

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner

v.

RAVGEN, INC.,
Patent Owner

Patent No. 7,727,720

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 7,727,720**

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LIST OF EXHIBITS

Ex. 1001	U.S. Patent No. 7,727,720 to Dhallan (“the ’720 patent”)
Ex. 1002	Assignment record of the ’720 patent from USPTO assignment database
Ex. 1003	International Publication No. WO 03/062441 to Landes et al. (“Landes”)
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> , <i>Clinical and Diagnostic Laboratory Immunology</i> , 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> , <i>Laboratory Medicine</i> , 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> , <i>British J. of Haematology</i> , 108:13-18 (2000)
Ex. 1012	File History of the ’720 patent (U.S. Patent Application No. 11/212,812)

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	International Publication No. WO 2004/078994 to Dhallan (International Application No. PCT/US2004/006337)
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, <i>Transfusion</i> , Vol. 31, No. 8, 743-747 (1991) (“ <i>Marx</i> ”)
Ex. 1030	Lo, Quantitative analysis of fetal DNA in maternal plasma and Serum, <i>Am J Hum Genet</i> 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	Yen-Leiberman, <i>et al.</i> , <i>Diagnosis of Human Cytomegalovirus Disease</i> , <i>Clinical Microbiology Newsletter</i> , Vol. 22(14), 105-109 (2000) (“ <i>Yen-Lieberman</i> ”)
Ex. 1034	U.S. Patent No. 6,156,504 to Gocke (“ <i>Gocke</i> ”)
Ex. 1035	U.S. Patent No. 6,919,17 to Shuber
Ex. 1036	Lo et al., Quantitative and Temporal Correlation between Circulating Cell-Free Epstein-Barr Virus DNA and Tumor Recurrence in Nasopharyngeal Carcinoma, <i>Cancer Research</i> 59, 5452-5455 (1999)
Ex. 1037	International Publication No. WO 1998/39474, to Lo
Ex. 1038	Giacona et al., <i>Cell-Free DNA in Human Blood Plasma</i> , <i>Pancreas</i> , Vol 17(1), 89-97 (1998)
Ex. 1039	Jen et al., An Overview on the Isolation and Analysis of Circulating Tumor DNA in Plasma and Serum, 906 <i>Ann. N.Y. Acad. Sci</i> 8 (2000)
Ex. 1040	Leon, et al., Free DNA in the Serum of Cancer Patients and the Effect of Therapy 37 <i>Cancer Research</i> 646 (1977)
Ex. 1041	Wolf, et al., <i>Early Diagnosis of Human Cytomegalovirus Disease in Transplant Recipients by DNA Amplification in Plasma</i> , <i>Transplantation</i> , Vol. 56(2), 330-334 (1993)
Ex. 1042	May 19, 2021 Scheduling Order (C.A. No. 20-1644 (D. Del.))
Ex. 1043	Declaration of Dr. Brynn Levy, M.Sc. (Med), Ph.D., FACMG
Ex. 1044	Curriculum Vitae of Dr. Brynn Levy, M.Sc. (Med), Ph.D., FACMG
Ex. 1045	Cobbs et al., <i>Human Cytomegalovirus Infection and Expression in Human Malignant Glioma</i> , <i>Cancer Research</i> 62, 3347-3350 (2002)

Ex. 1046	Griscelli et al., <i>Quantification of Human Cytomegalovirus DNA in Bone Marrow Transplant Recipients by Real-Time PCR</i> , Journal Of Clinical Microbiology, Vol 39(12), 4362-4369 (2001)
Ex. 1047	Leruez-Ville et al., <i>Monitoring Cytomegalovirus Infection in Adult and Pediatric Bone Marrow Transplant Recipients by a Real-Time PCR Assay Performed with Blood Plasma</i> , Journal of Clinical Microbiology, Vol. 41(5), 2040-2046 (2003)

Illumina, Inc. (“Petitioner”) respectfully requests *inter partes* review of claims 1, 3-9, 21, 22, and 24-30 (“the challenged claims”) of U.S. Patent No. 7,727,720 (“the ’720 patent”) (Ex. 1001), which, according to PTO records, is assigned to Ravgen, Inc. (“Patent Owner”). (Ex. 1002.)

I. INTRODUCTION

The ability to rapidly test cell-free nucleic acid in non-invasive ways has long been an important area of research in molecular biology and genetics. For years before the earliest priority date of the ’720 patent, researchers had been using conventional techniques to collect blood samples and analyze cell-free nucleic acid, such as DNA, for disease-related mutations and viruses. The challenged claims of the ’720 patent are directed to this broad concept of collecting a blood sample to analyze cell-free nucleic acid, where the sample comprises “an agent that impedes cell lysis, if cells are present.” (*See, e.g.*, Ex. 1001, 535:15-21, 535:28-46, 537:21-25, 537:33-538:40.) The use of such an agent during the collection of blood to analyze cell-free nucleic acid, however—the sole point of purported novelty—was not new at the time of Patent Owner’s filing.

This petition focuses in particular on one of the hundreds of agents identified in the ’720 patent itself as being an agent that impedes cell lysis: glucose. (*See, e.g.*, Ex. 1001 at 6:49-56 (“An agent that stabilizes cell membranes may be added to the maternal blood samples to reduce maternal cell lysis including but not

limited to . . . glucose”).) Glucose is notable because it is an ingredient in blood collection tubes commonly used at the time, including in the context of analyzing cell-free nucleic acid, such as Becton Dickinson’s Acid Citrate Dextrose (“ACD,” also referred to as Acid Citrate Dextrose Solution A (“ACDA”)) tubes. And, indeed, *Landes* and *Yen-Lieberman*, the principal prior-art references relied upon by Petitioner, describes methods of collecting blood samples for analyzing cell-free nucleic acid, such as DNA, where samples are collected in ACD tubes. (*See, e.g.*, Ex. 1003, 10:26-17:17; Ex. 1033, 107-08.)

As explained in more detail below, *Landes* and *Yen-Lieberman* anticipate the 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 ’720 patent is being asserted in the following pending litigations: *Ravgen, Inc. v. Illumina, Inc. et al.*, C.A. No. 20-1644

(D. Del.). The '720 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 '720 patent is also at issue in two *inter partes* review proceedings: IPR2021-00791 and IPR2021-01026. In addition, the '720 patent is at issue in an *ex parte* reexamination: No. 90/014,703. Petitioner is not a party, real party-in-interest, or privy to any of those proceedings.

The present '720 patent issued in 2008 from Application No. 11/212,812. The '720 patent claims priority to U.S. Application No. 10/661,165, which issued as U.S. Patent No. 7,332,277 ("the '277 patent"). The '277 patent is the subject of a separate *inter partes* review petition filed by Petitioner. In addition, the '277 patent is at issue in further *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 these Patent Office proceedings. The '277 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.

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 '720 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 1, 3-9, 21, 22, and 24-30 of the '720 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 1, 3-8, 21, and 24 are unpatentable under pre-AIA 35 U.S.C. § 102 as being anticipated by *Landes* (Ex. 1003).

Ground 2: Claim 22 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 1, 3-6, and 24 are unpatentable under pre-AIA 35 U.S.C. § 102 as being anticipated by *Yen-Lieberman* (Ex. 1033).

Ground 4: Claims 7-9, 21, 25-30 are unpatentable under pre-AIA 35 U.S.C. § 103 as being obvious in view of *Yen-Lieberman* (Ex. 1033) and *Gocke* (Ex. 1034).

Ground 5: Claim 22 is unpatentable under pre-AIA 35 U.S.C. § 103 as being obvious in view of *Yen-Lieberman* (Ex. 1033), *Gocke* (Ex. 1034), and *Marx* (Ex. 1029).

Landes, *Marx*, and *Yen-Lieberman* were not considered by the Patent Office during prosecution. (Ex. 1001, Cover (“References Cited” section).) Although *Gocke* appears in the “References Cited” section, the Patent Office did not consider *Gocke* in combination with a reference where a sample was collected with “an agent that impedes cell lysis” according to the ’720 patent, such as the method discussed in *Yen-Lieberman* (and *Landes*). *Landes* qualifies as prior art under at least 35 U.S.C. §§ 102(a) and/or (e), and *Marx*, *Yen-Lieberman*, and *Gocke* qualify as prior art under 35 U.S.C. § 102(b). (See Section VIII.)

VI. BACKGROUND

A. Overview of the Technology

Chromosomal abnormalities and other disease-related mutations and viruses are responsible for a substantial percentage of genetic defects, cancers, and other diseases. (Ex. 1001, 1:32-37, 24:41-57; Ex. 1003, 1:12-13; Ex. 1033, 105; Ex. 1034, Abstract, 7:33-60; *see also* Ex. 1043, ¶ 19.)¹ Researchers in the field of molecular biology and genetics in the late 1990s and early 2000s were focused on rapid and non-invasive testing methods that used cell-free nucleic acid present in blood plasma/serum to reveal potential genetic abnormalities or viruses to help with early detection or monitoring during and after treatment. (Ex. 1001, 2:42-51, 24:41-57; Ex. 1003, 2:1-28; Ex. 1033, 105; Ex. 1034, Abstract, 7:33-60; *see also* Ex. 1043, ¶ 19.) At that time, it was understood in the field that viruses and cancers could be detected by analyzing cell-free nucleic acid, such as DNA, in plasma or serum. (Ex. 1001, 4:59-5:35, 24:41-57; Ex. 1033, 105; Ex. 1003, 2:4-9; Ex. 1034, Abstract, 7:33-60; Ex. 1030, 768-9; Ex. 1019, 280-1; *see also* Ex. 1043, ¶ 20.) Researchers employed conventional techniques that were in use for decades to obtain blood samples and analyze the cell-free DNA for the purpose of assessing

¹ Petitioner submits the declaration of Dr. Brynn Levy, M.Sc. (Med), Ph.D., FACMG, an expert in the field of the '720 patent. (Ex. 1043, ¶¶ 3-8; Ex. 1044.)

abnormalities and other disease-related conditions. (Ex. 1001, 5:23-44, 24:41-57; Ex. 1003, 2:25-30; Ex. 1033, 107-08; Ex. 1034, Abstract, 7:33-60; *see also* Ex. 1019, 280 (“Serum or plasma samples have been widely used to characterize the concentration of cell-free genomic DNA or viral nucleic acid as a way to monitor various diseases, including malignancy . . . and viral infections.”); Ex. 1043, ¶¶ 20-1, 81.)

Landes, Yen-Lieberman, and the ’720 patent describe such methods using techniques that were conventional in the art at the relevant time. DNA isolation protocols were well-known and could be practiced at the time of the alleged invention using commercially available tools. (*See* Ex. 1003, 10:26-11:11; Ex. 1033, 107-08; *see also* Ex. 1043, ¶ 21.) The isolation and analysis of DNA can be performed by any number of conventional tools, including, polymerase chain reaction (“PCR”), mass spectrometry, hybridization, single base extension, and fluorescent probe binding, among others. (*See, e.g.*, Ex. 1003, 1:16-24, 2:9-30, 3:24-31, 9:31-10:3; *see also* Ex. 1001, 7:24-33; Ex. 1043, ¶ 21.) *Yen-Lieberman* also discusses a commercially available AMPLICOR CMV test, which “use[d] PCR nucleic acid amplification for qualitative detection of [human cytomegalovirus (‘HCMV’)] DNA in plasma separated from anticoagulated whole blood (EDTA or ACD anticoagulants).” (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶ 21.)

When collecting a blood sample for analysis, it was routine to do so in the presence of one or more preservative agents in appropriate blood collection tubes. (Ex. 1003, 10:28-30; Ex. 1033, 107; *see also* Ex. 1043, ¶ 22.) One such commercially available blood collection tube at the time was Becton Dickinson's ACD or ACDA tubes, which contained dextrose.² (*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. 1043, ¶¶ 23-5.)

B. Overview of the '720 Patent

The '720 patent purports to claim a novel method of collecting a blood sample to analyze cell-free nucleic acid, where the sample comprises an agent that impedes cell lysis, described in the claim as, *inter alia*, a “cell lysis inhibitor.” The first challenged independent claim, claim 1, reads as follows:

1. A method for detecting a free nucleic acid, wherein said method comprises: (a) isolating free nucleic acid from a non-cellular fraction of a sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said

² Dextrose is the naturally occurring dextrorotatory form of glucose, and these terms would have been understood by a POSA to be synonyms in the field of the '720 patent. (*See, e.g.*, Ex. 1031, 445; Ex. 1032, 268, 416; Ex. 1016, 231; *see also* Ex. 1043, ¶ 24.)

agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor; and (b) detecting the presence or absence of the free nucleic acid.

(Ex. 1001, 535:15-21.) The challenged dependent claims of claim 1, including claims 3-9, 21, 22, and 24-30, do not add anything of significance and instead recite basic features, such as specifying that the sample is blood or that the method is used to detect cancer. (*See id.* at, 535:28-46, 537:21-25, 537:33-538:40.) The '720 patent recognized that the claimed method was applicable for both cell-free tumor and viral nucleic acid, such as DNA. (*See, e.g.*, Ex. 1001, 23:37-60, 24:41-57; *see also id.* at 23:60-62, 142-143 (Table XV); Ex. 1043, ¶ 26.)

The specification identifies hundreds of agents that it states were known to inhibit cell lysis, including **glucose**. (*See, e.g., id.* at 11:57-12:5 (“An agent that stabilizes cell membranes may be added to the sample including but not limited to . . . **glucose**”), 33:12-29 (“[A]n agent that stabilizes cell membranes may be added to the maternal blood samples to reduce maternal cell lysis including but not limited to . . . **glucose**”); *see also id.* at 216-218 (Table XXIII); Ex. 1043, ¶ 27.)

Although the challenged claims recite an agent that impedes or inhibits lysis of cells, they do not require any specific level of cell lysis inhibition (or amount of cell-free nucleic acid collected from the sample). (*See* Ex. 1043, ¶ 28.) Rather, as

explained above and discussed in more detail in Section X below, the challenged claims broadly cover a previously known method of collecting a sample in the presence of “an agent that impedes cell lysis”, as described in the prior art, including in *Landes* and *Yen-Lieberman*.

C. Prosecution History of the '720 patent

During prosecution, the Examiner issued various 35 U.S.C. §§ 102 and 103 rejections based on prior art references that describe the analysis of cell-free nucleic acid from blood samples. (*See generally* Ex. 1012.) Additionally, the Examiner issued a Non-Statutory Obviousness-type Double Patenting rejection in view of the previously issued '277 patent.

In response, Patent Owner argued that “Applicant has discovered that the addition of a cell lysis inhibitor to a sample prior to detecting the presence of free nucleic acid can significantly and unexpectedly increase the proportion of free nucleic acid obtained from the non-cellular fraction of a sample.” (*See, e.g.*, Ex. 1012, June 2, 2009 Response to Non-final Office Action, 12.) In support of this assertion, Patent Owner cited Example 4 and Example 15 of the specification. (*See id.*)

After the Patent Owner filed a terminal disclaimer over the '277 patent, the Examiner allowed the challenged claims to issue in light of, *inter alia*, “the persuasive argument(s)” in the June 2, 2009 Response to Non-final Office Action.

(*See id.*, September 11, 2009 Office Action, 2; *id.*, December 15, 2009 Notice of Allowance.) The Examiner, however, did not evaluate the challenged claims in light of the primary prior art at issue here, *Landes* and *Yen-Lieberman*, where cell-free nucleic acid, such as DNA, was analyzed from a blood sample containing glucose—which the '720 patent identifies as “an agent that impedes cell lysis”.

D. The '720 Patent Priority Date

The '720 patent was filed as U.S. App. No. 11/212,812 on August 26, 2005, and issued on June 1, 2010. (Ex. 1001, Cover.) The '720 patent is a continuation of International Application No. PCT/US2004/006337, filed on March 1, 2004, which is in turn a continuation-in-part of International Application No. PCT/US/03/06198, filed on February 28, 2003, which claims priority to U.S. Provisional Application No. 60/378,354, filed on May 8, 2002. The cover page of the '720 patent also identifies several other applications (which differs from the identification of “related applications” in the '720 patent’s specification, Ex. 1001 at 1:7-18), including a provisional application filed March 1, 2002.³ As discussed

³ This petition assumes that the '720 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 any disclosure that could support the claim language “an agent that inhibits lysis of

below, *Landes* qualifies 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.A-C.)

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.)

For the purposes of this proceeding only, Petitioner does not dispute this definition of a POSA. (Ex. 1043, ¶¶ 13-6.) Based on this asserted level of skill, the POSA at the relevant time would have had academic or industry experience collecting and analyzing cell-free nucleic acid, such as DNA, from blood samples.

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.

(*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 ’720 patent can claim priority, and serves as prior art against the ’720 patent under at least 35 U.S.C. §§ 102(a) and/or (e).

Landes discusses “non-invasive methods to distinguish fetal DNA from maternal DNA and thereby detect fetal aneuploidies and alleles.” (Ex. 1003, Abstract; *see also* Ex. 1043, ¶¶ 29-33.) 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.) *Landes* states that such analyses can be conducted by using cell-free fetal DNA from “maternal serum or plasma,” “a

relatively rich source of fetal DNA.” (*Id.*, 2:19-20.) *Landes* explains that such 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.” (*Id.* at 2:20-25 (“[T]he lowest fetal DNA concentration in plasma as measured by PCR was greater than 20 fetal cell equivalents per mL of maternal blood with some instances where fetal DNA constituted as much as 5% of the total DNA in plasma.”).) *Landes* distinguishes this cell-free fetal DNA from DNA obtained from “samples of fetal cells.” (Ex. 1003, 1:14; *see also* Ex. 1043, ¶¶ 29-33.)

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.” (Ex. 1003, 2:25-28.) For example, *Landes* describes isolating cell-free DNA from maternal serum or plasma, and treating it with a reagent. (*See, e.g., id.*, 3:3-4, 10:23-13:28.) Analysis of the isolated cell-free DNA is undertaken, including amplification “using quantitative PCR and primers selected to amplify target sequences on a potentially abnormal chromosome.” (*See, e.g., id.*, 3:5-6, 14:15-23; *see also id.*, 13:29-17:16.)

In preparation for the isolation of cell-free fetal DNA, *Landes* describes a “Plasma Separation Protocol,” where the “[m]aternal blood is collected into ACDA blood collection tube (Becton Dickinson, Franklin Lakes, NJ).” (Ex. 1003, 10:28-

29; *see also* Ex. 1043, ¶¶ 29-33.) This is a reference to Becton Dickinson’s Acid Citrate Dextrose Solution A (“ACDA”) blood collection tubes (Ex. 1043, ¶¶ 33, 23-5), which are explained to contain dextrose (*i.e.*, glucose) and be used for DNA testing:

- U.S. Patent No. 5,667,963 (assigned to Becton Dickinson) provides that Solution A of “ACD or acid-citrate-dextrose” contains “24.5 gm” of dextrose (*i.e.*, glucose) per liter (Ex. 1007, 4:30-39);
- An exemplary article describes its collection of blood samples “in tubes containing anticoagulant citrate-dextrose solution, formula A (ACD-A) (Becton Dickinson Vacutainer Systems, Franklin Lakes, N.J.)” (Ex. 1008, 808));
- A screen capture of Becton Dickinson’s Vacutainer Systems website from 2002 provides that “Acid citrate dextrose additives (ACD): Solution A” contains “24.5g/L dextrose” and identifies the tubes use for “DNA and paternity testing” (Ex. 1009, 4);
- An article discusses blood collection devices and describes Becton Dickinson’s “Acid citrate dextrose” for the purpose of “DNA, and paternity testing” (Ex. 1010, Table 2 and 622);
- An article discussing blood collection in “acid/citrate dextrose,” which discusses the dextrose as “glucose” (Ex. 1017, 430).

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 effect of glucose); Ex. 1019, Figs. 4 and 5 (same); Ex. 1022, 68, 74 (same); Ex. 1027, 31 (same); Ex. 1028, 112 (noting that ACD “did not [a]ffect DNA isolation nor PCR amplification”); *see also* Ex. 1043, ¶ 25.) Consistent with the ’720 patent’s reference to glucose as “an agent that stabilizes cell membranes” that “reduce[s] maternal cell lysis” (Ex.1001, 33:12-29), *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 may properly claim 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. 1043, ¶¶ 34-6.) 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, as explained below, each claim of *Landes* finds support in the ’877 provisional application.

Specifically, *Landes* meets the test laid out in *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015) detailing when a non-provisional application can claim the benefit of its earlier provisional filing for

purposes of serving as prior art in the instant proceeding. In *Dynamic Drinkware*, the court stated that “[a] reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with § 112.” *Dynamic Drinkware, LLC*, 800 F.3d at 1382. The following chart demonstrates the enabling support in the provisional application for each claim in the anticipatory *Landes* reference.

<i>Landes</i> Claim 1 (Ex. 1003, 22:4-12)	Support in the '877 Provisional (Ex. 1006)
A method of detecting fetal aneuploidies comprising	<i>See, e.g.</i> , 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;	<i>See, e.g.</i> , 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;	<i>See, e.g.</i> , 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	<i>See, e.g.</i> , 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.	<i>See, e.g.</i> , 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

<i>Landes Claim 2</i> (Ex. 1003, 22:14-23)	Support in the '877 Provisional (Ex. 1006)
A method for detecting fetal aneuploidies comprising:	<i>See, e.g.</i> , 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;	<i>See, e.g.</i> , 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;	<i>See, e.g.</i> , 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
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	<i>See, e.g.</i> , 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
d) determining the ratio of the quantity of PCR product produced for the test chromosome compared with the control chromosome.	<i>See, e.g.</i> , 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

<i>Landes Claim 3</i> (Ex. 1003, 22:25-30)	Support in the '877 Provisional (Ex. 1006)
A method for detecting alleles of a gene of interest in fetal DNA comprising:	<i>See, e.g.</i> , 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
a) treating DNA isolated from maternal serum with bisulfite;	<i>See, e.g.</i> , 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

b) performing PCR with a primer pair that amplifies the gene of interest of step b); and	<i>See, e.g.</i> , 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
c) analyzing the resulting PCR product to identify the allele of the gene of interest.	<i>See, e.g.</i> , 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

<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:	<i>See, e.g.</i> , 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;	<i>See, e.g.</i> , 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	<i>See, e.g.</i> , 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.	<i>See, e.g.</i> , 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 the following sections 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 *Yen-Lieberman*

Yen-Lieberman, titled “Diagnosis of Human Cytomegalovirus Disease,” was published in 2000 and serves as prior art against the ’720 patent under at least 35 U.S.C. § 102(b). *Yen-Lieberman* is generally directed to methods using commercially available molecular diagnostic test kits for detection of human cytomegalovirus (“HCMV”).⁴ (Ex. 1033, 108.) This includes the AMPLICOR CMV test, which “uses PCR nucleic acid amplification for qualitative detection of HCMV DNA in plasma separated from anticoagulated whole blood (EDTA or ACD anticoagulants).” (See, e.g., Ex. 1033, 107; see also Ex. 1043, ¶ 38.) This is a method of detecting HCMV by analyzing cell-free viral DNA. (Ex. 1043, ¶ 38.) As discussed in Section VIII.A above, ACD blood collection tubes contain glucose (see, e.g., Ex. 1043, ¶¶ 33, 23-5), which the ’720 patent identifies as “an agent that impedes cell lysis”.

D. Overview of *Gocke*

Gocke, titled “Detection of Extracellular Tumor-Associated Nucleic Acid in Blood Plasma or Serum Using Nucleic Acid Amplification Assays,” was filed on

⁴ HCMV can cause mild “flulike” symptoms, serious illness in immunocompromised patients, and was associated with malignant tumors. (See Ex. 1033, 105; see also Ex. 1043, ¶ 38.)

March 14, 1997, and issued on December 5, 2000 (Ex. 1034, Cover), and serves as prior art against the '720 patent under at least 35 U.S.C. § 102(b). *Gocke* discusses methods for the detection of circulating (or cell-free) tumor nucleic acid, such as DNA, from a blood sample. (Ex. 1034, Abstract.) *Gocke* states that this method can also be used to detect cell-free viral nucleic acid. (*See, e.g., id.* at 7:33-60; *see also* Ex. 1043, ¶ 39.)

E. Overview of *Marx*

Marx, titled “Reducing white cells in platelet units,” was published in 1991. (Ex. 1029, 743.) Thus, *Marx* predates the earliest possible date of any application to which the '720 patent can claim priority, and serves as prior art against the '720 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; *see also* Ex. 1043, ¶ 37.)

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*). *See* 83 Fed. Reg. 51,340-59 (Oct. 11, 2018). Under *Phillips*, claim terms are typically given their ordinary and customary meanings, as would have been understood by a POSA, at the time of the invention, having taken into consideration the language of

the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313; *see also id.* at 1312-16.

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) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Here, given the correlation between the *Landes* reference and the challenged claims of the '720 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.⁵

X. DETAILED EXPLANATION OF GROUNDS

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

A. Ground 1: *Landes* Anticipates Claims 1, 3-8, 21, and 24

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 1,

⁵ 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.

3-8, 21, and 24 is present in *Landes*, these claims are invalid as anticipated by *Landes*.

1. Claim 1

- i) **[1.pre] “A method for detecting a free nucleic acid, wherein said method comprises:”**

As a preamble, this part of the claim is generally not limiting. Regardless, *Landes* recites a “method for detecting a free nucleic acid,” as recited in the preamble. For example, *Landes* discusses non-invasive methods to detect cell-free fetal DNA (*i.e.*, deoxyribonucleic acid, which is a type of nucleic acid) and “thereby detect fetal aneuploidies and alleles.” (*See, e.g.*, Ex. 1003, Abstract; Ex. 1006, Abstract, 2:21-3:22; *see also* Ex. 1043, ¶ 41.)

- ii) **[1.a] “(a) isolating free nucleic acid from a noncellular fraction of a sample”**

Landes discusses a method of isolating free nucleic acid from a noncellular fraction of a sample. For example, *Landes* provides exemplary methods for isolating free nucleic acid from a noncellular fraction of a sample of maternal blood under the heading, “Isolation of Fetal DNA from Maternal Blood.” (Ex. 1003, 10:26; Ex. 1006, 10:6; *see also* Ex. 1043, ¶¶ 42-5.) First, *Landes* describes a “Plasma Separation Protocol” where “[m]aternal blood is collected into ACDA blood collection tube,” which provides the requisite noncellular fraction of a sample from which the cell-free nucleic acid is then isolated. (Ex. 1003, 10:28-

11:2; *see also id.*, 3:2; Ex. 1006, 10:8, 2:21-3:22.) Then, *Landes* provides a “DNA isolation protocol,” where cell-free DNA is isolated using “commercially available” kits. (Ex. 1003, 11:3-12:6; Ex. 1006, 10:15-11:15.)

- iii) **[1.b] “wherein said sample comprises an agent that impedes cell lysis, 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 above, *Landes* discusses a method of isolating cell-free nucleic acid from a noncellular fraction of a sample of maternal blood, which was known to comprise cell-free fetal DNA. (Ex. 1003, 2:19-31, 10:26-28; *see also id.*, 3:2; Ex. 1006, 10:8, 2:21-23; *see also* Ex. 1043, ¶¶ 42-45.)

Landes also discusses that the blood sample comprises 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, 10:8-9.) 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. 1043, ¶¶ 33, 23-25.)

The ’720 patent identifies glucose as “an agent that impedes cell lysis” according to the alleged invention. (*See, e.g.*, Ex. 1001, 33:12-28 (“In another

embodiment, an agent that stabilizes cell membranes may be added to the maternal blood samples to *reduce maternal cell lysis* including . . . *glucose*”) (emphases added.) *Landes* therefore discusses the same method as is claimed in the ’720 patent, where “an agent that impedes cell lysis” is present in a 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 19:19-20 (providing additional examples where maternal blood was collected in ACDA tubes); *see also* Ex. 1043, ¶¶ 46-51.)

As shown above, *Landes* expressly describes the use of “an agent that impedes cell lysis” (*i.e.*, glucose) according to the ’720 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 Pharmaceuticals*, 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 noncellular fraction of a sample of maternal blood 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. 1043, ¶¶ 49-50.) As in *King Pharmaceuticals*, the method in *Landes* anticipates even though it does not expressly 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 impedes cell lysis", that 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

'720 patent states that glucose was a known “agent that stabilizes cell membranes” and “reduce[s] maternal cell lysis” (*see, e.g.*, Ex. 1001, 11:57-12:5, 33:12-28; *see also* Ex. 1043, ¶¶ 23-5, 49-50),⁶ 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 discussed 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, according to the '720 patent, “an agent that impedes cell lysis” as claimed in the '720 patent is found in *Landes*. When a POSA practices the method

⁶ “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).

in *Landes*, glucose is introduced to a sample containing cell-free nucleic acid 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 method of isolating cell-free nucleic acid, such as DNA, from a sample that comprises “an agent that impedes cell lysis”, *i.e.*, glucose.

iv) **[1.c] “and (b) detecting the presence or absence of the free nucleic acid.”**

As explained in Sections X.A.1.i and X.A.1.ii above, *Landes* describes methods of isolating and analyzing cell-free fetal nucleic acid (specifically DNA) to identify fetal aneuploidies and alleles. (*See, e.g.*, Ex. 1003, 10:26; Ex. 1006, 10:6; *see also* Ex. 1043, ¶ 52.) This method detects the presence (or absence) of cell-free fetal nucleic acid. (Ex. 1043, ¶ 52.)

2. Claim 3: “The method of claim 2, wherein the sample is obtained from a human source.”

As discussed in Section X.A.1.ii above, *Landes* discusses obtaining a sample that comprises cell-free nucleic acid from a human source, a pregnant human

female.⁷ (*See, e.g.*, Ex. 1003, 3:2-9, 8:22-24, 10:26-30; Ex. 1006, 10:8-14, 2:21-23; *see also* Ex. 1043, ¶¶ 53, 41-52.)⁸

3. **Claim 4: “The method of claim 1, wherein the sample is obtained from a source selected from the group consisting of: tissue, blood, serum, plasma, saliva, urine, tear, vaginal secretion, umbilical cord blood, chorionic villi, amniotic fluid, embryonic tissue, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascitic fluid, fecal matter, and body exudates.”**

As discussed in Section X.A.1.ii above, *Landes* describes a method of obtaining a sample that comprises cell-free nucleic acid from maternal blood, serum, or plasma. (*See, e.g.*, Ex. 1003, 3:3 (“DNA is first isolated from maternal serum”); *id.*, 10:26-32 (“Plasma Separation Protocol: Maternal blood is collected”); *id.* at 14:15-24, 16:18-19:17 (Ex. 4) (describing “Detection of ERG

⁷ When defining “subject,” from whom a sample for the recited 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, 7:19-21, 2:7-18; Ex. 1043, ¶ 53.)

⁸ Petitioner recognizes that claim 3 depends from claim 2, which is not challenged in this petition. The analysis provided herein, however, addresses the limitations of claim 2 by showing that the “sample is obtained from a source selected from the group consistent of ... humans.”

Methylation Profile”); *id.* at Fig. 2b, Fig. 3; Ex. 1006, 10:8, 2:21-23; *see also* Ex. 1043, ¶¶ 54, 41-52.)

4. Claim 5: “The method of claim 4, 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, 10:8, 2:21-23; *see also* Ex. 1043, ¶¶ 55, 41-52.)

5. Claim 6: “The method of claim 5, wherein said sample is obtained from plasma from said blood.”

As discussed in Section X.A.1.ii above, *Landes* describes a method of obtaining a sample that comprises cell-free nucleic acid from plasma from the maternal blood sample. (*See, e.g.*, Ex. 1003, 10:26-12:6 (“Plasma Separation Protocol”), 14:15-24, 16:18-19:17 (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. 1043, ¶¶ 56, 41-52.)

6. Claim 7: “The method of claim 1, wherein said nucleic acid contains at least one mutation.”

The method discussed in *Landes* analyzes cell-free fetal nucleic acid for mutations, including a point mutation or other small mutation. (*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, 10:17-18 (“The PCR product is analyzed to identify the polymorphism”), 4:22-5:6, 10:6-19 (“Specific examples include mutant alleles”), 14:26-15:3 (“Several primer sequences have been demonstrated for detection of aneuploidies or disease genes”), 16:18-19:17 (Ex. 4) (describing “Detection of ERG Methylation Profile”), 19:15-18, Figs. 1-3; Ex. 1006, 1:16-18, 3:4-22, 4:9-23, 9:13-28, 14:1-8, 15:21-18:17 (Ex. 4), 18:15-18, Figs. 1-3; *see also* Ex. 1043, ¶¶ 57, 41-52.)

7. Claim 8: “The method of claim 7, wherein said mutation is selected from the group consisting of: single point mutation, multiple point mutations, an insertion, a frameshift, a truncation, a deletion, a duplication, and a transversion.”

As discussed in Sections X.A.1 and X.A.6 above, *Landes* describes detecting the presence or absence of a cell-free nucleic acid with one or more point mutations or other small mutation. (*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, 10:17-18 (“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, 2:30, 3:17-22, 18:15-18, Fig. 1a, Fig. 1b, Fig. 2a; *see also* Ex. 1043, ¶¶ 58, 41-52.)

8. Claim 21: “The method of claim 1, wherein isolation of free nucleic acid comprises a centrifugation step.”

Landes discusses a method that isolates cell-free nucleic acid 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, 10:8-14; *see also* Ex. 1043, ¶ 59.)

9. Claim 24: “The method of claim 1, wherein said method is used to detect, diagnose, or monitor a disease.”

As discussed in Sections X.A.1 and X.A.6 above, *Landes* discusses a method that is used to detect, diagnose, or monitor a disease. For example, *Landes* provides that the detection of cell-free nucleic acid is done to identify specific nucleic acid defects associated with and used to detect or diagnose a disease. (*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”), 14:26-15:3 (“Several primer sequences have been demonstrated for detection of aneuploidies or disease genes”), 16:18-19:17 (Ex. 4) (describing “Detection of ERG Methylation Profile”), 19:15-18, Figs. 1-3; Ex. 1006, 1:16-18, 3:4-22, 4:9-23, 9:13-28, 14:1-8, 15:21-18:18, Ex. 4, Figs. 1-3; *see also* Ex. 1043, ¶¶ 60, 41-52.)

B. Ground 2: *Landes* in View of *Marx* Renders Claim 22 Obvious

1. Claim 22: “The method of claim 21, wherein the centrifugation step is performed with the centrifuge braking power set to zero.”

As discussed in Section X.A.8 above with respect to claim 21, *Landes* describes methods with various centrifugation steps. (*See, e.g.*, Ex. 1003, 10:20-11:2; Ex. 1006, 10:8-14.) Although *Landes* does not explicitly discuss that such centrifugation is performed “with the centrifuge braking power set to zero,” as recited in claim 22, a POSA would have understood the absence of instruction for setting the centrifuge brake to at least suggest no brake should be used. (Ex. 1043, ¶¶ 61-66, 97-100.) 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. 1043, ¶ 62.) 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. 1043, ¶ 63-4.)

Marx is generally directed to an analysis of variations in centrifugation braking rates during blood processing. (Ex. 1029, 743.) As such, a POSA would have had reason to consider *Marx*, which is in the same field as *Landes* and the ’720 patent. (Ex. 1043, ¶¶ 63-4.) *Marx* describes experiments where samples are centrifuged at various braking rates, including no braking. (Ex. 1029, 743-46.) Following such centrifugation, *Marx* concluded that, “[u]pon strong braking, the

separated cell layers are perturbed by the rapid deceleration” (*id.* at 747), and that “no brakes gave much more reasonable yields of platelets . . . as well as low WBC contamination” (*id.* at 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. 1043, ¶¶ 63-6, 99). 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. 1043, ¶¶ 61-6.) 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. 1043, ¶ 66.)

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. 1043, ¶¶ 64-6.) 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) (whether a component of a device was located on the top or bottom was “exactly the type of ‘finite number of identified, predictable solutions’ that justifies a legal conclusion that the result, when expected, is ‘the product not of innovation but of ordinary skill and common sense’”) (citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). In fact, 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, 21:15-26; *see also* Ex. 1043, ¶¶ 64-6.)

A POSA would have had a reasonable expectation of success with setting a braking power to zero. (Ex. 1043, ¶ 66.) 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. 1043, ¶ 66.) 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 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, 21:15-26). (Ex. 1043, ¶ 66.) In this context, leaving a centrifuge brake powered off would have been seen as a straightforward improvement. (Ex. 1043, ¶¶ 62-6.)

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) (“[W]here a claimed invention represents no more than the predictable use of prior art elements according to established functions, as here, evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness.”).

C. Ground 3: *Yen-Lieberman* Anticipates Claims 1, 3-6, and 24

Because each limitation of claims 1, 3-6, and 24 is present in *Yen-Lieberman*, these claims are invalid as anticipated by *Yen-Lieberman*. *See, e.g., Atofina*, 441 F.3d at 999.

1. Claim 1

- i) **[1.pre] “A method for detecting a free nucleic acid, wherein said method comprises:”**

As a preamble, this part of the claim is generally not limiting. Regardless, *Yen-Lieberman* states a “method for detecting a free nucleic acid,” as recited in the preamble. For example, *Yen-Lieberman* discusses “currently commercially available molecular diagnostic test kits for HCMV,” which use “PCR nucleic acid amplification for qualitative detection of HCMV DNA in plasma.” (*See, e.g.*, Ex. 1033, 107-8; *see also* Ex. 1043, ¶¶ 38, 68-9.) This is a method of detecting cell-free viral nucleic acid, such as DNA. (Ex. 1043, ¶¶ 38, 68.)

- ii) **[1.a] “(a) isolating free nucleic acid from a noncellular fraction of a sample”**

Yen-Lieberman describes a method of isolating cell-free nucleic acid from a noncellular fraction of a sample. For example, *Yen-Lieberman* describes a AMPLICOR CMV test, which “uses PCR nucleic acid amplification for qualitative detection of HCMV DNA in plasma separated from anticoagulated whole blood (EDTA or ACD anticoagulants).” (*See, e.g.*, Ex. 1033, 107-8; *see also* Ex. 1043, ¶ 69.) As seen in Table 1, the AMPLICOR test kit is a qualitative analysis of 50 µl of plasma (a noncellular fraction of the blood sample) that targets cell-free DNA (a type of nucleic acid). (*See, e.g.*, Ex. 1033, 108; *see also* Ex. 1043, ¶ 69.)

- iii) **[1.b] “wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein**

said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor;”

Yen-Lieberman describes a method where the blood sample comprises glucose, “an agent that impedes cell lysis” according to the ’720 patent. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶ 70.) For example, the AMPLICOR CMV detects DNA from plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 70-2.) This is a reference to Becton Dickinson’s ACD 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. 1043, ¶¶ 70, 23-5.)

For the same reasons explained in Section X.A.1 above with respect to *Landes*, *Yen-Lieberman* discusses a method using glucose, which the ’720 patent provides is “an agent that impedes cell lysis.” (*See, e.g.*, Ex. 1001, 11:57-12:5, 33:12-28.) Here, by instructing the collection of blood in an ACD tube, *Yen-Lieberman* necessarily describes the presence of glucose in said blood sample. Whether or not *Yen-Lieberman* intended, or even recognized, that property is “wholly irrelevant.” *Abbot Labs.*, 471 F.3d at 1365; *see also Schering*, 339 F.3d at 1377; *King Pharms.*, 616 F.3d at 1276.

Thus, *Yen-Lieberman* described a method of isolating cell-free nucleic acid from a sample that comprises “an agent that impedes cell lysis”, *i.e.*, glucose.

iv) **[1.c] “and (b) detecting the presence or absence of the free nucleic acid.”**

As explained in Sections X.C.1.i and X.C.1.ii above, the AMPLICOR test described in *Yen-Lieberman* is used to detect HCMV DNA in plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 73, 70-1.) This method detects the presence (or absence) of cell-free viral nucleic acid. (Ex. 1043, ¶ 73.)

2. **Claim 3: “The method of claim 2, wherein the sample is obtained from a human source.”**

As discussed in Section X.C.1.ii above, the AMPLICOR test described in *Yen-Lieberman* is used to detect human cytomegalovirus DNA in human plasma. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 74, 68-9.)⁹

3. **Claim 4: “The method of claim 1, wherein the sample is obtained from a source selected from the group consisting of: tissue, blood, serum, plasma, saliva, urine, tear, vaginal secretion, umbilical cord blood, chorionic villi, amniotic fluid, embryonic tissue, lymph fluid, cerebrospinal fluid,**

⁹ Petitioner recognizes that claim 3 depends from claim 2, which is not challenged in this petition. The analysis provided herein, however, addresses the limitations of claim 2 by showing that the “sample is obtained from a source selected from the group consistent of ... humans.”

**mucosa secretion, peritoneal fluid, ascitic fluid, fecal matter,
and body exudates.”**

As discussed in Section X.C.1.iii above, the AMPLICOR test described in *Yen-Lieberman* is used to detect HCMV DNA in plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 75, 68-9.)

4. Claim 5: “The method of claim 4, wherein said sample is blood.”

As discussed in Section X.C.1 above, the AMPLICOR test described in *Yen-Lieberman* is used to detect HCMV DNA in plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 76, 68-9.)

5. Claim 6: “The method of claim 5, wherein said sample is obtained from plasma from said blood.”

As discussed in Section X.C.1 above, the AMPLICOR test described in *Yen-Lieberman* is used to detect HCMV DNA in plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 77, 68-9.)

6. Claim 24: “The method of claim 1, wherein said method is used to detect, diagnose, or monitor a disease.”

As discussed in Section X.C.1 above, the AMPLICOR test described in *Yen-Lieberman* is used to detect HCMV DNA in plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 78, 70-1.)

HCMV is a disease that causes mild “flulike” symptoms, but can cause serious

illness in immunocompromised patients and was associated with malignant tumors.

(*See* Ex. 1033, 105; *see also* Ex. 1043, ¶¶ 78, 81.)

D. Ground 4: *Yen-Lieberman* in View of *Gocke* Renders Claims 7, 8, 9, 21, and 25-30 Obvious¹⁰

1. Claim 25: “The method of claim 24, wherein said disease is cancer.”

As discussed in Sections X.C.1 and X.C.6 above with respect to claim 24, *Yen-Lieberman* described a method of detecting HCMV DNA in plasma prepared from blood collected in an ACD tube. (*See, e.g.*, Ex. 1033, 107; *see also* Ex. 1043, ¶¶ 79-87.) Although *Yen-Lieberman* does not explicitly discuss that such a method can be used to detect cancer, a POSA would have understood that HCMV was associated with malignant tumors. (*See, e.g.*, Ex. 1033, 105; Ex. 1045, 3347; *see also* Ex. 1043, ¶ 81.) Additionally, cancer patients requiring immune-compromising treatments, such as bone marrow transplants, have been monitored for HCMV disease onset. (*See, e.g.*, Ex. 1041, 330; Ex. 1046, 4362; Ex. 1047, 2040; *see also* Ex. 1043, ¶ 81.)

The POSA would have understood that the method described in *Yen-Lieberman* could have been applied to the detection, diagnosis, or monitoring of

¹⁰ For convenience, Petitioner addresses claim 25 first, since the analysis of the remaining claims leverages the analysis provided for claim 25.

cell-free tumor DNA, and that such an application would have been obvious to try in view of the general knowledge in the art, such as *Gocke*. (See, e.g., Ex. 1034, Abstract, 7:33-60 (“Nucleic acid from any biological source, including . . . viral . . . nucleic acid, can be detected using the inventive method”); see also Ex. 1019, 280 (“Serum or plasma samples have been widely used to characterize the concentration of cell-free genomic DNA or viral nucleic acid as a way to monitor various diseases, including malignancy . . . and viral infections.”); Ex. 1035, 4:66-5:5, 7:44-54, 7:66-8:18 (providing a method of cell-free nucleic acid analysis to screen for cancers, “monitor viral” load, including for HIV, and “assess fetal abnormalities”); Ex. 1036, 5452 (demonstrating that viral DNA is detectable in plasma/serum “[p]rompted by recent reports that tumor-derived DNA is present in the plasma and serum of cancer patients” using cell-free fetal DNA protocols); Ex. 1037, 3:11-6, 36:6-8 (citing viral DNA protocols for preparation of maternal blood sample for analysis of cell-free fetal DNA); Ex. 1038, 89 (discussing circumstances where cell-free DNA is elevated, including in patients with cancer and viral hepatitis); Ex. 1039, 11 (employing “tumor-associated viral genomes” in the analysis of cell-free tumor DNA); Ex. 1040, 648 (discussing viral DNA as a potential source of cell-free DNA in cancer patients); Ex. 1043, ¶¶ 79-87.)

Yen-Lieberman and *Gocke* both discussed similar methods of collecting blood to analyze cell-free DNA from plasma. In particular, like *Yen-Lieberman*,

Gocke described a method for detecting cell-free tumor DNA from human plasma to evaluate cancer progression, which *Gocke* explains can also be used to detect cell-free viral DNA. (See, e.g., Ex. 1034, Abstract, 7:33-60; Ex. 1043, ¶¶ 79-87.) And as noted above, a POSA at the time of the alleged invention would have been aware that the HCMV discussed in *Yen-Lieberman* was associated with malignant tumors. (See, e.g., Ex. 1033, 105; see also Ex. 1043, ¶¶ 79-87.) As such, the POSA would have had reason to consider *Gocke*, which is in the same field as *Yen-Lieberman* and the '720 patent. (Ex. 1043, ¶¶ 79-87.) *Gocke* specifically described that “extracellular DNA in blood plasma or serum” can be analyzed “for the detection, monitoring, or evaluation of cancer or premalignant conditions.” (Ex. 1034, 3:66-4:7.)

Similar to *Yen-Lieberman*, *Gocke* describes a process where “blood is drawn by standard methods into a collection tube” that may contain “EDTA, sodium citrate, heparin, or similar anticoagulants.” (*Id.*, 11:8-13.) And just like *Yen-Lieberman*, “plasma or serum” is “fractionated from whole blood” (*id.*, 11:13-15; see also *id.*, 11:15-28), after which extracellular DNA is extracted from the plasma or serum (*id.*, 11:38-12:5; see also *id.*, 12:6-13:36 (describing alternative extraction methods)). *Gocke* explains that, once extracellular DNA is extracted, the DNA can be “amplified using a nucleic acid amplification assay” (*id.*, 14:23-25), and then

one of “numerous methods to detect amplified DNA” may be applied (*id.*, 18:55-57; *see also id.*, 18:58-20:16).

As *Gocke* states, “[t]he extraction of extracellular DNA from plasma or serum, and the amplification of tumor-associated or derived DNA to detectable levels, permits further analysis or other manipulation of that DNA, from which further clinical utility is realized.” (*Id.*, 20:18-22.) As a specific example, the *Gocke* process is used to detect colorectal cancer. (*Id.*, 21:51-25:32; *see also* Ex. 1043, ¶¶ 80-7.) In addition to general knowledge in the art discussed above (Ex. 1043, ¶ 81), *Gocke* also explains that “viral . . . nucleic acid, can be detected using the inventive method.” (*Id.*, 7:33-60.)

Because of the similarities between the methodologies discussed in *Yen-Lieberman* and *Gocke*, including the use of common anticoagulants, the POSA would have been motivated to use the method discussed in *Yen-Lieberman* for the analysis of cell-free tumor DNA (instead of cell-free HCMV DNA) where “EDTA or ACD anticoagulants” is used to collect blood/plasma for analysis. (Ex. 1033, 107-08; *see also* Ex. 1043, ¶¶ 80-7.)

The POSA would have had a reasonable expectation of success with the combination of *Yen-Lieberman* and *Gocke* discussed above. Indeed, as demonstrated above, the processes of *Yen-Lieberman* and *Gocke* are similar. While *Gocke* does not specifically describe the use of ACD tubes, the method in

Gocke permits the use of “EDTA, sodium citrate, heparin, or *similar anticoagulants*.” (See, e.g., Ex. 1034, 11:6-13 (emphasis added); see also Ex. 1043, ¶¶ 83-6.) The POSA would have been aware that ACD tubes were successfully used for isolation of similar cell-free DNA from plasma, so would have appreciated that, to the extent ACD worked efficaciously for the extraction and analysis of HCMV DNA, it would also work for cell-free tumor DNA. (See, e.g., Ex. 1033, 107-08; Ex. 1003, 10:26-11:2; Ex. 1019, Figs. 4 and 5; see also Ex. 1043, ¶¶ 83-6.) The proposed modification of *Yen-Lieberman* is a straightforward one, with the process simply being used for cell-free tumor DNA rather than HCMV DNA. (Ex. 1043, ¶¶ 80-7.) The ’720 patent also reflects the general knowledge in the art allowing this type of straightforward modification, as the methods of the ’720 patent are claimed to be applicable for both cell-free tumor and viral DNA. (Ex. 1001, 23:37-60, 24:41-57; see also *id.* at 23:60-62, 142-143 (Table XV).)

Petitioner is not aware of any alleged objective indicia that supports the nonobviousness of the “disease is cancer” limitation of claim 25. Regardless, the compelling case of obviousness established above would outweigh any such evidence. See, e.g., *Ohio Willow Wood*, 735 F.3d at 1344.

2. Claim 7: “The method of claim 1, wherein said nucleic acid contains at least one mutation.”

The combination of *Yen-Lieberman* and *Gocke* discussed above in Section X.D.1 with respect to claim 25 similarly meets the limitations of claim 7. For instance, the cell-free tumor DNA discussed in *Gocke* is identified by point mutations associated with tumor types. (*See, e.g.*, Ex. 1034, Abstract; *see also id.* at 21:51-25:32 (Example 1) (discussing colorectal cancer); Ex. 1043, ¶¶ 79-88.)

3. Claim 8: “The method of claim 7, wherein said mutation is selected from the group consisting of: single point mutation, multiple point mutations, an insertion, a frameshift, a truncation, a deletion, a duplication, and a transversion.”

The combination of *Yen-Lieberman* and *Gocke* discussed above in Section X.D.1 with respect to claim 25 similarly meets the limitations of claim 8. For instance, the cell-free tumor DNA discussed in *Gocke* can be identified by a single point mutation. (*See, e.g.*, Ex. 1034, Abstract; *see also id.* at 21:51-25:32 (Example 1) (discussing colorectal cancer); Ex. 1043, ¶¶ 89, 79-87.)

4. Claim 9: “The method of claim 7, wherein said mutation is in a gene selected from the group consisting of: BRCA1, BRCA2, MSH6, MSH2, MLH1, RET, PTEN, ATM, H-RAS, p53, ELAC2, CDH1, APC, AR, PMS2, MLH3, CYP1A1, GSTP1, GSTM1, AXIN2, CYP19, MET, NAT1, CDKN2A, NQ01, trc8, RAD51, PMS1, TGFBR2, VHL, MC4R, POMC, NROB2, UCP2, PCSK1, PPARG, ADRB2, UCP3, glurl, cart, SORBS1, LEP, LEPR, SIMI, TNF, IL-6, IL-1, IL-2, IL-3, IL1A, TAP2, THPO, THRB, NBS1, RBM15, LIE, MPL, RUNX1, Her-2, glucocorticoid receptor, estrogen receptor, thyroid receptor, p21, p27, K-RAS, N-RAS, retinoblastoma protein, Wiskott-Aldrich (WAS) gene,

Factor V Leiden, Factor II (prothrombin), methylene tetrahydrofolate reductase, cystic fibrosis, LDL receptor, HDL receptor, superoxide dismutase gene, SHOX gene, genes involved in nitric oxide regulation, genes involved in cell cycle regulation, tumor suppressor genes, oncogenes, genes associated with neurodegeneration, and genes associated with obesity.”

The combination of *Yen-Lieberman* and *Gocke* discussed above in Section X.D.1 with respect to claim 25 similarly meets the limitations of claim 9. For instance, the cell-free tumor DNA discussed in *Gocke* includes K-ras. (*See, e.g.*, Ex. 1034, 15:15-16:12, 21:51-25:32 (Example 1) (discussing colorectal cancer); Ex. 1043, ¶¶ 90, 79-87.)

5. Claim 21: “The method of claim 1, wherein isolation of free nucleic acid comprises a centrifugation step.”

The combination of *Yen-Lieberman* and *Gocke* discussed above in Section X.D.1 with respect to claim 25 similarly meets the limitations of claim 21. For instance, *Gocke* discusses using “gentle centrifugation” when isolating cell-free DNA. (*See, e.g.*, Ex. 1034, 11:22-26; Ex. 1043, ¶¶ 91, 79-87.) Although *Yen-Lieberman* does not specifically discuss the use of centrifugation (Ex. 1033, 107-8), a POSA would have understood that centrifugation would have been used to obtain the plasma sample discussed (Ex. 1043, ¶ 91). As such, a POSA would have understood that in the combination of *Yen-Lieberman* and *Gocke* discussed above for claim 25, isolation of cell-free DNA would have comprised a centrifugation step. (Ex. 1043, ¶¶ 91, 79-87.)

6. **Claim 26: “The method of claim 25, wherein said cancer is selected from the group consisting of: carcinoma of the bladder, breast, bronchial, colon, kidney, liver, lung, esophagus, gallbladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin; small cell lung cancer, squamous cell carcinoma, hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin’s lymphoma, nonHodgkin’s lymphoma, hairy cell lymphoma, Burkett’s lymphoma, hematopoietic tumors of myeloid lineage, acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia, tumors of mesenchymal origin, fibrosarcoma and rhabdomyosarcoma, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma and schwamiomas, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi’s sarcoma.”**

Gocke discusses a method for detecting various cancer types, such as pancreatic, lung, breast, bladder, ovarian, and lymphoma. (*See, e.g.*, Ex. 1034, Abstract; *see also id.* at 21:51-25:32 (Ex. 1) (discussing colorectal cancer); Ex. 1043, ¶¶ 92, 79-87.) As such, a POSA would have understood that, in the combination of *Yen-Lieberman* and *Gocke* discussed above for claim 25, various cancer types (such as pancreatic, lung, breast, bladder, ovarian, and lymphoma) could be detected. (Ex. 1043, ¶ 92.)

7. **Claim 27: “The method of claim 1, wherein said method is used to monitor response to treatment.”**

Gocke discusses the use of the method “to detect the presence of residual disease in a human following a course of treatment.” (*See, e.g.*, Ex. 1034, 6:59-61;

Ex. 1043, ¶¶ 93, 79-87.) As such, a POSA would have understood that, in the combination of *Yen-Lieberman* and *Gocke* discussed above for claim 25, the method could be used to monitor response to treatment, as claimed. (Ex. 1043, ¶ 93.)

8. Claim 28: “The method of claim 27, wherein the treatment is selected from the group consisting of surgery, radiation, lifestyle change, dietary protocol, supplementation and administration of a drug.”

Gocke discusses the use of the method “following surgery to remove a premalignant lesion or a cancer, to classify such patients for their risk of residual cancer” and “cancer therapies, including but not limited to chemotherapy.” (*See, e.g.*, Ex. 1034, 8:26-38; Ex. 1043, ¶¶ 94, 79-87.) As such, a POSA would have understood that, in the combination of *Yen-Lieberman* and *Gocke* discussed above for claim 25, the method could be used to monitor a response to surgery or administration of a drug. (Ex. 1043, ¶ 94.)

9. Claim 29: “The method of claim 28, wherein the treatment is administration of a drug.”

As discussed in Section X.D.8 above with respect to claim 28, *Gocke* discusses the use of the method “following surgery to remove a premalignant lesion or a cancer, to classify such patients for their risk of residual cancer” and “cancer therapies, including but not limited to chemotherapy.” (*See, e.g.*, Ex. 1034, 8:26-38; Ex. 1043, ¶¶ 95, 79-87.) As such, a POSA would have

understood that, in the combination of *Yen-Lieberman* and *Gocke* discussed above for claim 25, the method could be used to monitor a response to the administration of a drug. (Ex. 1043, ¶ 95.)

10. **Claim 30: “The method of claim 29, wherein said drug is selected from the group consisting of: chemotherapeutic agents, anti-bacterial agents, anti-viral agents, anti-fungal agents, targeted-cancer drugs, cytoxic agents, cytostatic agents, anti-proliferative agents, Avastin, altretamine, busulfan, chlorambucil, cyclophosphamide, Erbitux, Rituxan, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones, topotecan, irinotecan, 9-amino camptothecin, 9-nitro camptothecin, GS-211, etoposide, teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, methotrexate, octreotide, estramustine, and hydroxyurea.”**

As discussed in Section X.D.8 above with respect to claim 28, *Gocke* discusses the use of the method “following surgery to remove a premalignant lesion or a cancer, to classify such patients for their risk of residual cancer” and “cancer therapies, including but not limited to chemotherapy.” (*See, e.g.*, Ex. 1034, 8:26-38; Ex. 1043, ¶¶ 96, 79-87.) As such, a POSA would have understood that, in the combination of *Yen-Lieberman* and *Gocke* discussed above

for claim 25, the method could be used to monitor a response to the administration of a chemotherapeutic agent. (Ex. 1043, ¶ 96.)

E. Ground 5: *Yen-Lieberman* in View of *Gocke* and *Marx* Renders Claim 22 Obvious

1. Claim 22: “The method of claim 21, wherein the centrifugation step is performed with the centrifuge braking power set to zero.”

Gocke and *Yen-Lieberman* do not explicitly discuss that centrifugation is performed “with the centrifuge braking power set to zero,” as recited in claim 22. A POSA would have understood, however, the instruction to use “gentle centrifugation” in *Gocke* (Ex. 1034, 11:22-26), and the absence of instruction for setting the centrifuge brake, to at least suggest no brake should be used (*see* Ex. 1043, ¶¶ 97-101, 62-66). In any event, as discussed in Section X.B.1 above with respect to *Landes*, 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. 1043, ¶¶ 97-101.)

A POSA would have had reason to consider *Marx*, which is in the same field as *Yen-Lieberman*, *Gocke*, and the '720 patent. (Ex. 1043, ¶¶ 97-101.) *Marx* concluded that, “[u]pon strong braking, the separated cell layers are perturbed by the rapid deceleration” (Ex. 1029 at 744-46), and that “no brakes gave much more reasonable yields of platelets . . . as well as low WBC contamination” (*id.* at 746).

A POSA would have been motivated to combine *Yen-Lieberman*, *Gocke*, 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 *Yen-Lieberman* and *Gocke* (Ex. 1033, 107-08; Ex. 1034, 11:24-25.) 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. 1025, ¶ 224; see also Ex. 1043, ¶¶ 97-101.)

At a minimum, for the same reasons discussed in Section X.B.1 above, performing centrifugation with braking power set to zero would have been obvious to try (see, e.g., Ex. 1029, Abstract; see also Ex. 1043, ¶¶ 97-101), where there are a finite number of predictable options for the braking power of a centrifuge. See, e.g., *Geo. M. Martin Co.*, 618 F.3d at 1302. For the same reasons discussed in Section X.B.1 above, a POSA would have had a reasonable expectation of success with setting a braking power to zero. (Ex. 1043, ¶¶ 97-101, 62-66.)

Petitioner is not aware of any alleged objective indicia that supports the nonobviousness of the centrifugation braking power limitation of claim 22.

Regardless, the compelling case of obviousness established above would outweigh any such evidence. *See, e.g., Ohio Willow Wood*, 735 F.3d at 1344.

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 '720 patent. Patent Owner may argue that the '720 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 '720 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 ’720 patent. *Id.* at 7-8 (“Once resolution of factor 1 indicates that Petitioner had not previously filed a petition against the same patent, factors 2-5 bear little relevance unless there is evidence in the record of extenuating circumstances such as a showing that there was a previous petitioner who challenged the same patent and that the previous petitioner and the current petitioner planned the staggered petitions.”) (internal citation omitted). Petitioner has no relationship to the earlier challenges to the ’720 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* and *Yen-Lieberman*, which anticipate many of the challenged claims.

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. 1042, 16-8)), there is a strong likelihood such a stay will be granted.

The second *Fintiv* factor favors institution. The 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. 1042, 16-8.).

The fourth *Fintiv* factor favors institution. Petitioner has not yet presented 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

A patent from the same family as *Gocke*, which is part of Grounds 4 and 5, was considered during prosecution. (*See* Ex.1012, May 5, 2008 Office Action, 7.) Nonetheless, discretionary denial under 35 U.S.C. § 325(d) is inappropriate for at least two reasons. First, the anticipatory *Landes* and *Yen-Lieberman* references, discussed in Grounds 1 and 3, were not considered during prosecution. Second, and perhaps more importantly, the Examiner did not consider *Gocke* in conjunction with *Yen-Lieberman*. This is critical since, as discussed in Section X.C.1, *Yen-Lieberman* anticipates the broad claims and renders obvious the precise feature that the Examiner stated was missing from the prior art. (*See* Ex. 1012, December 15, 2009 Notice of Allowance, 2.)

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 *Yen-Lieberman* was not considered during prosecution, nor are *Landes* and *Yen-Lieberman* cumulative to art considered during prosecution. *Id.* at 18-22. And while a patent in the *Gocke* family was evaluated during prosecution, it was not evaluated in conjunction with *Yen-Lieberman*. *Id.* at 22-23. In addition, during prosecution, no glucose-based agent (like those in *Landes* and *Yen-Lieberman*) was considered as “an agent that impedes cell lysis”. *Id.* at 23-24. And as discussed in Sections X.A.1 and X.C.1 above, the Examiner only found the claims patentable because the Examiner was not aware of the anticipatory descriptions from *Landes* and *Yen-Lieberman*. *Id.* at 24-28.

XII. CONCLUSION

Petitioner requests institution of IPR for claims 1, 3-9, 21, 22, and 24-30 of the '720 patent based on the grounds specified in this petition.

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. 7,727,720 contains, as
measured by the word-processing system used to prepare this paper, 12,427 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. 7,727,720 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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