165)

Ex.1013	International Publication No. WO 03/074723 to Dhallan (International Application No. PCT/US03/06198)
Ex.1014	U.S. Patent No. 6,977,162 to Dhallan (U.S. Application No. 10/093,618)
Ex.1015	U.S. Patent No. 7,208,274 to Dhallan (U.S. Application No. 10/376,770)
Ex.1016	Bryant, Terminology of Sugars, <i>Ind. Eng. Chem.</i> , 26(2):231 (1933)
Ex.1017	Rosado, Tyrosine kinases activate store-mediated Ca ²⁺ entry in human platelets through the reorganization of the actin cytoskeleton, <i>Biochem. J.</i> , 351 :429-437(2000)
Ex.1018	Bomna, Human Blood Coagulation Factor XI, <i>The Journal of Biological Chemistry</i> , 252(18):6432-6437 (1977)
Ex.1019	Lee, Quantitation of genomic DNA in plasma and serum samples: higher concentrations of genomic DNA found in serum than in plasma, <i>Transfusion</i> , 41:276-282 (2001)
Ex.1020	Patent Owner's December 15, 2020 Claim Constriction Brief (C.A. No. 20-692 (W.D. Tex.)), with the Declaration of Dr. Wayne Grody
Ex.1021	February 8, 2021 Correspondence from Court providing Preliminary Claim Construction (C.A. No. 20-692 (W.D. Tex.))
Ex.1022	Carter, Flow Cytometric Analysis of Whole Blood Lysis, Three Anticoagulants, and Five Cell Preparations, <i>Cytometry</i> 13:68-74 (1992)
Ex.1023	Dhallan et al., Methods to Increase the Percentage of Free Fetal DNA Recovered From the Maternal Circulation, <i>JAMA</i> , 291:9, 1114-1119 (2004)
Ex.1024	International Publication No. WO 02/04672 to Hulten
Ex.1025	U.S. Patent Application Publication No. 2002/0099015 to Barber
Ex.1026	February 9, 2021 Transcript of Videoconference <i>Markman</i> Hearing Before the Honorable Alan D. Albright (C.A. No. 20-692)
Ex.1027	Nicholson, Selection of anticoagulants for lymphocyte immunophenotyping, <i>J. of Immuno. Methods</i> , 165, 31-35 (1993)
Ex.1028	Martin, A Method for Using Serum or Plasma as a Source of DNA for HLA Typing, <i>Human Immunology</i> 33, 108-113 (1992)

Ex.1029	Marx, Reducing white cells in platelet units, Transfusion, Vol. 31, No. 8, 743-747 (1991) (“ <i>Marx</i> ”)
Ex.1030	Lo, Quantitative analysis of fetal DNA in maternal plasma and Serum, Am J Hum Genet 62, 768-75 (1998)
Ex.1031	Holum, Fundamentals of General, Organic and Biological Chemistry, Optical Isomerism, Ch. 18, 3d. (1986)
Ex.1032	USP Dictionary of USAN and International Drug Names, U.S. Pharmacopeia Convention (2002)
Ex.1033	International Publication No. WO 1998/39474, to Lo (“ <i>Lo</i> ”)
Ex.1034	Valli et al., An Anticoagulant for Transport of Bovine Blood, Can. Vet. J. 21:252-257 (1980) (“ <i>Valli</i> ”)
Ex.1035	Hahn et al., Quantification of Circulating DNA: In the Preparation Lies the Rub, Clinical Chemistry 47, No. 9, 1577-78 (2001)
Ex.1036	Chiu et al., Effects of Blood-Processing Protocols on Fetal and Total DNA Quantification in Maternal Plasma, Clinical Chemistry 47:9 1607-1613 (2001)
Ex.1037	Reserved
Ex.1038	Angert, Fetal Cell-free Plasma DNA Concentrations in Maternal Blood Are Stable 24 Hours after Collection, Clinical Chemistry 49, No. 1, 2003
Ex.1039	Kolialexi, Apoptosis in maternal peripheral blood during pregnancy, Fetal Diagn. Therap., 16:32-37 (2001)
Ex.1040	U.S. Patent No. 6,156,504 to Gocke
Ex.1041	U.S. Patent No. 6,919,17 to Shuber
Ex.1042	Darzynkiewicz et al., Analysis of Apoptotic Cells by Flow and Laser Scanning Cytometry 322 Methods in Enzymology 18 (2000)
Ex.1043	van Vianen, et al., Flow Cytometric Screening of Blood Samples for Malaria Parasites 14 Cytometry 276 (1993)
Ex.1044	U.S. Patent No. 5,618,664 to Kiessling
Ex.1045	U.S. Patent No. 5,891,734 to Gill
Ex.1046	Kiernan, Formaldehyde, formalin, paraformaldehyde and glutaraldehyde: What they are and what they do, Microscopy Today, 1:8-12 (2000)
Ex.1047	U.S. Patent No. 5,486,477 to Carver

Ex.1048	U.S. Patent No. 5,648,220 to Bianchi
Ex.1049	PCT Publication No. WO 95/01796 to Granger
Ex.1050	U.S. Patent No. 4,040,785 to Kim
Ex.1051	May 19, 2021 Scheduling Order (C.A. No. 20-1644 (D. Del.))
Ex.1052	Chinnapapagari et al., Treatment of Maternal Blood Samples with Formaldehyde Does Not Alter the Proportion of Circulatory Fetal Nucleic Acids (DNA and mRNA) in Maternal Plasma 51 Clinical Chemistry 652 (2005)
Ex.1053	Chung et al., Lack of Dramatic Enrichment of Fetal DNA in Maternal Plasma by Formaldehyde Treatment 51 Clinical Chemistry 655 (2005)
Ex.1054	Lo, Y.M.D. et al. (2007). Prenatal diagnosis: progress through plasma nucleic acids, <i>Nature Reviews</i> , 8:71-77.
Ex.1055	Waterfall & Cobb, <i>Single Tube Genotyping of Sickle Cell Anaemia Using PCR-Based SNP Analysis</i> , Nuc. Acids Res.29(23):119 (2001)
Ex.1056	Declaration of Dr. Brynn Levy, M.Sc.(Med)., Ph.D., FACMG
Ex.1057	Curriculum Vitae of Dr. Brynn Levy, M.Sc.(Med)., Ph.D., FACMG
Ex.1058	Copy of <i>Valli</i> with publication information

Illumina, Inc. (“Petitioner”) respectfully requests *inter partes* review of claims 55-63, 66-69, 80-91, 94-96, 126-130, 132, and 133 (“the challenged claims”) of U.S. Patent No. 7,332,277 (“the ’277 patent”) (Ex.1001), which, according to PTO records, is assigned to Ravgen, Inc. (“Patent Owner”). (Ex.1002.)

I. INTRODUCTION

The ability to rapidly test for fetal abnormalities in non-invasive ways has long been an important area of research in molecular biology and genetics. In 1997, shortly before the earliest priority date of the ’277 patent, Dr. Dennis Lo and colleagues discovered maternal plasma was a source of cell-free fetal DNA using conventional techniques for collecting blood and analyzing DNA that had been previously used in the field for decades. The challenged claims of the ’277 patent are directed to this broad concept of collecting blood samples to analyze DNA, where the sample comprises “an agent that inhibits lysis of cells, if cells are present.” (*See, e.g.*, Ex.1001, 472:66-473:5, 474:52-57.) The use of such an agent during the collection of maternal blood to analyze cell-free fetal DNA, however—the sole point of purported novelty—was not new at the time of Patent Owner’s filing.

This petition focuses in particular on two of the hundreds of agents identified in the ’277 patent itself as allegedly inhibiting lysis of cells: glucose and

formaldehyde. (*See, e.g.*, Ex.1001, 32:4-12.) Glucose is notable because it is an ingredient in blood collection tubes commonly used at the time for analyzing cell-free DNA, such as Becton Dickinson's Acid Citrate Dextrose ("ACD," also referred to as Acid Citrate Dextrose Solution A ("ACDA")).

And, indeed, *Landes*, a principal prior-art reference relied upon by Petitioner, describes a method of collecting a maternal blood sample for analyzing cell-free fetal DNA where the sample was collected in an ACDA blood tube. (*See, e.g.*, Ex.1003, 3:1-3:6, 10:26-17:17.) As explained in more detail below, *Landes* anticipates the vast majority of the challenged claims.

The use of formaldehyde (referred to as formalin when in solution) in combination with another commonly used blood collection tube at the time, EDTA, was also described in prior art such as *Valli*, another reference relied upon by Petitioner. *Valli*, which concludes that formalin-EDTA preparations "were greatly superior to EDTA" alone (Ex.1034, 257), exemplifies this known blood stabilization method for diagnostic applications. As explained in more detail below, *Lo* (an application filed by Dr. Lo and colleagues related to the discovery of cell-free fetal DNA in maternal blood samples) in combination with *Valli* renders obvious the vast majority of the challenged claims.

The evidence overwhelmingly shows that there is, at a minimum, a reasonable likelihood that Petitioner will prevail with respect to each of the

challenged claims and establish the unpatentability of those claims by a preponderance of evidence.

II. MANDATORY NOTICES

Real Parties-in-Interest: Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies Illumina, Inc., Illumina Cambridge, Ltd., and Verinata Health, Inc. as the real parties-in-interest.

Related Matters: Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner identifies the following related matters. The '277 patent is being asserted in the following pending litigations: *Ravgen, Inc. v. Illumina, Inc. et al.*, C.A. No. 20-1644 (D. Del.). The '277 patent is also being asserted in the following pending litigations: *Ravgen, Inc. v. Natera, Inc. et al.*, C.A. No. 20-692 (W.D. Tex.); *Ravgen, Inc. v. Ariosa Diagnostics, Inc. et al.*, C.A. No. 20-1646 (D. Del.); *Ravgen, Inc. v. Myriad Genetics, Inc. et al.*, C.A. No. 20-1730 (D. Del.); *Ravgen, Inc. v. Progenity, Inc.*, C.A. No. 20-1734 (D. Del.); *Ravgen, Inc. v. Natera, Inc. et al.*, C.A. No. 20-451 (W.D. Tex.); *Ravgen, Inc. v. PerkinElmer, Inc. et al.*, C.A. No. 20-452 (W.D. Tex.); *Ravgen, Inc. v. Laboratory Corp. of America Holdings et al.*, C.A. No. 20-969 (W.D. Tex.); and *Ravgen, Inc. v. Quest Diagnostics Inc.*, C.A. No. 20-972 (W.D. Tex.).

The '277 patent is also at issue in several *inter partes* review proceedings: IPR2021-00788, IPR2021-00789, IPR2021-00790, IPR2021-00902, and IPR2021-

01054. The '277 patent is also at issue in an *ex parte* reexamination:

No. 90/014,792. Petitioner is not a party, real party-in-interest, or privy to any of those proceedings.

The present '277 patent issued in 2008 from Application No. 10/661,165. Patent Owner filed a continuation of that application, Application No. 11/212,812, in August of 2005.¹ The latter application issued as Patent No. 7,727,720 on June 1, 2010. The '720 patent is the subject of a separate *inter partes* review petition filed by Petitioner. In addition, the '720 patent is at issue in *inter partes* review proceedings, IPR2021-00791 and IPR2021-01026, as well as an *ex parte* reexamination, No. 90/014,703; Petitioner is not a party, real party-in-interest, or privy to any of these additional Patent Office proceedings. The '720 patent is also being asserted in the district court cases cited above.

Counsel and Service Information: Lead counsel is Naveen Modi (Reg. No. 46,224). Backup counsel are Eric W. Dittmann (Reg. No. 51,188), Daniel Zeilberger (Reg. No. 65,349), and Max H. Yusem (*pro hac vice* to be filed). Service information is Paul Hastings LLP, 2050 M Street NW, Washington, D.C. 20036, Tel.: 202.551.1700, Fax: 202.551.1705, email: PH-Illumina-IPR@paulhastings.com. Petitioner consents to electronic service.

¹ There are no pending applications in this family of patents.

III. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15 AND 42.103

The PTO is authorized to charge any fees due during this proceeding to Deposit Account No. 50-2613.

IV. GROUNDS FOR STANDING

Petitioner certifies under 37 C.F.R. § 42.104(a) that the '277 patent is available for review and Petitioner is not barred or estopped from requesting review on the grounds identified herein.

V. PRECISE RELIEF REQUESTED AND GROUNDS RAISED UNDER 37 C.F.R. § 42.104(b)

Petitioner respectfully requests review of claims 55-63, 66-69, 80-91, 94-96, 126-130, 132, and 133 of the '277 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 55-59, 61-63, 66-69, 80-89, 94, 96, and 126-130 are unpatentable under pre-AIA 35 U.S.C. § 102 as being anticipated by *Landes* (Ex.1003).

Ground 2: Claim 95 is unpatentable under pre-AIA 35 U.S.C. § 103 as being obvious in view of *Landes* (Ex.1003) and *Marx* (Ex.1029).

Ground 3: Claims 55-63, 66-69, 80-91, 94, 96, 126-130, 132, and 133 are unpatentable under pre-AIA 35 U.S.C. § 103 as being obvious in view of *Lo* (Ex.1033) and *Valli* (Ex.1034).

Ground 4: Claim 95 is unpatentable under pre-AIA 35 U.S.C. § 103 as being obvious in view of *Lo* (Ex.1033), *Valli* (Ex.1034), and *Marx* (Ex.1029).

Landes, *Marx*, and *Valli* were not considered by the Patent Office during prosecution. (Ex.1001, Cover (“References Cited”).) Although *Lo* was considered, the Patent Office did not consider *Lo* in combination with *Valli* (*i.e.*, where formalin-EDTA preparations were reported as “greatly superior” to EDTA alone). *Landes* qualifies as prior art under at least 35 U.S.C. §§ 102(a) and/or (e), and *Marx*, *Lo*, and *Valli* qualify as prior art under 35 U.S.C. § 102(b).

(Section VIII.)

VI. BACKGROUND

A. Overview of the Technology

Chromosomal abnormalities and other disease-related mutations are responsible for a substantial percentage of genetic defects in newborns. (Ex.1001, 1:41-57; Ex.1003, 1:12-13; Ex.1033, 1:7-27; *see also* Ex.1056, ¶20.)² Researchers in the field of molecular biology and genetics in the 1990s and early 2000s were focused on rapid and non-invasive testing methods that could reveal potential fetal

² Petitioner submits the declaration of Dr. Brynn Levy, M.Sc.(Med)., Ph.D.,

FACMG, an expert in the field of the '277 patent. (Ex.1056, ¶¶5-10; Ex.1057.)

abnormalities before birth. (Ex.1001, 1:30-39; Ex.1003, 2:1-2; Ex.1033, 1:2-2:6; *see also* Ex.1056, ¶20.)

In 1997, Dr. Dennis Lo and colleagues discovered cell-free fetal DNA is a component of maternal plasma/serum. (Ex.1001, 5:7-59; Ex.1003, 2:4-20; Ex.1033, 1:7-2:6; *see also* Ex.1056, ¶21.) The discovery of this type of fetal source enabled researchers to use conventional techniques, used in the field for decades, to analyze the cell-free fetal DNA from a maternal blood sample. (Ex.1001, 5:39-59; Ex.1003, 2:25-30; Ex.1033, 4:5-8, 5:3-6, 23:18-21; *see also* Ex.1056, ¶21.)

Landes, Lo, and the '277 patent describe such steps using techniques that were conventional in the art at the relevant time. DNA isolation protocols, which could be performed using serum or plasma derived from a blood sample, were well-known and could be practiced at the time of the alleged invention using commercially available tools. (*See* Ex.1003, 2:19-20, 3:2-3, 10:28-11:11; Ex.1033, 10:16-22; *see also* Ex.1001, 5:39-59; Ex.1056, ¶22.) The analysis of DNA could also be performed by any number of conventional tools, including, as identified by *Landes and Lo*, PCR, mass spectrometry, hybridization, single base extension, fluorescence detection, and fluorescent probe binding, among others. (*See, e.g.*, Ex.1003, 1:16-24, 2:13-30, 3:24-31, 9:31-10:3; Ex.1033, 10:24-12:30; *see also* Ex.1001, 6:26-34; Ex.1056, ¶22.)

Where serum is prepared by allowing the blood sample to clot, this process results “in the presence of a larger quantity of background maternal DNA” compared to plasma “possibly due to the liberation of DNA during the clotting process.” (*See e.g.*, Ex.1033, 30:8-12.) This liberation of cell-free maternal DNA would have been recognized to be a result of maternal white blood cell lysis in the sample. (*See* Ex.1056, ¶23-4.) For this reason, the prior art recognized “maternal plasma may be preferable to maternal serum for robust foetal DNA detection” because it helps avoid this type of contamination of cell-free maternal DNA released by cell lysis. (Ex.1033, 30:16-17; *see also, e.g.*, Ex.1036, 1613 (finding blood-processing can have an effect on the amount of total DNA, but not on the amount of fetal DNA); Ex.1038, 196 (“The total DNA, which increases in the test tube over time, is most likely attributable to apoptosis, cell death, and lysis.”); Ex.1039, 32 (concluding “[a]poptosis is stimulated in maternal peripheral blood during pregnancy”); Ex.1019, 276, 279 (recognizing serum contains more cell-free DNA than plasma); Ex.1056, ¶24.)

When collecting a maternal sample for isolation of DNA from plasma, it was routine to do so in the presence of one or more preservative agents in appropriate, commercially available blood collection tubes. (Ex.1003, 10:28-30; Ex.1033, 6:29, 7:9-11, 16:20, 24:22-4, 25:5; *see also* Ex.1056, ¶25.) One blood collection tube

available at the time was Becton Dickinson's ACDA, which contained dextrose.³ (See, e.g., Ex.1007, 4:30-39; Ex.1008, 808; Ex.1009, 4; Ex.1010, Table 2 and 622; Ex.1017, 430; Ex.1018, 6433; see also Ex.1056, ¶¶26-27.) Another common blood collection tube available at the time contained EDTA. (Ex.1033, 6:29, 7:9-11, 16:20, 24:22-4, 25:5; see also Ex.1056, ¶28.)

Other types of fixing agents, such as acids, alcohols, and aldehydes, were similarly used to preserve white blood cells in blood samples to help prevent lysis. (See, e.g., Ex.1034, 252-3, 257; see also Ex.1042, 34 (“DNA-protein cross-linking by this fixative [formaldehyde] prevents the extraction of the fragmented low molecular weight DNA from the cell”); Ex.1043, 276-77 (discussing the use of formaldehyde to preserve white blood cells); Ex.1044, 3:21-26, 13:34-14:16, Figs.2-3 (same); Ex.1045, 14:2-6 (discussing the use of aldehydes, like formaldehyde, to “fix white blood cells”); Ex.1046, 8-12; Ex.1047, 5:28-48; Ex.1048, 3:32-44; Ex.1049, 12:1-7; Ex.1056, ¶29.) Agents were also used in combination during blood collection, and the prior art observed preservatives like formalin could *further* reduce lysis of white blood cells *in the presence of EDTA*.

³ Dextrose is the naturally occurring dextrorotatory form of glucose, and can also be referred to as “glucose.” (See, e.g., Ex.1031, 445, Ex.1032, 268, 416; Ex.1016, 231; see also Ex.1056, ¶26.)

(*See e.g.*, Ex.1034, 257; *see also* Ex.1045, 15:9-15; Ex.1049, 13:5-6; Ex.1050, 2:28-43, 2:18-27; Ex.1056, ¶29.)

B. Overview of the '277 Patent

The '277 patent purports to claim a novel method of collecting a maternal blood sample to analyze cell-free fetal DNA, where the sample comprises an agent that inhibits lysis of cells. (Ex.1056, ¶¶30-1.) The specification identifies hundreds of agents that it states were known agents that inhibit cell lysis, including glucose and formaldehyde.⁴ (*See, e.g.*, Ex.1001, 32:4-12, 226-229 (Table XXIII); *see also* Ex.1056, ¶¶32-3.) In addition, although the challenged claims recite an agent that inhibits lysis of cells, they do not require any specific level of cell lysis inhibition or amount of cell-free fetal DNA collected from the sample. (Ex.1056, ¶34.)

C. Prosecution History of the '277 patent

During prosecution, the Examiner issued various 35 U.S.C. §§ 102 and 103 rejections based on prior art references discussing the analysis of cell-free fetal DNA from maternal blood samples, as well as references describing the analysis of

⁴ This petition also discusses “formalin,” which is a liquid that contains formaldehyde and water. (*See, e.g.*, Ex.1046, 8; *see also* Ex.1056, ¶29.)

fetal cells from maternal blood samples fixed with formalin. (*See generally* Ex.1012.)

In response, Patent Owner argued “Applicant has discovered that the addition of a cell lysis inhibitor during the sample preparation process can significantly and unexpectedly increase the proportion of fetal DNA versus maternal DNA obtained from a sample such as a plasma sample obtained from the blood of a pregnant woman.” (*See, e.g.*, Ex.1012, July 14, 2006 Response to Non-final Office Action, 31-32; *see also id.*, May 30, 2007 Response to Non-final Office Action, 36.) In support of this assertion, Patent Owner cited Example 4 and Example 15 of the specification, where formalin was added to EDTA blood tubes in an attempt to demonstrate an increase of the proportion of fetal DNA, compared to EDTA alone. (*See id.*)

The Examiner allowed the challenged claims to issue in light of, *inter alia*, these “persuasive argument(s).” (*See id.*, September 26, 2007 Notice of Allowance, 2.) The Examiner, however, did not evaluate the challenged claims in light of a primary prior art reference at issue here, *Landes*, where cell-free fetal DNA was analyzed from a maternal blood sample containing glucose (*see, e.g.*, 1003, 10:26-11:2), which the ’277 patent identifies as an agent that inhibits lysis of cells (*see, e.g.*, Ex.1001, 32:4-12).

The Examiner also did not consider another primary prior art reference, *Valli*, where formalin-EDTA preparations were shown to be “greatly superior” to EDTA alone for maintaining white blood cell stability. (Ex.1034, 257.) Nor did the Examiner recognize that *Lo* described a preference for maternal plasma (prepared using EDTA) over serum for more “robust foetal DNA detection” with less “background maternal DNA . . . possibly due to the liberation of DNA during the clotting process.” (See *e.g.*, Ex.1033, 30:8-17; see also Ex.1056, ¶¶47-8.)

D. The '277 Patent Priority Date

The '277 patent was filed as U.S. App. No. 10/661,165 on September 11, 2003, and issued on February 19, 2008. (Ex.1001, Cover.) The '277 patent is a continuation-in-part of PCT/US03/06198, filed on February 28, 2003, which claims priority to U.S. Provisional App. No. 60/378,354, filed May 8, 2002, and which is a continuation-in-part of U.S. App. No. 10/093,618, filed on March 11, 2002, which claims priority to U.S. Provisional App. No. 60/360,232, filed on March 1, 2002. (Ex.1001, 1:6-14.) The '277 patent is also a continuation-in-part of PCT/US03/27308, filed on August 29, 2003. (Ex.1001, 1:14-16.) Further, the '277 patent is also a continuation-in-part of U.S. App. No. 10/376,770, filed on February 28, 2003, which also claims priority to the '354 and '232 provisionals.

(Ex.1001, 1:16-25.)⁵ As discussed below, *Landes, Lo, Valli, and Marx* qualify as prior art under 35 U.S.C. § 102 regardless of whether the challenged claims could claim priority to any of these earlier-filed applications. (*See* Sections VIII.)

VII. LEVEL OF ORDINARY SKILL

In one of the “Related Matters” identified above, Patent Owner’s expert asserted that a person of ordinary skill in the art at of the time of the alleged invention (“POSA”) would have had “a M.D. and/or Ph.D. in a related area such as genetics, biochemistry, molecular biology, cell biology, or microbiology and at least one to two years of work in one of those related areas . . . [or] a Bachelor’s degree in one of the foregoing areas and at least three to four years of work in that area.” (Ex.1020, Grody December 14, 2020 Declaration, ¶15.)

⁵ This petition assumes that the ’277 patent can claim priority to March 1, 2002. Petitioner, however, does not concede that Patent Owner may properly claim priority to any of the foregoing applications. (*See, e.g.*, Ex.1004 (lacking disclosure that could support the claimed “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”).) Petitioner reserves the right to challenge any priority date asserted by Patent Owner.

For the purposes of this proceeding only, Petitioner does not dispute this definition of a POSA. (Ex.1056, ¶¶15-18.) Based on this asserted level of skill, a POSA would have had academic or industry experience collecting and analyzing cell-free DNA from blood samples. (*Id.*) More or less experience, however, would not affect the invalidity of the challenged claims.

VIII. OVERVIEW OF THE PRIOR ART

A. Overview of *Landes*

Landes, titled “Methods for Fetal DNA Detection and Allele Quantitation,” claims priority to U.S. Provisional Application 60/349,877 (“the ’877 provisional”), filed on January 18, 2002. (Ex.1003, Cover.) *Landes* was filed in the English language and designated the United States. (*See id.*) As discussed below, *Landes* may properly claim the benefit of the ’877 provisional. (*See* Section VIII.B.) Thus, *Landes* predates the earliest possible date of any application to which the ’277 patent can claim priority, and serves as prior art against the ’277 patent under at least 35 U.S.C. §§ 102(a) and/or (e).

Landes describes “non-invasive methods to distinguish fetal DNA from maternal DNA and thereby detect fetal aneuploidies and alleles.” (Ex.1003, Abstract; *see also* Ex.1056, ¶¶39, 52.) Recognizing the need in the art for non-invasive genetic screening, *Landes* provides that “specific genetic defects such as point mutations in disease-associated genes can be detected by molecular analyses

designed to identify single nucleotide polymorphisms (SNPs) and other small mutations.” (Ex.1003, 1:19-21; Ex.1056, ¶41.) *Landes* states that such analyses can be conducted by using “maternal serum or plasma,” “a relatively rich source of fetal DNA.” (*Id.*, 2:19-20.) *Landes* explains that such fetal DNA can be detected “as early as 7 weeks, increases in abundance during gestation, and are detectable 1 month but not 2 months postpartum.” (*Id.*, 2:20-25.) *Landes* distinguishes this cell-free fetal DNA from DNA obtained from “samples of fetal cells.” (Ex.1003, 1:14; *see also* Ex.1056, ¶40.)

To detect fetal genetic defects using “[t]his type of fetal source,” *Landes* provides methods of “PCR-based genetic testing” that can be made “fetal-specific” or that “fetal amplicons can be discriminated from maternal amplicons.” (*Id.*, 2:25-8; *see also id.*, 3:3-6, 10:23-17:16.)

In preparation for the isolation of cell-free fetal DNA, *Landes* describes a “Plasma Separation Protocol,” where the “[m]aternal blood is collected into [an] ACDA blood collection tube (Becton Dickinson, Franklin Lakes, NJ).” (Ex.1003, 10:20-29; *see also* Ex.1056, ¶¶41-2.) This is a reference to Becton Dickinson’s Acid Citrate Dextrose Solution A (“ACDA”) blood collection tubes (Ex.1056, ¶¶26, 60), which are explained to contain dextrose (*i.e.*, glucose) and be used for DNA testing. (Ex.1007, 4:30-39; Ex.1008, 808; Ex.1009, 4; Ex.1010, Table 2 and

622; Ex.1017, 430; Ex.1028, 112 (noting that ACD “did not [a]ffect DNA isolation nor PCR amplification”); *see also* Ex.1056, ¶¶26, 60.)

Before the publication of *Landes*, the properties of glucose were known, including when present in ACD blood collection tubes. (*See, e.g.*, Ex.1011, 15-16 (discussing effects of glucose); Ex.1019, Figs.4-5 (same); Ex.1022, 68, 74 (same); Ex.1027, 31 (same); *see also* Ex.1056, ¶27.) Consistent with the '277 patent's reference to glucose as “an agent that stabilizes cell membranes” that “reduce[s] maternal cell lysis” (Ex.1001, 32:4-21), *Landes* discusses the collection of maternal blood with such an agent to analyze cell-free fetal DNA.

B. *Landes* Properly Claims Priority to the '877 Provisional

Landes properly claims the benefit of the earlier '877 provisional, which was filed on January 18, 2002, pursuant to 35 U.S.C. § 119(a). (Ex.1006, Cover; *see also* Ex.1056, ¶¶43-5.) The non-provisional application published as *Landes* was properly filed within a year of the '877 provisional application on January 17, 2003. (Ex.1003, Cover.) *Landes* further names at least one inventor in common, includes a specific reference to the '877 provisional, and claims the benefit of its earlier filing. (Ex.1003, Cover; Ex.1006, Cover.) Finally, the following chart demonstrates the enabling support in the provisional application for each claim in the anticipatory *Landes* reference.

Landes Claim 1 (Ex.1003, 22:4-12)	Support in the '877 Provisional (Ex.1006)
A method of detecting fetal aneuploidies comprising	Ex.1006, 21:4-12; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
a) treating DNA isolated from maternal serum with a reagent that differentially modifies methylated and non-methylated DNA;	Ex.1006, 21:4-12; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
b) performing quantitative PCR with a first primer pair on a potentially aneuploid chromosome;	Ex.1006, 21:4-12; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
c) performing a control quantitative PCR with a second primer pair on a non-aneuploid chromosome; and	Ex.1006, 21:4-12; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
d) determining the ratio of the quantity of the two PCR products, thereby detecting fetal aneuploidies.	Ex.1006, 21:4-12; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12

Landes Claim 2 (Ex.1003, 22:14-23)	Support in the '877 Provisional (Ex.1006)
A method for detecting fetal aneuploidies comprising:	Ex.1006, 21:14-23; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
a) treating DNA isolated from maternal serum with bisulfite;	Ex.1006, 21:14-23; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
b) performing quantitative PCR on the sample with a primer pair homologous to a test chromosome sequence that is differentially methylated in maternal DNA and in fetal DNA, where the primer pair only primes bisulfate treated unmethylated DNA;	Ex.1006, 21:14-23; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12

<p>c) performing a control quantitative PCR with a primer pair homologous to a control chromosome sequence that is differentially methylated in maternal DNA and in fetal DNA, where the primer only primes bisulfate treated unmethylated DNA; and</p>	<p>Ex.1006, 21:14-23; <i>see also id.</i>, 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12</p>
<p>d) determining the ratio of the quantity of PCR product produced for the test chromosome compared with the control chromosome.</p>	<p>Ex.1006, 21:14-23; <i>see also id.</i>, 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12</p>

<p><i>Landes</i> Claim 3 (Ex.1003, 22:25-30)</p>	<p>Support in the '877 Provisional (Ex.1006)</p>
<p>A method for detecting alleles of a gene of interest in fetal DNA comprising:</p>	<p>Ex.1006, 21:25-30; <i>see also id.</i>, 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12</p>
<p>a) treating DNA isolated from maternal serum with bisulfite;</p>	<p>Ex.1006, 21:25-30; <i>see also id.</i>, 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12</p>
<p>b) performing PCR with a primer pair that amplifies the gene of interest of step b); and</p>	<p>Ex.1006, 21:25-30; <i>see also id.</i>, 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12</p>
<p>c) analyzing the resulting PCR product to identify the allele of the gene of interest.</p>	<p>Ex.1006, 21:25-30; <i>see also id.</i>, 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12</p>

<i>Landes</i> Claim 4 (Ex.1003, 23:1-7)	Support in the '877 Provisional (Ex.1006)
A method for detecting imprinted genes in a subject comprising:	Ex.1006, 22:1-6; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
a) treating DNA isolated from a subject with bisulfite;	Ex.1006, 22:1-6; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
b) performing PCR with a primer pair for a polymorphic region that only amplified bisulfite treated unmethylated DNA; and	Ex.1006, 22:1-6; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12
c) analyzing the PCR product to identify the polymorphism thereby detecting imprinted genes in a subject.	Ex.1006, 22:1-6; <i>see also id.</i> , 1:5-6, 2:21-4:23, 8:7-9:27, 10:1-20:12

In addition, as seen in the supporting citations below, each of the anticipatory statements in *Landes* relied on in Section X were carried forward verbatim from the '877 provisional.

Given the ample support found in the specification of the '877 provisional for the non-provisional *Landes* publication, *Landes* is entitled to the priority date of the earlier '877 provisional, January 18, 2002.

C. Overview of *Lo*

Lo, titled “Non-invasive Prenatal Diagnosis,” was published in 1998 and serves as prior art against the '277 patent under at least 35 U.S.C. § 102(b).

(Ex.1033, Cover.) *Lo* describes a method to isolate and analyze cell-free fetal nucleic acid from a blood sample (serum or plasma) of a pregnant human female to

detect alleles to determine fetal aneuploidy. (*See id.*, 15:4-19:28, 23:14-33:10.) *Lo* explains that “[i]t has now been discovered that foetal DNA is detectable in maternal serum or plasma samples” (*id.*, 2:5-6), where the “method according to the invention can be applied to screening for Down’s Syndrome and other chromosomal aneuploidies” (*id.*, 5:3-6; *see also* 1:12-27, 4:5-8). *Lo* explained that serum contains “a larger quantity of background maternal DNA” compared to plasma “possibly due to the liberation of DNA during the clotting process.” (*See e.g.*, Ex.1033, 30:8-12.) For “robust foetal DNA detection,” *Lo* stated that “maternal plasma may be preferable to maternal serum.” (Ex.1033, 30:16-17; *see also* Ex.1056, ¶¶47-8.)

D. Overview of *Valli*

Valli, titled “An Anticoagulant for Transport of Bovine Blood,” was published in 1980 and serves as prior art against the ’277 patent under at least 35 U.S.C. § 102(b). (Ex.1034, 252; *see also* Ex.1058, Cover (noting publication in 1980, as well as availability in library as of 1980).) *Valli* assessed the ability of various agents to “improve leukocyte stability” during transportation of blood samples for “screening or for diagnostic purposes.” (Ex.1034, 252.) For example, *Valli* experimented with common blood collection tubes, such as ACD and EDTA, alone and in combination with common fixing agents, including formalin. (*Id.*,

252-53 n.4, 257; *see also id.*, Table 1 (discussing two formalin-EDTA preparations, Titriplex I and IV, and ACD-formalin-ASA); Ex.1056, ¶¶49-50.)

Valli concludes that the formalin-EDTA preparations tested “were greatly superior to EDTA without additives for maintaining the stability of leukocytes during transport,” and “deserving of a far wider utilization.” (Ex.1034, 257.)

E. Overview of *Marx*

Marx, titled “Reducing white cells in platelet units,” was published in 1991. (Ex.1029, Cover.) Thus, *Marx* predates the earliest possible date of any application to which the ’277 patent can claim priority, and serves as prior art against the ’277 patent under at least 35 U.S.C. § 102(b). *Marx* is generally directed to an analysis of variations in centrifugation braking rates during blood processing, including when no brake is used. (Ex.1029, Abstract; Ex.1056, ¶46.)

IX. CLAIM CONSTRUCTION

For IPR proceedings, the Board applies the claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). The Board, however, only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-00633, Paper No. 11 at 16 (P.T.A.B. Aug. 14, 2015). Given the correlation between the prior art and the challenged claims of the ’277 patent, the Board need

not construe any terms of the challenged claims to resolve the underlying controversy, as any reasonable construction reads on the prior art.⁶

X. DETAILED EXPLANATION OF GROUNDS

As detailed below, each of the challenged claims are unpatentable.

A. Ground 1: *Landes* Anticipates Claims 55-59, 61-63, 66-69, 80-89, 94, 96, and 126-130

A patent is invalid for anticipation when “each limitation of a claim is found in a single reference, either expressly or inherently.” *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Because each limitation of claims 55-59, 61-63, 66-69, 80-89, 94, 96, and 126-130 is present in *Landes*, these claims are invalid as anticipated by *Landes*.

1. Claim 55

i) [55.pre] “A method comprising:”

Landes describes a “method,” as recited in the preamble. For example, *Landes* discusses “non-invasive methods to distinguish fetal DNA and thereby

⁶ Petitioner reserves all rights to raise claim construction and other arguments in other venues. Petitioner notes that a claim construction hearing involving some of the terms of the challenged patents was held in a pending district court litigation (*see* Ex.1026), but that court’s guidance is not relevant to the instant petition.

detect fetal aneuploidies and alleles.” (*See, e.g.*, Ex.1003, Abstract; Ex.1006, Abstract, 2:21-3:22; *see also* Ex.1056, ¶52.)

ii) [55.a] “determining the sequence of a locus of interest on free fetal DNA isolated from a sample obtained from a pregnant female;”

Landes describes a method of determining the sequence of a locus of interest on cell-free fetal DNA isolated from a sample obtained from a pregnant female.

For example, *Landes* provides exemplary methods for isolating cell-free fetal DNA from a sample of maternal blood⁷ under the heading, “Isolation of Fetal DNA from Maternal Blood.” (Ex.1003, 10:26; Ex.1006, 10:6; *see also* Ex.1056, ¶¶53-58.)

First, *Landes* describes a “plasma separation protocol” where “[m]aternal blood is collected into ACDA blood collection tube,” which provides the requisite maternal sample from which the cell-free fetal nucleic acid is then isolated. (Ex.1003, 10:28-11:2; *see also id.*, 3:2; Ex.1006, 10:8-10, 2:21-23.) Then, *Landes* provides a “DNA isolation protocol,” where DNA can be isolated using “commercially available” kits. (Ex.1003, 11:3-12:6; Ex.1006, 10:15-14:9.)

⁷ *Landes* uses the term “maternal” to refer to a pregnant female, which is contrasted with blood samples from a “non-pregnant female.” (Ex.1003, 20:25-21:5, 16:20-24; Ex.1006, 15:23-25, 17, 19:25-20:5; *see also* Ex.1056, ¶54.)

Landes recognizes that “specific genetic defects such as point mutations in disease-associated genes can be detected by molecular analyses designed to identify single nucleotide polymorphisms (SNPs) and other small mutations.” (Ex.1003, 1:19-21, 3:18-4:6, 4:22-5:6; *see also* Ex.1006, 1:16-18, 3:4-22, 4:9-23.) For example, *Landes* discusses “loci of interest,” including “from chromosomes 13, 18 or 21,” where “chromosome aneuploidy can be readily revealed” using known quantitative PCR strategies. (Ex.1003, 8:25-9:11, 10:6-9, 14:26-15:3; *see also id.*, Ex.4, Fig.1a (evaluating “[f]etal-specific primers for PCR at specific locus on chromosomes 13, 18, or 21”), Fig.1b (same), *id.*, Fig.2a (same), Fig.3; Ex.1006, 8:10-28, 9:13-28, 14:1-8, 16:16-20, Ex.4, Figs.1-3; *see also* Ex.1056, ¶¶53-8.)

Landes further provides that a sequence of a locus of interest on the cell-free fetal DNA can be “detected by treating DNA isolated from maternal serum with bisulfite,” where PCR analysis can “be performed by method[s] known in the art” with a “primer pair that amplifies the gene of interest . . . to identify the allele.” (Ex.1003, 3:19-31; *see also id.*, 19:15-18 (discussing quantities of fetal “DNA Recovered” from maternal samples); Ex.1006, 2:30-3:2, 18:15-18; *see also* Ex.1056, ¶¶53-8.) The PCR product can be “analyzed to identify the polymorphism [of a polymorphic region],” where “[a]nalysis can be performed by method[s] known in the art, *e.g.*, DNA sequence, DNA microarrays, SSCP, LAMP.” (Ex.1003, 4:1-6, 10:14-19; Ex.1006, 3:17-22, 9:22-27.) Thus, *Landes*

describes a method of determining the sequence of a locus of interest on cell-free fetal DNA isolated from a maternal blood sample.

- iii) **[55.b] “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.”**

As discussed above, *Landes* describes a method of isolating cell-free fetal DNA from a maternal blood sample, which was known to comprise cell-free fetal DNA. (Ex.1003, 2:19-31, 10:26-28; *see also id.*, 3:2; Ex.1006, 10:6-8, 2:21-23; *see also* Ex.1056, ¶¶59-64.)

Landes also discusses that the blood sample comprises “an agent that inhibits lysis of cells”, *i.e.*, glucose. (*See, e.g.*, Ex.1003, 10:20-29; Ex.1006, 10:6-14.) For example, the “Plasma Separation Protocol” states that the “[m]aternal blood is collected into ACDA blood collection tube.” (*See, e.g.*, Ex.1003, 10:28-29; Ex.1006, 10:15-14.) As explained in Sections VI.A and VIII.A above, this is a reference to Becton Dickinson’s ACDA blood collection tubes, which contain dextrose (*i.e.*, glucose). (*See, e.g.*, Ex.1007, 4:30-39; Ex.1008, 808; Ex.1009, 4; Ex.1010, Table 2 and 622; Ex.1017, 430; Ex.1018, 6433; *see also* Ex.1056, ¶¶59-64.)

The ’277 patent specifically provides that glucose is an agent that inhibits lysis of cells according to the alleged invention. (*See, e.g.*, Ex.1001, 32:4-21 (“In

another embodiment, an agent that stabilizes cell membranes may be added to the maternal blood samples to *reduce maternal cell lysis* including . . . glucose”) (emphasis added.) *Landes* therefore described the same method as is claimed in the ’277 patent, where “an agent that inhibits lysis of cells” is present in a maternal blood sample by virtue of the glucose ingredient in the ACDA blood collection tube. (See, e.g., Ex.1003, 10:28-29; see also *id.*, 16:20-21 and 19:17-19 (providing additional examples where maternal blood was collected in ACDA tubes); see also Ex.1056, ¶¶59-64.)

As shown above, *Landes* expressly discussed the use of “an agent that inhibits lysis of cells” (*i.e.*, glucose) according to the ’277 patent. But even if Patent Owner attempts to dispute this fact, such limitation is nevertheless inherently anticipated by *Landes*. Under Federal Circuit precedent, a “prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); see also *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010) (“To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does.”). In *King Pharms.*, the patent-at-issue claimed that the natural result of taking a certain drug with food is an increase in the bioavailability of that drug, which the Federal

Circuit found was still anticipated by a prior art reference discussing taking the drug with food, even though it did not discuss the natural result of this process. *Id.* at 1275-6.

Here, by instructing the collection of a maternal blood sample in an ACDA blood collection tube, *Landes* necessarily describes the presence of glucose in said blood sample. This is because glucose is necessarily present in the ACDA blood collection tube described in *Landes*'s "Plasma Separation Protocol." (*See, e.g.*, Ex.1007, 4:30-39; Ex.1008, 808; Ex.1009, 4; Ex.1010, Table 2 and 622; *see also* Ex.1056, ¶¶26, 60.) As in *King Pharms.*, the method in *Landes* anticipates even though it does not discuss the effect of glucose in the blood sample.

To the extent Patent Owner argues that *Landes* itself does not recognize the presence of "an agent that inhibits lysis of cells", the prior art reference is no less anticipatory. *Cf. Schering*, 339 F.3d at 1377 ("[T]his court rejects the contention that inherent anticipation requires recognition in the prior art."). Instead, "[w]here, the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results." *Id.* (quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999); *see also Abbot Labs. v. Baxter Pharm. Prods.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006) ("Our cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time."). The

'277 patent states that glucose was a known “agent that stabilizes cell membranes” and “reduce[s] maternal cell lysis” (*see, e.g.*, Ex.1001, 15:58-16:7, 32:4-21; *see also* Ex.1056, ¶¶27, 63),⁸ which Patent Owner’s expert confirmed (Ex.1020, Grody December 14, 2020 Declaration, ¶¶37, 39-40.)

Abbot Laboratories also demonstrates the anticipatory effect of *Landes* in the present occasion. There, the patent covered a composition containing a chemical compound used for anesthetics and water. *Abbot Labs.*, 471 F.3d at 1365. The Federal Circuit found the patent was anticipated because a prior art reference contemplated a technique for purifying the same chemical compound that involved the addition of water. *Id.* at 1367. In doing so, the Federal Circuit rejected the patentee’s argument that a POSA would not have recognized the acid degradation-resistance properties of the claimed invention because “lack of knowledge is wholly irrelevant to the question” of anticipation. *Id.*

Likewise, accordingly to the '277 patent, “an agent that inhibits lysis of cells” as claimed in the '277 patent is found in *Landes*. When a POSA practices

⁸ “To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence.” *Cont’l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

the method in *Landes*, glucose is introduced to the maternal blood sample containing cell-free fetal DNA via the ACDA tube. Whether or not *Landes* intended, or even recognized, that property is “wholly irrelevant.” *Abbot Labs.*, 471 F.3d at 1365.

Thus, *Landes* describes a maternal blood sample that contains cell-free fetal DNA and “an agent that inhibits the lysis of cells”, *i.e.*, glucose.

2. Claim 56: “The method of claim 55, wherein said sample is selected from the group consisting of: blood, serum, plasma, urine, and vaginal secretion.”

As discussed in Section X.A.1.ii above, *Landes* describes a method wherein the sample is maternal blood, serum, or plasma. (*See, e.g.*, Ex.1003, 3:2-4 (“DNA is first isolated from maternal serum”); *id.*, 10:26-32 (“Plasma Separation Protocol: Maternal blood is collected”); Ex.1006, 10:6-10, 2:21-23; *see also* Ex.1056, ¶¶53-8, 65.)

3. Claim 57: “The method of claim 56, wherein said sample is blood.”

As discussed in Section X.A.1.ii above, *Landes* describes a method wherein the sample is maternal blood. (*See, e.g.*, Ex.1003, 10:26-32 (“Plasma Separation Protocol: Maternal blood is collected”); Ex.1006, 10:6-10; *see also* Ex.1056, ¶¶53-8, 66.)

4. Claim 58: “The method of claim 55, wherein said sample comprises free maternal template DNA and free fetal template DNA.”

As discussed in Section X.A.1.ii above, *Landes* describes a method wherein a sample contains both cell-free maternal template DNA and cell-free fetal template DNA. (*See, e.g.*, Ex.1003, 10:26-11:6 (“Isolation of Fetal DNA from Maternal Blood”), 14:15-24, Ex.4 (providing total DNA recovered from maternal plasma, as well as Fetal DNA recovered), Fig.1a (discussing “Maternal DNA” and “Fetal DNA”), Fig.2b (same), Fig.3 (same); Ex.1006, 10:6-15, 13:20-29, Ex.4, Fig.2b, Fig.3; *see also* Ex.1056, ¶¶53-8, 67.)

5. Claim 59: “The method of claim 55, wherein said agent is a cell lysis inhibitor.”

As discussed in Section X.A.1.iii above, *Landes* describes a method wherein a maternal blood sample is collected in an ACDA blood collection tube, which comprises a “cell lysis inhibitor”. (*See, e.g.*, Ex.1003, 10:20-30 (“Plasma Separation Protocol: Maternal blood is collected into ACDA blood collection tube”); Ex.1006, 10:6-14; *see also* Ex.1056, ¶¶59-64, 68.)

To the extent Patent Owner argues that the ’277 patent clearly defined glucose as a “membrane stabilizer” (another member of the Markush group set forth in claim 55), and not as a “cell lysis inhibitor,” this argument is contradicted

by Patent Owner’s own expert and the specification of the ’277 patent.⁹ Patent Owner’s expert described the term “cell lysis inhibitor” to include agents like glucose, stating that a POSA would understand “cell lysis inhibitors to be the category of agents that prevents or reduces the rupture of cell membranes and release of cellular contents by *protecting or preserving structural integrity of the cell membrane.*” (See, e.g., Ex.1020, Grody December 14, 2020 Declaration, ¶37.)

The ’277 patent also refers to “aldehydes,” which includes formaldehyde, and glucose as “agent[s] that stabilize[] cell membranes” and “reduce maternal cell lysis.” (See, e.g., Ex.1001, 15:58-16:7, 32:4-21.)¹⁰ As such, where the ’277 patent specification describes formaldehyde as an example of a “cell lysis inhibitor” (see, e.g., Ex.1001, 6:54-57, claim 60 (identifying formaldehyde as a “cell lysis

⁹ Any such lexicography argument would also be inconsistent with the Patent Owner’s argument in a pending district court litigation, where it argued the terms of the challenged patents carry their “plain and ordinary meaning.” (See, e.g., Ex.1020, Ravgen’s Opening Claim Construction Brief, 9; see also Ex.1021.)

¹⁰ The alleged inventor (Ravider Dhallan) confirmed this in an article published during the pendency of the prosecution of the ’277 patent, where he described formaldehyde in the same way as glucose, stating that “formaldehyde stabilizes cell membranes, thereby preventing cell lysis.” (See, e.g., Ex.1023, 1117.)

inhibitor”)), the same description should apply for glucose (*see, e.g.*, Ex.1056, ¶¶59-64, 68-70).

6. Claim 61: “The method of claim 55, wherein prior to determining the sequence, template DNA is isolated.”

The method discussed in *Landes* (*see* Section X.A.1.ii), describes an isolation of template DNA step occurring prior to a step of determining the sequence. (*See, e.g.*, Ex.1003, 3:22-24 (“PCR is performed with a primer pair that amplifies the gene of interest when it has been modified by bisulfite treatment and analyzing the PCR product to identify the allele”), 10:26-11:11 (“DNA Isolation Protocol”), 14:15-24 (“In this method, any target-specific primer pair is used in combination with a universal energy transfer-labeled primer”), Ex.4 (describing “Detection of ERG Methylation Profile”), Fig.2b, Fig.3; Ex.1006, 10:6-15, 13:20-29, Ex.4, Fig.2b, Fig.3; *see also* Ex.1056, ¶¶53-8, 71.)

7. Claim 62: “The method of claim 57, wherein said template DNA is obtained from plasma of said blood.”

As discussed in Section X.A.1.ii above, *Landes* describes a method wherein template DNA is obtained from plasma of the maternal blood sample. (*See, e.g.*, Ex.1003, 10:26-11:11 (“DNA Isolation Protocol”), 14:15-24, Ex.4 (describing “Detection of ERG Methylation Profile”), Fig.2b, Fig.3; *see also* Ex.1056, ¶¶53-8, 72.)

8. Claim 63: “The method of claim 57, wherein said template DNA is obtained from serum of said blood.”

As discussed in Section X.A.1.ii above, *Landes* describes a method wherein template DNA is obtained from serum of the maternal blood sample. (*See, e.g.*, Ex.1003, 3:2-12 (“[T]he invention provides a method for detecting fetal chromosome aneuploidies by performing quantitative PCR on bisulfite-treated DNA isolated from maternal serum”), 3:21-24, 8:23-24; Ex.1006, 2:21-30; *see also* Ex.1056, ¶¶53-8, 73.)

9. Claim 66: “The method of claim 55, wherein said locus of interest is a single nucleotide polymorphism.”

The sequence of the locus of interest determined in the method provided in *Landes* (*see* Section X.A.1.ii), can be a single nucleotide polymorphism. (*See, e.g.*, Ex.1003, 1:8-20 (“[S]pecific genetic defects such as point mutations in disease-associated genes can be detected by molecular analyses designed to identify single nucleotide polymorphisms (SNPs) and other small mutations”), 3:17-4:6 (“The PCR product is analyzed to identify the polymorphism”), 19:15-18, Fig.1a (“Fetal-specific primers for PCR at specific locus on chromosomes 13, 18 or 21”), Fig.1b (same), Fig.2a; Ex.1006, 1:16-18, 3:17-22, 18:15-18, Figs.1-2; *see also* Ex.1056, ¶¶53-8, 74.)

10. Claim 67: “The method of claim 55, wherein said locus of interest is a mutation.”

The sequence of the locus of interest determined in the method provided in *Landes* (see Section X.A.1.ii), can be a mutation, such as a point mutation or other small mutations. (See, e.g., Ex.1003, 1:8-21 (“[S]pecific genetic defects such as point mutations in disease-associated genes can be detected by molecular analyses designed to identify single nucleotide polymorphisms (SNPs) and other small mutations”), 3:19-4:6 (“The PCR product is analyzed to identify the polymorphism”), 4:22-5:6, 10:4-19 (“Specific examples include mutant alleles”), 14:26-15:3 (“Several primer sequences have been demonstrated for detection of aneuploidies or disease genes”), 19:15-18, Ex.4 (describing “Detection of ERG Methylation Profile”), Figs.1-3; Ex.1006, 1:16-18, 3:4-22, 4:9-23, 9:13-28, 14:1-8, 18:15-18, Ex.4, Figs.1-3; see also Ex.1056, ¶¶53-8, 75.)

11. Claim 68: “The method of claim 55, wherein the sequence of multiple loci of interest is determined.”

Multiple loci of interest can be determined with the method discussed in *Landes* (see Section X.A.1.ii), including, for example, on chromosomes 13, 18, or 21. (See, e.g., Ex.1003, 1:8-21 (“[S]pecific genetic defects such as point mutations in disease-associated genes can be detected by molecular analyses designed to identify single nucleotide polymorphisms (SNPs) and other small mutations”), 3:18-4:6, 10:17-19 (“The PCR product is analyzed to identify the polymorphism”),

4:22-5:6, 8:22-9:11 (“Another means to detect fetal specific DNA is to identify loci that are methylated in fetal DNA and unmethylated in adult/maternal DNA”), 10:4-19 (“Specific examples include mutant alleles”), 14:26-15:3 (“Several primer sequences have been demonstrated for detection of aneuploidies or disease genes”), Ex.4, Fig.1a (“Fetal-specific primers for PCR at specific locus on chromosomes 13, 18 or 21”); Fig.2b, Fig.3; Ex.1006, 3:4-22, 4:9-23, 8:7-28, 9:13-28, 14:1-8, Ex.4, Fig.2b, Fig.3; *see also* Ex.1056, ¶¶53-8, 76.)

12. Claim 69: “The method of claim 68, wherein the multiple loci of interest are on multiple chromosomes.”

The sequence of the multiple loci of interest determined in the method provided in *Landes* (*see* Sections X.A.1.ii and X.A.11), can be on multiple chromosomes (*e.g.*, 13, 18, or 21). (*See, e.g.*, Ex.1003, 3:18-4:6, 4:22-5:6, 8:22-9:11, 10:6-19, 14:26-15:3, Ex.4, Fig. 1a, Fig.2b, Fig.3; Ex.1006, 3:4-22, 4:9-23, 8:7-28, 9:13-28, 14:1-8, Ex.4, Fig.2b, Fig.3; *see also* Ex.1056, ¶¶53-8, 77.)

13. Claim 80: “The method of claim 55, wherein the sequence of a locus of interest is determined using a method selected from the group consisting of: allele specific PCR, mass spectrometry, hybridization, primer extension, fluorescence polarization, fluorescence resonance energy transfer (FRET), fluorescence detection, sequencing, Sanger dideoxy sequencing, DNA microarray, southern blot, slot blot, dot blot, and MALDI-TOF mass spectrometry.”

Landes discusses a method (*see* Section X.A.1.ii) that can determine the sequence of the locus of interest using various methods, including allele specific

PCR and fluorescence detection. (*See, e.g.*, Ex.1003, 3:18-4:6 (“The PCR product is analyzed to identify the polymorphism. Analysis can be performed by method known in the art, *e.g.*, DNA sequence, DNA microarrays, SSCP, LAMP”), 4:22-5:6 (describing “conventional techniques of molecular biology . . . which are within the skill of the art”), 10:4-19 (describing analyses that “can be performed by method known in the art”), 14:26-15:3 (“Several primer sequences have been demonstrated for detection of aneuploidies or disease genes”), Ex.4, Fig.2b, Fig.3; Ex.1006, 3:4-22, 4:9-23, 9:13-28, 14:1-8, Ex.4, Fig.2b, Fig.3; *see also* Ex.1056, ¶¶53-8, 78.)

14. Claim 81

i) [81.pre] “A method for preparing a sample for analysis comprising;”

Landes describes “a method for preparing a sample for analysis” as recited in the preamble for the same reasons discussed in Section X.A.1.i above. (*See, e.g.*, Ex.1003, 10:20-29 (“Plasma Separation Protocol”); Ex.1006, 10:6-14; *see also* Ex.1056, ¶¶79, 52.)

ii) [81.a] “isolating free fetal nucleic acid from [a] sample;”¹¹

¹¹ The Western District of Texas granted an unopposed motion to correct claim 81 of the '277 patent to remove “the” from “a the sample.”

As discussed in Section X.A.1.ii above, *Landes* describes a method isolating cell-free fetal nucleic acid from a maternal blood sample. (*See, e.g.*, Ex.1003, 10:28-12:6 (“Isolation of Fetal DNA from Maternal Blood”); Ex.1006, 10:6-14:9; *see also* Ex.1056, ¶¶80, 53-8.)

- iii) **[81.b] “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.”**

As discussed in Section X.A.1.iii above, *Landes* describes a method wherein a maternal blood sample is collected in an ACDA blood collection tube, which comprises “an agent that inhibits lysis of cells”. (*See, e.g.*, Ex.1003, 10:20-29 (“Maternal blood is collected into ACDA blood collection tube”); Ex.1006, 10:6-14; *see also* Ex.1056, ¶¶81, 59-64.)

- 15. **Claim 82: “The method of claim 81, wherein said sample is obtained from a source selected from the group consisting of human, non-human, mammal, reptile, cattle, cat, dog,**

goat, swine, pig, monkey, ape, gorilla, bull, cow, bear, horse, sheep, poultry, mouse, rat, fish, dolphin, whale, and shark.”

As discussed in Sections X.A.1.ii and X.A.14.ii above, *Landes* describes obtaining a sample from a human source, a pregnant human female.¹² (*See, e.g.*, Ex.1003, 3:2, 8:22, 10:26-30; Ex.1006, 10:8, 2:21-23; *see also* Ex.1056, ¶¶82, 53-8.)

16. Claim 83: “The method of claim 82, wherein the sample is obtained from a human source.”

As discussed in Sections X.A.1.ii and X.A.14.ii, *Landes* describes the method of claim 82, wherein the sample is obtained from a pregnant human female. (*See, e.g.*, Ex.1003, 3:2, 8:23, 10:26-30; Ex.1006, 2:21-23, 10:8, 2:7-18; *see also* Ex.1056, ¶¶83, 53-8.)

17. Claim 84: “The method of claim 81, wherein the sample is obtained from a source selected from the group consisting of blood, serum, plasma, saliva, urine, tear, vaginal secretion, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascetic fluid, fecal matter, and body exudates.”

As discussed in Sections X.A.1.ii and X.A.14.ii, *Landes* describes the method of claim 81 wherein the sample is obtained from, at least, blood, serum, or

¹² When defining “subject,” from whom a sample for the discussed method is obtained, *Landes* states that “[a] subject” is “more preferably a human.” (Ex.1003, 8:4; *see also id.*, 2:20-22; Ex.1006, 7:19, 2:7-18; Ex.1056, ¶82.)

plasma. (*See, e.g.*, Ex.1003, 3:2, 8:23, 10:26-32; Ex.1006, 10:8, 2:21-23; *see also* Ex.1056, ¶¶84, 53-8.)

18. Claim 85: “The method of claim 84, wherein said sample is blood.”

As discussed in Sections X.A.1.ii and X.A.14.ii, *Landes* describes a method of claim 84 wherein the sample is maternal blood. (*See, e.g.*, Ex.1003, 10:26-30; Ex.1006, 10:6-10; *see also* Ex.1056, ¶¶85, 53-8.)

19. Claim 86: “The method of claim 85, wherein said blood is from a pregnant female.”

As discussed in Sections X.A.1.ii and X.A.14.ii, *Landes* describes method of claim 85 wherein the sample blood is from a pregnant female. (*See, e.g.*, Ex.1003, 10:26-30; Ex.1006, 10:6-10; *see also* Ex.1056, ¶¶86, 53-8.)

20. Claim 87: “The method of claim 86, wherein said blood is obtained from a human pregnant female when the fetus is at a gestational age selected from the group consisting of: 0-4, 4-8, 8-12, 12-16, 16-20, 20-24, 24-28, 28-32, 32-36, 36-40, 40-44, 44-48, 48-52, and more than 52 weeks.”

Claim 87 covers all gestational ages from 0-52 weeks, where full-term pregnancy for a human is typically 40-42 weeks. (*See, e.g.*, Ex.1056, ¶87.) As discussed in Sections X.A.1.ii and X.A.14.ii, *Landes* describes the method of claim 86, wherein the blood sample is obtained from a pregnant female within the claimed gestational ages because the claim covers all possible ages. (*See, e.g.*, Ex.1003, 3:2, 8:22, 10:26-32 15:15-23; Fig. 1a; Ex.1006, 2:21-27, 10:6-14, 14:20-

27; Fig. 1a, 15:23-27 (discussing “12 weeks gestation”); *see also* Ex.1056, ¶¶87, 53-8.) As *Landes* explained, cell-free fetal DNA can be detected “as early as 7 weeks, increases in abundance during gestation, and are detectable 1 month but not 2 months postpartum.” (Ex.1003, at 2:20-25; Ex.1006, 2:8-10.)

21. Claim 88: “The method of claim 87, wherein said sample is obtained from plasma from said blood.”

As discussed in Sections X.A.1.ii and X.A.14.ii above, *Landes* describes a method wherein cell-free fetal DNA is obtained from plasma of the maternal blood sample. (*See, e.g.*, Ex.1003, 10:25-11:2; Ex.1006, 10:6-14; *see also* Ex.1056, ¶¶88, 53-8.)

22. Claim 89: “The method of claim 81, wherein said agent is a cell lysis inhibitor.”

As discussed in Sections X.A.1.iii and X.A.14.iii above, *Landes* describes a method wherein a maternal blood sample is collected in an ACDA blood collection tube, which comprises a “cell lysis inhibitor”. (*See, e.g.*, Ex.1003, 10:20-29; Ex.1006, 10:6-14; *see also* Ex.1056, ¶¶89, 53-8.)

23. Claim 94: “The method of claim 81, wherein isolation of nucleic acid comprises a centrifugation step.”

Landes describes a method of isolating cell-free fetal DNA using a variety of centrifugation steps, including where the sample is “centrifuged at 600 x g for 10 minutes.” (*See, e.g.*, Ex.1003, 10:20-32; Ex.1006, 10:10-11; *see also* Ex.1056, ¶90.)

- 24. Claim 96: “The method of claim 94, wherein the centrifugation step is performed at a speed selected from the group consisting of 0-50 rpm, 50-100 rpm, 100-200 rpm, 200-300 rpm, 300-400 rpm, 400-500 rpm, 500-600 rpm, 600-700 rpm, 700-800 rpm, 800-900 rpm, 900-1000 rpm, 1000-2000 rpm, 2000-3000 rpm, 3000-4000 rpm, 4000-5000 rpm, 5000-6000 rpm, 6000-7000 rpm, 7000-8000 rpm, and greater than 8000 rpm.”**

As discussed in Section X.A.23 above, *Landes* describes a method where the sample is “centrifuged at 600 x g for 10 minutes,” as well as “6000 x g (8000 rpm) for 1 minute,” and “20,000 x g (14000 rpm) for 3 minutes.” (*E.g.*, Ex.1003, 10:26-12:6; Ex.1006, 10:6-11:15; *see also* Ex.1056, ¶¶91.)

- 25. Claim 126: “The method of claim 55, wherein the sample was obtained from a pregnant female.”**

As discussed in Section X.A.1.ii above, *Landes* describes the method of claim 55 wherein the sample is from a pregnant female. (*See, e.g.*, Ex.1003, 3:2, 8:23, 10:26-30; Ex.1006, 2:21-23, 19-21, 2:7-18, 10:6-10; *see also* Ex.1056, ¶¶92, 53-8.)

- 26. Claim 127: “The method of claim 126, wherein the pregnant female is human.”**

As discussed in Section X.A.1.ii above, *Landes* describes the method of claim 126, wherein the sample is obtained from a pregnant human female. (*See, e.g.*, Ex.1003, 3:2, 8:23, 10:26-30; Ex.1006, 10:8, 2:21-23, 19-21, 2:7-18; *see also* Ex.1056, ¶¶93, 53-8.)

- 27. Claim 128: “The method of claim 127, wherein said sample is selected from the group consisting of: blood, serum, plasma, urine, and vaginal secretion.”**

As discussed in Section X.A.1.ii above, *Landes* describes the method of claim 127 wherein the sample is, at least, blood, serum, or plasma. (*See, e.g.*, Ex.1003, 3:2, 8:23, 10:26-32; Ex.1006, 10:8, 2:21-23; *see also* Ex.1056, ¶¶94, 53-8.)

- 28. Claim 129: “The method of claim 128, wherein said sample is blood.”**

As discussed in Section X.A.1.ii above, *Landes* describes the method of claim 128 wherein the sample is blood. (*See, e.g.*, Ex.1003, 10:26-30; Ex.1006, 10:6-10; *see also* Ex.1056, ¶¶95, 53-8.)

- 29. Claim 130: “The method of claim 129, wherein the free fetal DNA is obtained from plasma from said blood.”**

As discussed in Section X.A.1.ii above, *Landes* describes the method of claim 129 where cell-free fetal DNA is obtained from a maternal blood sample. (*See, e.g.*, Ex.1003, 10:28-12:6; Ex.1006, 10:6-14:9; *see also* Ex.1056, ¶¶96, 53-8.)

B. Ground 2: *Landes* in View of *Marx* Renders Claim 95 Obvious

- 1. Claim 95: “The method of claim 94, wherein the centrifugation step is performed with the centrifuge braking power set to zero.”**

As discussed in Section X.A.23 above with respect to claim 94, *Landes* describes a method of isolating cell-free fetal DNA using a variety of centrifugation steps, including where the sample is “centrifuged at 600 x g for 10

minutes.” (See, e.g., Ex.1003, 10:20-11:2; Ex.1006, 10:10-14.) Although *Landes* does not explicitly discuss that such centrifugation is performed “with the centrifuge braking power set to zero,” as recited in claim 95, a POSA would have understood the absence of instruction for setting the centrifuge brake to at least suggest no brake should be used. (Ex.1056, ¶¶97-8.) In addition, since braking can be set to different powers, should a braking step have been integral to the *Landes* protocol, it would have been specified. (Ex.1056, ¶98.) Setting the centrifuge braking power to zero would in any event have been obvious to a POSA in view of the general knowledge in the art, such as *Marx*. (See, e.g., Ex.1029, Abstract; Ex.1056, ¶¶97-102.)

Marx is generally directed to an analysis of variations in centrifugation braking rates during blood processing. (Ex.1029, Abstract.) As such, a POSA would have had reason to consider *Marx*, which is in the same field as *Landes* and the '277 patent. (Ex.1056, ¶¶99-100.) *Marx* describes experiments where samples are centrifuged at various braking rates, including no braking. (Ex.1029, 744-46.) Following such centrifugation, *Marx* concluded that, “[u]pon strong braking, the separated cell layers are perturbed by the rapid deceleration” (*id.*, 747), and that “no brakes gave much more reasonable yields of platelets . . . as well as low WBC contamination” (*id.*, 746).

A POSA would have had motivation to combine *Landes* and *Marx*. For instance, a POSA would have recognized that such centrifugation with braking power set to zero would help prevent disturbance of the “buffy-coat” (*see, e.g.,* Ex.1030, 769 (“Great care was taken to ensure that the buffy coat or the blood clot was undisturbed when plasma or serum samples, respectively, were removed”)), when removing plasma in the method discussed in *Landes* (*see, e.g.,* Ex.1003, 10:31 (“The clear plasma is removed above the red cell pellet”); *see also* Ex.1056, ¶100). As such, given the known benefits of performing centrifugation with braking power set to zero in this context (*e.g.,* preventing disturbance of the buffy coat separating plasma from the blood cells), a POSA would have been motivated to do the same in *Landes*. (Ex.1056, ¶¶97-102.) Indeed, a POSA would have known that leaving a centrifuge brake off was commonly done to prevent a sample from being disturbed by the brake. (*See, e.g.,* Ex.1029, 746; *see also* Ex.1025, ¶224; Ex.1056, ¶¶101-2.)

At a minimum, performing centrifugation with braking power set to zero would have been obvious to try. Centrifugation can be performed either with or without a brake. (*See, e.g.,* Ex.1029, Abstract (describing variations in centrifugation braking rates for blood processing including no brake); *see also* Ex.1056, ¶101.) Thus, there are a finite number of predictable options for the braking power of a centrifuge. *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*,

618 F.3d 1294, 1302 (Fed. Cir. 2010). A POSA would have appreciated that it was common for a single process to at times make use of centrifuge brakes and at other times not to make use of centrifuge brakes. (*See, e.g.*, Ex.1024, 21:15-24; *see also* Ex.1056, ¶¶101-2.)

A POSA would have had a reasonable expectation of success with setting a braking power to zero. (Ex.1056, ¶¶97-102.) In particular, a POSA would have appreciated that, although not using a brake would have caused a centrifugation step to take longer to complete (Ex.1029, Abstract), it would have less disturbance of the buffy coat. (Ex.1056, ¶¶100-2.) In other words, leaving a centrifuge brake powered off would have only improved the operation of *Landes* (to the extent *Landes* did not already intend for the brake to be powered off). (*Id.*)

A POSA would have been very familiar with the use of a centrifuge brake, since centrifuges with and without brakes are commonly used in the art. (*Id.*) For instance, a POSA would have known that leaving a centrifuge brake off was commonly done to prevent a sample from being disturbed by the brake, just as is suggested by *Marx* (*see, e.g.*, Ex.1029, 746; *see also* Ex.1025, ¶224), and that, depending on needs, a centrifuge brake is sometimes left off and sometimes turned on (*see, e.g.*, Ex.1024, 21:15-24). (Ex.1056, ¶101.) In this context, leaving a centrifuge brake powered off would have been seen as a straightforward improvement. (Ex.1056, ¶101-2.)

Petitioner is not aware of any alleged objective indicia that supports the nonobviousness of the centrifugation braking power limitation of claim 95. Regardless, the compelling case of obviousness established above would outweigh any such evidence. *See, e.g., Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013).

C. Ground 3: *Lo* in View of *Valli* Renders Claims 55-63, 66-69, 80-91, 94, 96, 126-130, 132, and 133 Obvious

1. Claim 55

i) [55.pre]¹³

Lo describes a “method” to isolate and analyze cell-free fetal nucleic acid from a blood sample of a pregnant human female. (*See, e.g., Ex.1033, Abstract; see also Ex.1056, ¶104.*)

ii) [55.a]

Lo describes a method of determining the sequence of a locus of interest on cell-free fetal DNA isolated from a pregnant female blood sample. *Lo* provides exemplary methods for isolating cell-free fetal DNA from a sample of maternal blood in Examples 3 and 5. (*Ex.1033, 15:4-20:3, 23:14-33:30; see also Ex.1056, ¶105-6.*) First, *Lo* provides a “sample preparation” where plasma is collected from

¹³ For claims that are addressed in Grounds 1 and 2, Petitioner does not repeat claim language.

EDTA tubes containing maternal blood, which contains the cell-free fetal nucleic acid. (Ex.1033, 16:10-27, 24:15-25:11; *see also* Ex.1056, ¶¶105-6.) *Lo* then provides a “DNA extraction from plasma,” where fetal DNA can be isolated using a commercially available “QIAamp Blood Kit.” (Ex.1033, 17:1-6, 25:12-18.)

Finally, *Lo* provides a “Real time quantitative PCR,” as described in Example 2 (*id.*, 10:23-12:29), to perform a non-invasive prenatal determination of fetal rhesus D (“RhD”) status (*id.*, 17:7-26) or quantitative analysis of fetal DNA (*id.*, 25:19-27) in the maternal plasma. (Ex.1056, ¶¶105-6.) This PCR step determines the sequence of a locus of interest on cell-free fetal DNA. (Ex.1056, ¶¶105-6.) For example, *Lo* uses this method for the detection of Down’s syndrome and other chromosomal aneuploidies, as well as “any paternally-inherited sequences which are not possessed by the mother,” including RhD status, mutation in the beta-globin gene, paternally-inherited DNA polymorphisms, or mutations. (Ex.1033, 4:5-5:5; *see also* Ex.1056, ¶¶105-6.) Thus, *Lo* discusses a method of analysis that determines the sequence of a locus of interest on cell-free fetal DNA isolated from a sample obtained from a pregnant female.

iii) [55.b]

Lo describes a method of isolating cell-free fetal DNA from a maternal blood sample collected in EDTA tubes to detect alleles to determine fetal aneuploidy. (Ex.1033, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶107.) To the

extent EDTA is not an “agent . . . selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor,” it would have been obvious to a POSA to include such an agent in view of *Valli*.

Various blood collection agents are assessed in *Valli* to “improve leukocyte stability” during transportation of blood. (Ex.1034, 252.) A POSA would have understood that unstable maternal leukocytes (or white blood cells) in a blood sample could release maternal cell-free DNA, which would make “robust foetal DNA detection” more difficult. (See Ex.1033, 30:8-17; see also Ex.1019, 276, 279 (recognizing that serum contains more cell-free DNA than plasma); Ex.1056, ¶¶108-9.)

A POSA would have had motivation to combine *Lo* and *Valli*. For instance, a POSA would have recognized the issue of maternal cell lysis in a blood sample. (See, e.g., Ex.1035, 1577 (“The contamination of the plasma sample by maternal cells or cell remnants would, however, affect the apparent concentration of maternal DNA in the sample”); Ex.1036, 1612 (finding that blood processing can affect the amount of total DNA, but not the amount of fetal DNA); Ex.1038, 196 (“The total DNA, which increases in the test tube over time, is most likely attributable to apoptosis, cell death, and lysis.”); Ex.1039, 33 (concluding that “[a]poptosis is stimulated in maternal peripheral blood during pregnancy”); Ex.1056, ¶109.) Where the prior art discussed the ability of formalin to further

reduce cell lysis in the presence of EDTA, a POSA isolating cell-free fetal DNA from a maternal sample would have been motivated to improve white-blood-cell stability, and thus would have been motivated to combine *Lo* with conventional methods for doing so, such as those discussed in *Valli*. (See Ex.1056, ¶109-10.)

Valli, like *Lo*, relates to methods of preparing blood samples for “screening or for diagnostic purposes.” (See, e.g., Ex.1034, 252; Ex.1033, 1:1-6 (discussing applications in prenatal diagnosis); see also Ex.1056, ¶110.) *Valli* exemplifies the decades of experimentation with blood stabilization methods in the prior art to which a POSA would have had access when isolating cell-free fetal DNA from maternal plasma. (See, e.g., Ex.1034, 252-3, 257; see also Ex.1042, 34 (“DNA-protein cross-linking by this fixative [formaldehyde] prevents the extraction of the fragmented low molecular weight DNA from the cell”); Ex.1043, 276-77 (discussing the use of formaldehyde to preserve white blood cells); Ex.1044, 3:21-26, 13:34-14:16, Figs.2-3 (same); Ex.1045, 14:2-6 (discussing the use of aldehydes, like formaldehyde, to “fix white blood cells”); Ex.1046, 8-12; Ex.1047, 5:28-48; Ex.1048, 3:32-44; Ex.1049, 12:1-7; Ex.1056, ¶¶28-9, 110.) Indeed, the initial blood-processing step in *Valli* is equivalent to that used in *Lo*, which further emphasizes the motivation for a POSA to combine these references with a reasonable expectation of success. (Ex.1056, ¶110.)

That *Valli* discusses bovine blood makes it no less applicable to the method of *Lo*. *Lo* itself—like the '277 patent¹⁴—is not limited to human use. (Ex.1056, ¶¶111-2.) *Valli* references experiments regarding the stability of human white blood cells as part of its discussion of bovine blood. (Ex.1034, 255-6.)

Other prior art likewise discussed the applicability of methods for collecting and analyzing human and animal cell-free nucleic acid, confirming the motivation for a POSA to combine *Lo* and *Valli* with a reasonable expectation of success. (See, e.g., Ex.1040, Abstract, 1:15-3:63 (“This invention relates to detection of specific extracellular nucleic acid in plasma or serum fractions of human or animal blood”); Ex.1041, Abstract, 2:27-28 (same); Ex.1003, 8:4-6, 4:29-5:2 (discussing collection and analysis of cell-free DNA from mammals, including “humans, farm animals, sport animals, and pets”); Ex.1056, ¶112.) A POSA would have recognized that *Valli* addresses the same or similar technical problem (e.g., preparing a blood sample for analysis) in the same or similar technical field as *Lo* and the '277 patent, and would have been motivated to consider *Valli* when implementing the methods discussed in *Lo* with a reasonable expectation of success. (Ex.1056, ¶¶ 112-5.)

¹⁴ The '277 patent states its methods are applicable to cattle and humans. (See, e.g., Ex.1001, claims 81-2, 6:35-36, 16:13-14, 30:1-3).

A POSA would have understood that *Valli* discusses experiments comparing white blood cell stability using various common blood collection tubes, such as ACD and EDTA, alone and in combination with common fixing agents, such as acids, alcohols, and aldehydes (including formaldehyde and glutaraldehyde). (Ex.1034, 252 & n.4; *see also* Ex.1056, ¶¶112-5.) For example, *Valli* tested two formalin-EDTA preparations (Titriplex I and IV) and ACD-formalin-ASA. (*See id.*, 253, 257, Table 1.) According to the '277 patent, formalin is an agent that inhibits cell lysis, which the '277 patent refers to as a “cell lysis inhibitor.” (*See, e.g.*, Ex.1001, 15:39-51; *see also* Ex.1056, ¶113.)

Valli concludes that formalin-EDTA preparations tested was “greatly superior to EDTA without additives for maintaining the stability of leukocytes during transport.” (Ex.1034, 257; *see also* Ex.1056, ¶114.) Further, *Valli* stated that formalin preparations “are deserving of a far wider utilization.” (Ex.1034, 257.) Indeed, the experiments of *Valli* are similar to those described in the '277 patent (such as Example 4), where EDTA alone was compared to a formalin-

EDTA preparation in an effort to improve stability of white blood cells.¹⁵ (See Ex.1001, 89:16-34, Table V; *see also* Ex.1056, ¶36.)

A POSA following *Lo* to isolate cell-free fetal DNA from a maternal plasma in the presence of EDTA (Ex.1033, 15:4-19:28, 23:14-33:10) would have been motivated to substitute a formalin-EDTA preparation, as suggested by *Valli*, to improve white-blood-cell stability (thereby reducing background cell-free maternal DNA resulting from cell lysis). (Ex.1056, ¶115.) And, based on the results described in *Valli*, the POSA would have applied the prior art methods of using formalin to the method of isolating cell-free fetal DNA in *Lo* to yield predictable results with a reasonable expectation of success. (Ex.1056, ¶¶107-15, 29, 35-7.)

iv) Objective indicia do not support nonobviousness

During prosecution of the '277 patent, Patent Owner argued that the claimed methods “serve a long-felt need in the medical community, and provide unexpected results,” relying on the percentage of fetal DNA obtained from maternal blood treated with formalin as associated with Examples 4 and 15. (Ex.1012, May 30, 2007 Response to Non-final Office Action, 35-8.) Patent

¹⁵ As explained in Section X.C.1.iv below, the purported experiments of the '277 patent do not provide sufficiently reliable results to justify the meaningfulness of using formalin or formaldehyde during maternal blood collection.

Owner, however, will not be able to demonstrate such objective indicia, and any such evidence would be outweighed by the compelling case of obviousness established above.¹⁶ *See, e.g., Ohio Willow Wood*, 735 F.3d at 1344.

First, Patent Owner’s claimed invention also did not satisfy any long-felt need. Even if Patent Owner could establish a long-felt need after the 1997 discovery of cell-free fetal DNA in maternal plasma, the formaldehyde treatment of Examples 4 and 15 did not meet this need. Patent Owner does not market any product that is commensurate with the scope of the challenged claims of the ’277 patent. And, when other independent researchers attempted to verify Patent Owner’s purported results, they “were not able to discern any effect of

¹⁶ Where evidence of objective indicia is considered after institution, Petitioner reserves the right to respond to any showing by Patent Owner. *See, e.g., Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1378 (Fed. Cir. 2019) (Patent Owner “bear[s] the burden of proving . . . evidence of secondary considerations”); *see also Arctic Cat, Inc. v. Polaris Industries Inc.*, IPR2017-00433, Paper 17 at (P.T.A.B. July 5, 2017) (no requirement “to address secondary considerations, not previously presented to the Office, in the Petition.”).

formaldehyde on the proportion of fetal DNA.” (Ex.1052, 654; *see also* Ex.1053, 658; Ex.1054, 74; Ex.1056, ¶37.)¹⁷

Further, the purported results from Examples 4 and 15 are not reliable. For example, Example 15 did not use a positive control, but instead improperly compared the purported results to Ex.1030. (*See* Ex.1056, ¶35.) About 10% of the samples tested in Example 15 (eight) did not contain formalin, but were included in the formalin-containing data reported in Table XXII. (*See* Ex.1001, 223:51-62, 226:19-26; *see also* Ex.1056, ¶35.) Even assuming these eight samples resulted in the lowest percentages reported in Table XXII, at least half of those results would still have identified fetal DNA percentages almost double those reported in Ex.1030 (according to the improper comparison method of the '277 patent). (Ex.1056, ¶35.)

Similarly, although a positive control was discussed in Example 4, the information provided is still insufficient to determine the reliability of the purported results. (*See* Ex.1056, ¶36.) For example, the percent fetal DNA in

¹⁷ Although these references were published in 2004/2005, Patent Owner did not make the Examiner aware of the inability of independent researchers to reproduce the results of Examples 4 and 15, even when arguing for patentability based on Examples 4 and 15 during prosecution in 2006/2007. (Section VI.C.)

Table V reported an overlap of the higher range of “Without Formalin” and lower range of “Formalin” (*see* Ex.1001, 89:1-91:60, Table V; *see also* Ex.1056, ¶36), which could mean that a potentially significant number blood samples *not* treated with formalin provided a higher percentage of fetal DNA, compared to samples that *were* treated with formalin. The ’277 patent, however, does not provide sufficient details of this experiment for a POSA to have been able to determine if the data supported Patent Owner’s conclusion in light of this overlap. (*See* Ex.1056, ¶36.)

The data from Examples 4 and 15—even if reliable—would have been expected in light of *Valli* and the prior art, where formalin was discussed as *further* reducing lysis of white blood cells *in the presence of EDTA*. (*See* Sections VI.A, X.C.1.iii.) At most, the purported increase of the percentage of fetal DNA using formalin is “merely in degree” and not “different in kind” from EDTA alone, which the Federal Circuit has explained cannot establish unexpected results. *See, e.g., Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

2. Claim 56

As discussed in Section X.C.1.ii, *Lo* describes a method wherein the sample is maternal blood, serum, or plasma. (*See, e.g.,* Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶116, 105-6.)

3. Claim 57

As discussed in Section X.C.1.ii, *Lo* describes a method wherein the sample is maternal blood. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶117, 105-6.)

4. Claim 58

As discussed in Section X.C.1.ii, *Lo* describes a method wherein a sample contains both cell-free maternal template DNA and cell-free fetal template DNA, including, for example, in Examples 2, 3, and 5. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶118, 105-6.)

5. Claim 59

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes the limitations of claim 59, where *Valli* describes the use of formalin-EDTA preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶119, 107-15, 35-7.) The '277 patent refers to formalin as an agent that inhibits cell lysis or a "cell lysis inhibitor." (*See, e.g.*, Ex.1001 at 15:39-51; *see also* Ex.1056, ¶¶119, 113.)

6. Claim 60: "The method of claim 59, wherein said cell lysis inhibitor is selected from the group consisting of: glutaraldehyde, derivatives of glutaraldehyde, formaldehyde, derivatives of formaldehyde, and formalin."

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes the limitations of claim 60, where *Valli* describes the use of formalin-EDTA

preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶120, 107-15, 35-7.)

7. Claim 61

As discussed in Section X.C.1.ii, *Lo* describes isolating the template DNA before determining the sequence, including, for example, in Examples 2, 3, and 5. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶121, 107-15, 35-7.)

8. Claim 62

As discussed in Section X.C.1.ii, *Lo* describes obtaining template DNA from plasma of the maternal blood sample, including, for example, in Examples 3 and 5. (*See, e.g.*, Ex.1033, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶122, 105-6.)

9. Claim 63

As discussed in Section X.C.1.ii, *Lo* describes obtaining template DNA from serum of the maternal blood sample, including, for example, in Example 2. (*See, e.g.*, Ex.1033, 9:15-15:2; *see also* Ex.1056, ¶¶123, 105-6.)

10. Claim 66

As discussed in Section X.C.1.ii, *Lo* provides that a sequence of a locus of interest can be a single nucleotide polymorphism. (*See, e.g.*, Ex.1033, 4:5-5:2, 31:27-32:30; *see also id.*, 9:15-15:2, 15:4-20:3, 23:14-33:30; Ex.1056, ¶¶124, 105-6.) *Lo* describes the method as “most useful in situations where the determination

of foetal-derived paternally-inherited polymorphisms/mutations or genes would be helpful in clinical prenatal diagnosis,” including, for example “certain hemoglobinopathies.” (*See, e.g.*, Ex.1033, 31:27-32:7, 4:17-22.) A POSA would have understood that sickle cell anemia, a hemoglobinopathy, was caused by a single nucleotide polymorphism in the β -globin gene, and that methods for detecting such a single transversion were known in the art. (*See, e.g.*, Ex.1055, 2; *see also* Ex.1056, ¶124.)

11. Claim 67

As discussed in Sections X.C.1.ii and X.C.10, *Lo* provides that a sequence of a locus of interest can be a mutation, such as mutations of the β -globin gene. (*See, e.g.*, Ex.1033, 4:5-5:2, 31:27-32:30; *see also id.*, 9:15-15:2, 15:4-20:3, 23:14-33:30; Ex.1056, ¶¶125, 105-6.)

12. Claim 68

As discussed in Section X.C.1.ii, *Lo* determines the sequence of multiple loci of interest. (*See, e.g.*, Ex.1033, 4:23-5:2, 31:27-32:30; *see also id.*, 9:15-15:2, 15:4-20:3, 23:14-33:30; Ex.1056, ¶¶126, 105-6.) For example, *Lo* analyzes the SRY gene (located on the Y chromosome) and the β -globin gene (located on chromosome 11). (Ex.1033, 25:19-28:17, 30:18-24; *see also* Ex.1056, ¶126.)

13. Claim 69

As discussed in Section X.C.1.ii and X.C.12, *Lo* determines the sequence of multiple loci of interest on multiple chromosomes, such as the SRY gene (located on the Y chromosome) and the β -globin gene (located on chromosome 11). (Ex.1033, 25:19-28:17, 30:18-24; *see also id.*, 4:23-5:2, 9:15-15:2, 15:4-20:3, 23:14-33:30, 31:27-32:30; Ex.1056, ¶¶127, 105-6.)

14. Claim 80

As discussed in Section X.C.1.ii, *Lo* uses conventional methods such as allele specific PCR and fluorescence detection to determine the sequence of a locus of interest, including various TaqMan systems for SRY, RhD, and β -globin. (*See, e.g.*, Ex.1033, 10:23-12:3, 17:7-26, 25:20-22; *see also* Ex.1056, ¶¶128, 105-6.)

15. Claim 81

i) [81.pre]

As discussed in Section X.C.1.i, *Lo* describes a method to isolate and analyze cell-free fetal nucleic acid from a blood sample of a pregnant human female. (*See, e.g.*, Ex.1033, Abstract; *see also* Ex.1056, ¶¶129, 104.)

ii) [81.a]

As discussed in Section X.C.1.ii, *Lo* describes isolating cell-free fetal nucleic acid from a maternal blood sample, including in Examples 2, 3, and 5. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶130, 105-6.) For example, *Lo* provides a “DNA extraction from plasma,” where DNA

can be isolated using a commercially available “QIAamp Blood Kit.” (Ex.1033, 17:1-6, 25:12-18.)

iii) [81.b]

For the same reasons discussed in Section X.C.1.iii, to the extent EDTA is not an “agent that inhibits lysis of cells,” it would have been obvious to a POSA to include such an agent in the method of *Lo*, in view of *Valli*, which concludes that formalin-EDTA preparations were “greatly superior” to EDTA alone. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶131, 107-15, 35-7.)

16. Claim 82

As discussed in Section X.C.1.ii, *Lo* describes obtaining a sample from a human source, a pregnant human female, including in at least Examples 2, 3, and 5. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶132, 105-6.)

17. Claim 83

As discussed in Section X.C.1.ii, *Lo* describes obtaining a sample from a human source, a pregnant human female. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶133, 105-6.)

18. Claim 84

As discussed in Section X.C.1.ii, *Lo* describes the method of claim 81 wherein the sample is obtained from, at least, blood, serum, or plasma. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶134, 105-6.)

19. Claim 85

As discussed in Section X.C.1.ii, *Lo* describes a method of claim 84 wherein the sample is maternal blood. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶135, 105-6.)

20. Claim 86

As discussed in Section X.C.1.ii, *Lo* describes method of claim 85 wherein the sample blood is from a pregnant female. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶136, 105-6.)

21. Claim 87

Claim 87 covers all gestational ages from 0-52 weeks, where full-term pregnancy for a human is typically 40-42 weeks. (*See, e.g.*, Ex.1056, ¶137.) As discussed in Section X.C.1.ii, *Lo* describes the method of claim 86, wherein the blood sample is obtained from a pregnant female within the claimed gestational ages because the claim covers all possible ages. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also id.*, 27:10-11 (discusses samples from gestational ages 11-17 weeks, and 37-43 weeks); Ex.1056, ¶¶137, 105-6.)

22. Claim 88

As discussed in Section X.C.1.ii, *Lo* describes a method wherein cell-free fetal DNA is obtained from plasma of the maternal blood sample, including, for example, in Example 3 and 5. (*See, e.g.*, Ex.1033, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶138, 105-6.)

23. Claim 89

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes the limitations of claim 89, where *Valli* describes the use of formalin-EDTA preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶139, 107-15, 35-7.) The '277 patent refers to formalin as an agent that inhibits cell lysis or a “cell lysis inhibitor.” (*See, e.g.*, Ex.1001 at 15:39-51; *see also* Ex.1056, ¶¶139, 113.)

24. Claim 90: “The method of claim 81, wherein said cell lysis inhibitor is selected from the group consisting of glutaraldehyde, derivatives of glutaraldehyde, formaldehyde, formalin, and derivatives of formaldehyde.”

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes the limitations of claim 90, where *Valli* describes the use of formalin-EDTA preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶140, 107-15, 35-7.)

25. Claim 91: “The method of claim 90, wherein said cell lysis inhibitor is formalin.”

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes the limitations of claim 90, where *Valli* describes the use of formalin-EDTA preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶141, 107-15, 35-7.)

26. Claim 94

Lo describes a method of isolating cell-free fetal DNA using a centrifugation step, including where the sample is “centrifuged at 3000 g.” (*See, e.g.*, Ex.1033, 10:13, 16:20-7, 21:25, 25:4-11; *see also* Ex.1056, ¶142.)

27. Claim 96

As discussed in Section X.C.1.ii, *Lo* describes a method where the sample is “centrifuged at 3000 g,” which falls within the claimed range of 0 rpm to greater than 8000 rpm. (*See, e.g.*, Ex.1033, 10:13, 16:20-7, 21:25, 25:4-11; *see also* Ex.1056, ¶143.)

28. Claim 126

As discussed in Section X.C.1.ii, *Lo* describes the method of claim 55 wherein the sample is from a pregnant female. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶144, 105-6.)

29. Claim 127

As discussed in Section X.C.1.ii, *Lo* describes the method of claim 126, wherein the sample is obtained from a pregnant human female. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶145, 105-6.)

30. Claim 128

As discussed in Section X.C.1.ii, *Lo* describes the method of claim 127 wherein the sample is, at least, blood, serum, or plasma. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶146, 105-6.)

31. Claim 129

As discussed in Section X.C.1.ii, *Lo* describes the method of claim 128 wherein the sample is blood. (*See, e.g.*, Ex.1033, 9:15-15:2, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶147, 105-6.)

32. Claim 130

As discussed in Section X.C.1.ii, *Lo* describes the method of claim 129 where cell-free fetal DNA is obtained from a maternal blood sample, including, for example, in Examples 3 and 5. (*See, e.g.*, Ex.1033, 15:4-20:3, 23:14-33:30; *see also* Ex.1056, ¶¶148, 105-6.)

33. Claim 132: “The method of claim 60, wherein said cell lysis inhibitor is selected from glutaraldehyde, formaldehyde and formalin.”

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes limitations of claim 132, where *Valli* describes the use of formalin-EDTA

preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶149, 107-15, 35-7.)

34. Claim 133: “The method of claim 90, wherein said cell lysis inhibitor is selected from the group consisting of glutaraldehyde, formaldehyde, and formalin.”

As discussed in Section X.C.1.iii, *Lo* in combination with *Valli* describes the limitations of claim 133, where *Valli* describes the use of formalin-EDTA preparations. (*See, e.g.*, Ex.1034, 253, 257, Table 1; Ex.1056, ¶¶150, 107-15, 35-7.)

D. Ground 4: *Lo* and *Valli* in View of *Marx* Renders Claim 95 Obvious

1. Claim 95

Although *Lo* and *Valli* do not explicitly discuss that centrifugation is performed “with the centrifuge braking power set to zero,” as recited in claim 95, a POSA would have understood the absence of instruction for setting the centrifuge brake to at least suggest no brake should be used. (Ex.1056, ¶152.) In any event, for the same reasons discussed in Section X.B.1, setting the centrifuge braking power to zero would have been obvious to a POSA in view of the general knowledge in the art, such as *Marx*. (*See, e.g.*, Ex.1029, Abstract; Ex.1056, ¶¶152-3.)

A POSA would have been motivated to combine *Lo*, *Valli*, and *Marx*. For instance, a POSA would have recognized that such centrifugation with braking

power set to zero would help prevent disturbance of the “buffy-coat” when removing plasma in the method discussed in *Lo*. (See, e.g., Ex.1033, 7:11-13 (“Great care was taken to ensure that the buffy coat or the blood clot was undisturbed when plasma or serum samples, respectively, were removed”); see also Ex.1056, ¶153.) For the same reasons discussed in Section X.B.1, a POSA would have had a reasonable expectation of success with setting a braking power to zero (to the extent that the method of *Lo* did not already intend for the break to be off). (Ex.1056, ¶¶152-3.)

Petitioner is not aware of any alleged objective indicia that supports the nonobviousness of the centrifugation braking power limitation of claim 95, and the compelling case of obviousness established above would outweigh any such evidence. (See Section X.B.1.)

XI. DISCRETIONARY DENIAL IS NOT APPROPRIATE HERE

A. Discretionary Denial Under *General Plastic* Is Not Appropriate

Petitioner has never before filed a Patent Office challenge to the ’277 patent. Patent Owner may argue that the ’277 patent is already at issue in proceedings initiated by different parties. (See Section II.) The facts here, however, do not support a discretionary denial based on those proceedings.

The Board has set forth seven factors that it considers in determining whether to exercise its discretion to deny a petition under 35 U.S.C. § 314(a) due

to an earlier proceeding involving the same patent. *General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 15-19 (Sept. 6, 2017) (precedential) (“*General Plastic*”). The *General Plastic* factors confirm that this Petition should be considered on the merits.

With respect to the first factor, Petitioner is not a party, real party-in-interest, or privy to the other Patent Office proceedings and this is Petitioner’s first challenge to the ’277 patent, which “weighs especially heavily against a discretionary denial.” See *Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7 at 7-8 (PTAB Sept. 5, 2018).

The second to fifth factors “bear little relevance” here because Petitioner has never before challenged the ’277 patent. *Id.* at 7-8. Petitioner has no relationship to the earlier challenges to the ’277 patent. Indeed, while the prior petitioners are in litigation with Patent Owner in the Western District of Texas, Petitioner is in litigation with Patent Owner in Delaware. And there is no indication that the prior petitioners were aware of the key prior art at issue here—*Landes*, which anticipates many of the claims, and *Valli*, which renders the use of formalin obvious.

As to the sixth factor, while the Board certainly has finite resources, instituting this petition would be no more a burden on these finite resources than instituting any other petition.

And as to the seventh factor, there is no readily identifiable roadblock for the Board to issue a final determination within the statutory one-year limit.

Accordingly, the Board should reach the merits of this Petition, and institute trial.

B. Discretionary Denial Under *Fintiv* Is Not Appropriate

The factors under *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (“*Fintiv*”) favor institution.

The first *Fintiv* factor favors institution. Petitioner represents that it will seek a stay in district court upon institution. Given that the district court case between Petitioner and Patent Owner is in an early stage, with the complaint having been filed approximately six months ago, and key dates very far in the future (*e.g.*, the *Markman* hearing is scheduled for April 12, 2022, and trial is scheduled to begin September 11, 2023 (*see* Ex.1051, 16-8)), there is a strong likelihood such a stay will be granted.

The second *Fintiv* factor strongly favors institution. Trial is not scheduled to begin until September 11, 2023—over two years from the filing of the petition. As such, a final written decision would precede trial.

The third *Fintiv* factor also favors institution. There is still significant investment required in the district court litigation. Claim construction, discovery,

pre-trial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice, all lie in the future. (*See* Ex.1051, 16-8.)

The fourth *Fintiv* factor favors institution. Petitioner has not yet presented final invalidity contentions given the early stage of the litigation. There is thus no overlap that warrants non-institution.

The fifth *Fintiv* factor is neutral or favors institution. Petitioner and Patent Owner are involved in district court litigation, and from that perspective this factor is neutral. To the extent Patent Owner raises district court litigation it has brought against other parties, however, this factor would favor institution.

The sixth *Fintiv* factor also favors institution. There is a significant public interest against “leaving bad patents enforceable.” *Thryv, Inc v. Click-To-Call Techs., LP*, 140 S. Ct. 1367, 1374 (2020).

C. Discretionary Denial Under 35 U.S.C. § 325(d) Is Not Appropriate

The *Lo* reference, which was part of Grounds 3 and 4, was considered during prosecution. (*See* Ex.1012, March 17, 2006 Office Action, 5, 9.) Nonetheless, discretionary denial under 35 U.S.C. § 325(d) is inappropriate for at least two reasons. First, the anticipatory *Landes* reference, discussed in Grounds 1 and 2, was not considered during prosecution. Second, and perhaps more importantly, the Examiner did not consider *Lo* in conjunction with *Valli*. This is critical since, as discussed in Section VI.C, *Valli* renders obvious the precise feature that the

Examiner stated was missing from *Lo*—that formalin could *further* reduce lysis of white blood cells *in the presence of EDTA*. (*See id.*, 9.)

For the same reasons, the factors articulated in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 18-28 (Dec. 15, 2017) (precedential), favor institution. Prior art similar to *Landes* and *Valli* was not considered during prosecution, nor are *Landes* and *Valli* cumulative to art considered during prosecution. *Id.* at 18-22. And while *Lo* was evaluated during prosecution, it was not evaluated in conjunction with *Valli*. *Id.* at 22-23. In addition, during prosecution, no glucose-based agent was considered (as in *Landes*), nor was any argument made that the prior art describes the benefits of using formalin/formaldehyde as opposed to just EDTA (as in *Valli*). *Id.* at 23-24. And, as discussed above, the Examiner only found the claims patentable over *Lo* because, as discussed in Section VI.C, the Examiner overlooked parts of *Lo* and was not aware of *Valli*, both of which provided critical discussions of the prior art. *Id.* at 24-28.

XII. CONCLUSION

Petitioner requests institution of IPR for claims 55-63, 66-69, 80-91, 94-96, 126-130, 132, and 133 of the '277 patent based on the grounds specified in this petition.

Petition for *Inter Partes* Review
Patent No. 7,332,277

Respectfully submitted,

Dated: July 20, 2021

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,332,277 contains, as measured by the word-processing system used to prepare this paper, 13,997 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: July 20, 2021

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on July 20, 2021, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,332,277 and supporting exhibits to be served via express mail on the Patent Owner at the following correspondence address of record as listed on PAIR:

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Whyte Hirschboeck Dudek
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A courtesy copy was also sent via electronic mail to the Patent Owner's litigation counsel at the following addresses:

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