UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

_____

Case No.: IPR2024-01330
U.S. Patent 11,970,746

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT 11,970,746

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TABLE OF AUTHORITIES

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Cases

Advanced Bionics, LLC v. Med-El Elekromedizinische Geräte GmbH,
IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) 69, 71

Alcon Research, LTD. v. Apotex Inc.,
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Exact Sciences Corporation v. Geneoscopy, Inc.,
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37 C.F.R. § 42.6(e) 74

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PETITIONER'S EXHIBIT LIST

Exhibit No.	Short Name	Description
EX1001	'746 patent	U.S. Patent No. 11,970,746.
EX1002	Whitney Declaration	Expert Declaration of Dr. Whitney Ph.D.
EX1003	Whitney CV	Curriculum Vitae of Dr. Duncan Whitney
EX1004	Lenhard	Konstanze Lenhard et al., "Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer," *Clinical Gastroenterology and Hepatology*, 3:142-149 (2005).
EX1005	Vilkin	Alex Vilkin et al., "Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical Fecal Occult Blood Screening Test," *American Journal of Gastroenterology*, 100:2519-2525 (2005).
EX1006	Itzkowitz	Steven Itzkowitz et al., "Improved Fecal DNA Test for Colorectal Cancer Screening," *Clinical Gastroenterology and Hepatology*, 5:111-117 (2007).
EX1007	Kanaoka	U.S. Patent Publication Number US 2006/0216714.
EX1008	Shuber	International Patent Application Publication Number WO2005/113769.
EX1009	Inbar	International Patent Application Publication Number WO97/25925.
EX1010	Melvin	Dorothy Melvin and Marion Brooke, "Laboratory Procedures for the Diagnosis of Intestinal Parasites", *U.S. Department of Health and Human Services Centers for Disease Control* (1982).

EX1011	Nishikawa	Takashi Nishikawa et al., "A Simple Method of Detecting K-Ras Point Mutations in Stool Samples for Colorectal Cancer Screening Using One-Step Polymerase Chain Reaction/Restriction Fragment Length Polymorphism Analysis," *Clinica Chimica Acta*, 318 107–112 (2002).
EX1012	Kutzner	Nadie Kutzner et al., "Non-Invasive Detection of Colorectal Tumours by the Combined Application of Molecular Diagnosis and the Faecal Occult Blood Test," *Cancer Letters*, 229:33-41 (2005).
EX1013	Levin	Bernard Levin et al., "Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, a Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology," *Gastroenterology*, 134:1570–1595 (2008).
EX1014	'581 Provisional Application	US Provisional Patent Application US61/149,581.
EX1015	'581 Transmittal	Transmittal Notice for U.S. Provisional Patent Application US61/149,581.
EX1016	Joost Louwagie Profile	LinkedIn Page of Joost Louwagie.
EX1017	Recorded Assignment	Recorded Assignment of OncoMethylome patent family dated April 25, 2017.
EX1018	Nonfinal Office Action	Nonfinal Office Action of July 6, 2023 issued during prosecution of '746 patent
EX1019	Response to Nonfinal Office Action	Response to Nonfinal Office Action filed on October 26, 2023 during prosecution of '746 patent
EX1020	Young 2007	GP Young et al., "New Stool Screening Tests for Colorectal Cancer," *Digestion*, 76:26-33 (2007).

EX1021	Guittet	Lydia Guittet et al., "Comparison of A Guaiac Based and An Immunochemical Faecal Occult Blood Test in Screening for Colorectal Cancer In A General Average Risk Population," *Gut*, 56:210-214 (2007).
EX1022	Olson	Jeff Olson et al., "DNA Stabilization is Critical for Maximizing Performance of Fecal DNA-Based Colorectal Cancer Tests," *Diagnostic Molecular Pathology*, 3:183-191 (2005).
EX1023	Hoepffner	N. Hoepffner et al., "Comparative Evaluation of a New Bedside Faecal Occult Blood Test in a Prospective Multicentre Study," *Alimentary Pharmacology & Therapeutics*, 23:145-154 (2006).
EX1024	Nechvatal	Jordan Nechvatal et al., "Fecal Collection, Ambient Preservation, and DNA Extraction for PCR Amplification of Bacterial and Human Markers from Human Feces," *Journal of Microbiological Methods*, 72(2):124-32 (2008).
EX1025	Cologuard Launch Press Release`	"FDA Approves Exact Sciences' Cologuard; First and Only Stool DNA Noninvasive Colorectal Cancer Screening Test" PR Newswire Association LLC, August 12, 2014
EX1026	Cologuard Patent Coverage, 2024	Printout of Exact Sciences' "Patents and Trademarks" page from their website, as visited on August 9, 2024.
EX1027	Cologuard Patent Coverage, 2014	Printout of Exact Sciences' "Patents and Trademarks" page from their website as of December 6, 2104. Downloaded from Wayback Machine on August 9, 2024.
EX1028	'278 patent	U.S. Patent No. 9,163,278
EX1029	'278 patent Office Action Response	Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of '278 patent
EX1030	'781 patent	U.S. Patent No. 11,634,781.

EX1031	IPR2024-00459 Petition	IPR2024-00459 Petition
EX1032	IPR2024-00459 POPR	IPR2024-00459 Patent Owner's Preliminary Response
EX1033	IPR2024-00459 Institution Decision	IPR2024-00459 Institution Decision
EX1034	Simon	JB Simon, "Occult Blood Screening for Colorectal Carcinoma: A Critical Review," *Gastroenterology*, 88:820-837 (1985).
EX1035	Sidransky	D. Sidransky, "Identification of Ras Oncogene Mutations in the Stool of Patients with Curable Colorectal Tumors," *Science*, 256:102–105 (1992).
EX1036	Müller	Hannes Müller et al., "Methylation Changes in Faecal DNA: A Marker for Colorectal Cancer Screening?" *Lancet*, 63:1283-1285 (2004).
EX1037	Schuebel	Kornel Schuebel et al., "Comparing the DNA Hypermethylome with Gene Mutations in Human Colorectal Cancer," *PLoS Genet*., 3:1709–1723 (2007).
EX1038	Shen	Lanlan Shen et al., "Integrated Genetic and Epigenetic Analysis Identifies Three Different Subclasses of Colon Cancer." *Proc Natl. Acad. Sci. U.S.A.,* 104(47): 18654–18659 (2007).
EX1039	Tagore	K.S. Tagore et al. "Review Article: The Evolution to Stool DNA Testing for Colorectal Cancer," *Aliment Pharmacol. Ther.,* 19: 1225-1233 (2004).
EX1040	Rennert	Rennert et al., "Detecting K-Ras Mutations in Stool from Fecal Occult Blood Test Cards in Multiphasic Screening for Colorectal Cancer," *Cancer Letters*, 253: 258-264 (2007).
EX1041	Grow	U.S. Patent No. 5,198,365.

EX1042	Imperiale 2004	Thomas Imperiale et al., "Fecal DNA Versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population," *New England Journal of Medicine,* 351(26): 2704-2714 (2004).
EX1043	Ahlquist 2008	David Ahlquist et al., "Stool DNA and Occult Blood Testing for Screen Detection of Colorectal Neoplasia," *Annals of Internal Medicine*, 149(7): 441–W81 (2008).
EX1044	Young 2004	G.P. Young, "Fecal Immunochemical Tests (FIT) vs. Office-Based Guaiac Fecal Occult Blood Test (FOBT)," *Practical Gastroenterology* 28(6): 46-56 (2004).
EX1045	Karl	Karl, et al., Improved Diagnosis of Colorectal Cancer Using a Combination of Fecal Occult Blood and Novel Fecal Protein Markers," *Clinical Gastroenterology and Hepatology*, 6:1122–1128 (2008).
EX1046	White	Victoria White and Richard Miller, "Colorectal Cancer: Prevention and Early Diagnosis," *Medicine,* 35(6) 297-301 (2007).
EX1047	Mahon	Suzanne Mahon, " Prevention and Screening of Gastrointestinal Cancers," *Seminars in Oncology Nursing,* 25(1): 15-31 (2009).
EX1048	Beaulieu	U.S. Patent No. 9,891,223.
EX1049	Ostrow	Donald Ostrow, "Tests for Fecal Occult Blood, in Clinical Methods: The History, Physical, and Laboratory Examinations." Boston: Butterworths; Chapter 98 (1990).
EX1050	Cleator	U.S. Patent No. 7,195,878.
EX1051	Kahi	Charles Kahi et al., "Screening, Surveillance, and Primary Prevention for Colorectal Cancer: A Review of the Recent Literature," *Gastroenterology,* 135: 380-399 (2008).

EX1052	Zou	H Zou et al., "Highly Methylated Genes in Colorectal Neoplasia: Implications for Screening," *Cancer Epidemiol Biomarkers Preview,* 16(12):2686-96 (2007).
EX1053	Eguchi	Susumu Eguchi et al., "Mutations of the P53 Gene in Stool of Patients with Resectable Colorectal Cancer," *Cancer*, 77:1707–1710 (1996).
EX1054	Villa	E. Villa, et al., "Identification of Subjects at Risk for Colorectal Carcinoma through a Test Based on K-Ras Determination in the Stool," *Gastroenterology*, 110:1346–1353 (1996).
EX1055	Boynton	Boynton et al., "DNA Integrity as a Potential Marker for Stool-based Detection of Colorectal Cancer," *Clinical Chemistry,* 49:7 1058–1065 (2003).
EX1056	Jessup	J. Milburn Jessup et al., "Diagnosing Colorectal Carcinoma: Clinical and Molecular Approaches," *A Cancer Journal for Clinicians,* 47(2):70-92 (1997).
EX1057	Chen	WD Chen et al., "Detection in Fecal DNA of Colon Cancer-Specific Methylation of the Nonexpressed Vimentin Gene." *Journal of National Cancer Institute,* 97:1124-1132 (2005).
EX1058	Itzkowitz 2008	Steven Itzkowtiz, "A Simplified, Noninvasive Stool DNA Test for Colorectal Cancer Detection," *American Journal of Gastroenterology,* 103: 2862-2870 (2008).
EX1059	Li	L-C Li and R. Dahiya, "MethPrimer: Designing Primers for Methylation Pcrs," *Bioinformatics,* 18(11): 1427-1431 (2002).
EX1060	Kanaoka 2004	Shigeru Kanaoka et al., "Potential Usefulness of Detecting Cyclooxygenase 2 Messenger RNA in Feces for Colorectal Cancer Screening," *Gastroenterology*, 127:422-427 (2004).

EX1061	Matsumura 1992	Y Matsumura and D Tarin "Significance of CD44 Gene Products for Cancer Diagnosis and Disease Evaluation," *Lancet*, 340: 1053-1058 (1992).
EX1062	Matsumura 1994	Y Mastumura et al., "Non-Invasive Detection of Malignancy by Identification of Unusual CD44 Gene Activity in Exfoliated Cancer Cells," *BMJ,* 308:619-624 (1994).
EX1063	Leung	Wai Leung et al., "Detection of Hypermethylated DNA or Cyclooxygenase-2 Messenger RNA in Fecal Samples of Patients with Colorectal Cancer or Polyps" *American Journal Gastroenterology*, 102: 1070-1076 (2007).
EX1064	Ahmed	Farid Ahmed et al., "Transcriptomic Molecular Markers for Screening Human Colon Cancer in Stool and Tissue," *Cancer Genomics and Proteomics* 4:1-20 (2007).
EX1065	Ahlquist 2000	D.A. Ahlquist et al., "Colorectal Cancer Screening by Detection of Altered Human DNA in Stool: Feasibility of a Multitarget Assay Panel," *Gastroenterology*, 119(5):1219-1227 (2000).
EX1066	Ahlquist 2000(b)	D.A. Ahlquist et al., "Molecular Stool Screening for Colorectal Cancer. Using DNA Markers May Be Beneficial, But Large Scale Evaluation is Needed." *BMJ*, 29;321(7256):254-5 (2000).
EX1067	Taylor	International Patent Application Publication Number WO2009/102788.
EX1068	Lapidus '650	U.S. Patent No. 5,741,650
EX1069	Lapidus '178	U.S. Patent No. 5,952,178
EX1070	Hirata	I Hirata et al., "Usefulness of Fecal Lactoferrin and Hemoglobin in Diagnosis of Colorectal Diseases," *World Journal of Gastroenterology*, 14;13(10):1569-74 (2007).

EX1071	Ahlquist 1988	D.A. Ahlquist et al., "A Stool Collection Device: The First Step in Occult Blood Testing," *Annals of Internal Medicine*, (108)4:609-612 (1988).
EX1072	Lenhard Printout	Printout of *Clinical Gastroenterology and Hepatology* Website.
EX1073	Van Engeland	International Patent Application Publication Number WO2008/084219.
EX1074	Itzkowitz Printout	Printout of *Clinical Gastroenterology* and Hepatology Website.
EX1075	Itzkowitz Press Release	Exact Sciences and Mount Sinai School of Medicine Press Release issued December 13, 2006.
EX1076	Cologuard Patient Guide	Cologuard Patient Guide as approved by the Food and Drug Administration
EX1077	Imperiale 2014	Imperiale, et al., "Multitarget Stool DNA Testing for Colorectal-Cancer Screening," *The New England Journal of Medicine*, 370(14):1287-1297 (2014)
EX1078	Exact Sciences 2023 Form 10-K	Exact Sciences Corporation's 2023 Form 10-K.
EX1079	Exact Sciences Cologuard web page	Exact Science's webpage regarding the Cologuard test as obtained from https://www.exactsciences.com/our-tests/cologuard on August 15, 2024.
EX1080	Cologuard Physician Brochure	Cologuard Physician Brochure as approved by the Food and Drug Administration
EX1081	Cologuard Instructions for Use	Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use as approved by the Food and Drug Administration
EX1082	Whitney Declaration in IPR2024-00459	Duncan Whitney Ph.D.'s Declaration submitted in IPR2024-00459
EX1083	Jones Declaration	Declaration of Brendan T. Jones

I. Introduction

The claims of United States Patent No. 11,970,746 ("the '746 patent") are directed to the separation of a fecal sample into two portions to permit two standard diagnostic tests—one detecting blood proteins and the other detecting nucleic acids—to be performed on the sample. Nothing in these claims is inventive. Separating a fecal sample so two tests can be performed is reported throughout the prior art, including in Lenhard (EX1004) and Inbar (EX1009). Fecal tests for detecting blood protein and nucleic acids were known and routine, as confirmed by Lenhard, Inbar, Vilkin (EX1005), Itzkowitz (EX1006), and Shuber (EX1008). The method claimed by the '746 patent amounts to no more than the routine use of conventional methods to prepare a fecal sample for performance of well-established complementary diagnostic assays. The claimed method is not new, and claims directed to the method are invalid.

In IPR2024-00459, Petitioner challenged the claims of United States Patent No. 11,634,781 ("the '781 patent), the parent of the '746 patent, as obvious in view of Lenhard, Itzkowitz, Vilkin, and Shuber, essentially for the reasons set forth in Grounds I-IV of this petition. EX1031. The Board instituted IPR2024-00459, finding there was "a reasonable likelihood … that the challenged claims would have been unpatentable as obvious" over the ***same prior art*** asserted in Grounds I-IV of this petition. EX1033 at 19, 20. As explained below, the scope of the

currently challenged claims is broader than, and completely encompasses, that of the corresponding claims of the ’781 patent. Accordingly, the Board’s holdings in its IPR2024-00459 institution decision concerning the obviousness of the ’781 claims applies equally to the currently challenged claims. EX1030; EX1001; EX1002 ¶¶107-111.

An additional consequence of expanding the scope of the ’746 patent’s claims is that some of the claims now read on Inbar, a decades-old patent application that Petitioner did not assert in IPR2024-00459, but that anticipates the broader claims 1 and 2 of the ’746 patent.

The Board should institute IPR based on Lenhard, Itzkowitz, Vilkin, Shuber, Inbar, and the other references cited in the grounds herein and should cancel claims 1-4 and 12-19 of the ’746 patent.

The Petitioner, Geneoscopy, Inc. (“Geneoscopy”) is a life sciences company focused on transforming gastrointestinal health through innovative diagnostics, including through its work developing a noninvasive, at-home screening test for colorectal cancer (CRC). Geneoscopy has an interest in ensuring that the Patent Owner does not foreclose innovation and advancement in the field of cancer detection by claiming exclusive rights to diagnostic methods it did not invent.

II. STANDING AND PROCEDURAL STATEMENTS

Geneoscopy certifies: (1) the '746 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any '746 patent claim on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Geneoscopy is submitting a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e), and all required fees pursuant to 37 C.F.R. § 42.15(a), concurrently with this Petition. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Acct. No. 06-1448.

III. MANDATORY NOTICES & PROCEDURAL STATEMENTS

A. Real Party-in-Interest, 37 C.F.R. § 42.8(b)(1)

The real party-in-interest is Geneoscopy, Inc., which is located at 2220 Welsch Industrial Court, St. Louis, MO 63146.

B. Related Matters, 37 C.F.R. § 42.8(b)(2)

The Patent Owner, Exact Sciences, Inc. ("Exact") asserted the '746 patent against Geneoscopy in *Exact Sciences Corporation v. Geneoscopy, Inc.,* No. 24-cv-00583-MN (D. Del.). Geneoscopy was served with the complaint in this litigation on May 16, 2024. On June 18, 2024, this matter was consolidated with *Exact Sciences Corporation v. Geneoscopy, Inc.,* No. 23-cv-1319-MN (D. Del.) ("the Exact Litigation"), which is currently pending.

Geneoscopy filed a Petition for *Inter Partes* Review of the '781 patent on January 11, 2024 in Case No. IPR2024-00459. The '781 patent is the parent of the '746 patent. The Board instituted IPR2024-00459 on July 26, 2024.

C. Lead and Backup Counsel and Service Information, 37 C.F.R. § 42.8(b)(3) and (b)(4)

Petitioner provides the following designation of counsel for which a power of attorney is being filed contemporaneously. 37 C.F.R. § 42.10(b).

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IV. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR

Geneoscopy requests institution of IPR and cancellation of claims 1-4 and 12-19 of the '746 patent, for the reasons stated herein.

V. BACKGROUND

A. Technical Background

1. Sample Collection and Preparation

By February 3, 2009 (the earliest priority date asserted by the '746 patent; "the Priority Date"), fecal samples had been used in non-invasive diagnostic tests for CRC for decades. EX1002 ¶¶17-27, 50-60. Such tests generally involved obtaining a stool sample from a patient and testing it for one or more biomarkers associated with CRC. EX1002 ¶¶50-66. The CRC biomarkers known to be present in feces included blood proteins, mutated DNA, long DNA fragments, hypermethylated DNA, and RNA. *Id*. It was broadly recognized that increasing the number of biomarkers used in such a test could improve its sensitivity and/or specificity. EX1002 ¶¶28-34, 61-66.

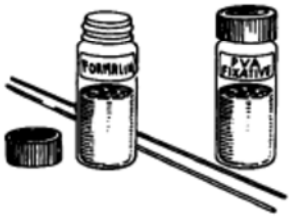
Many fecal diagnostic assays require specialized equipment and/or expertise, and accordingly are usually performed in diagnostics laboratories. EX1002 ¶67. For such assays, patients typically collect their own stool samples at home using a specially-designed kit and then ship them to the laboratory for testing. EX1002 ¶¶35-49, 67-82. To eliminate the need to freeze samples during shipment, scientists developed buffers that stabilize components of the fecal sample. *Id.* For example, certain buffers prevent degradation of DNA, and are employed when DNA biomarkers are used. EX1002 ¶¶75-78. Other buffers stabilize proteins and are used when blood proteins are used as biomarkers. EX1002 ¶¶79-82.

Decades before the Priority Date, scientists and clinicians recognized that testing different biomarkers could be facilitated by instructing patients to separate their fecal sample into portions stabilized in separate containers prior to shipment to a diagnostic laboratory. EX1002 ¶¶68-70, 72, 83-88. Such a process is illustrated in the below figure, from a 1985 laboratory manual, adapted from a 1949 publication. EX1002 ¶84; EX1010 p.12.

Figure 2.
Use of PVA-Fixative and Formalin for Submitting Stool Specimens to be Examined for Parasites

ADAPTED FROM BROOKE AND GOLDMAN, 1949

NOTE: BOTH SOFT AND *FORMED* SPECIMENS SHOULD BE SUBMITTED BY THIS METHOD. SPECIMENS MUST BE *FRESH* WHEN PLACED IN VIALS.



1 THE KIT CONSISTS OF TWO GLASS VIALS (ONE WITH 5% FORMALIN AND ONE WITH PVA-FIXATIVE) AND TWO APPLICATOR STICKS.



2 THE STOOL SHOULD BE PASSED INTO A DRY CONTAINER. URINE SHOULD NOT BE PASSED INTO THE SAME CONTAINER.



3 USING APPLICATOR STICKS, PLACE A QUANTITY OF THE STOOL (ABOUT THE DIAMETER OF A QUARTER) INTO THE VIAL CONTAINING FORMALIN, SCREW CAP ON TIGHTLY.



4 PLACE A SIMILAR QUANTITY INTO THE VIAL CONTAINING THE PVA-FIXATIVE.



5 THOROUGHLY BREAK UP SPECIMEN IN THE PVA-FIXATIVE, USING APPLICATOR STICKS. SCREW CAP ON TIGHTLY AND SHAKE VIGOROUSLY.



6 PACK THE TWO VIALS SO AS TO PROTECT AGAINST BREAKAGE, ENCLOSE APPROPRIATE IDENTIFICATION, AND MAIL OR DELIVER TO YOUR PUBLIC HEALTH LABORATORY.

2. Fecal Occult Blood Tests

Many early tests for CRC were based on detecting small amounts of blood in a patient's stool. EX1002 ¶¶51-53. Such tests are referred to as fecal occult blood tests (FOBT). *Id.* The earliest FOBT, referred to as guaiac FOBT (gFOBT), used a chemical process to detect the peroxidase activity of blood hemoglobin in stool. EX1002 ¶52. Because peroxidase activity is also found in certain foods, gFOBT require patients to undergo dietary restrictions prior to testing. *Id.*

By the Priority Date, a newer type of FOBT had become available that used antibodies to detect human hemoglobin. EX1002 ¶53. Such tests were referred to as either immunochemical FOBT (iFOBT) or fecal immunochemical tests (FIT). *Id.* Because the antibodies detected only human hemoglobin, no dietary restrictions were required. *Id.* iFOBT were generally more sensitive than gFOBT. *Id.* Certain automated iFOBT also provided quantitative results, allowing physicians to select a threshold hemoglobin level above which a patient would undergo colonoscopy. *Id*.

3. Fecal Nucleic Acid Tests

By the 1990s it was known that DNA biomarkers could be detected in the stool of people with CRC and used in diagnostics. EX1002 ¶54-59. CRC-associated DNA could be distinguished from normal DNA in several ways. *Id.* CRC cells often die in a way that causes long DNA fragments to be released into a

patient's stool. EX1002 ¶56. Such long fragments can be detected using a DNA integrity assay (DIA). *Id.* Certain gene mutations that appear more often in CRC cells than normal cells also can be detected in fecal DNA. EX1002 ¶55. CRC DNA can also be distinguished by detecting DNA methylation, an epigenetic DNA modification used by cancer cells to silence certain genes. EX1002 ¶¶58-59. By the Priority Date some scientists had begun detecting RNA biomarkers in stool as well. EX1002 ¶60.

It was recognized by the Priority Date that diagnostic assay sensitivity could be improved by combining fecal DNA tests with FOBT. EX1002 ¶¶61-66. For example, one paper reported that a fecal DNA assay "should provide a more sensitive and specific tool for mass screening of colorectal cancer than is currently available, **especially if used in combination with fecal occult blood testing**." EX1011 p.112, emphasis added. Another paper reported that "[t]he **combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs**" and "**all localized cancers**." EX1004 pp.143, 147, emphasis added. Another reported that "[t]he combined application of FOBT and MD [a DNA methylation assay] **resulted in an overall sensitivity, which could not be achieved by any of the methods alone**" EX1012 Abstract, emphasis added. Indeed, the 2008 joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology

proposed investigating whether "including a sensitive gFOBT or FIT at the time of testing would **improve sensitivity [of DNA-based assays] without adversely affecting specificity**." EX1013 p.1578, emphasis added.

B. The '746 Patent

The '746 patent is in a family of applications claiming priority to a provisional application filed February 3, 2009 by the Belgian company OncoMethylome. EX1014; EX1015. The '746 patent names as sole inventor Joost Louwagie, an OncoMethylome employee. EX1015; EX1016.

The common disclosure of OncoMethylome's patent family is directed to methods of separately detecting blood proteins and epigenetically-modified DNA in fecal samples ("The invention is based upon a combination of tests for detecting proteins and epigenetic modification markers respectively in the same fecal sample."). EX1001 4:3-16, 6:50-7:11; EX1002 ¶¶100-102. The '746 patent acknowledges that such tests were known in the art, but asserts that "immunochemical tests and DNA tests for CRC detection have been evaluated and compared on a separate basis only." EX1001 1:56-64, 3:5-22, 3:41-45.

In 2017, the OncoMethylome family was assigned to Exact. EX1017. Exact filed the application that gave rise to the '746 patent on March 7, 2023. The only rejections issued by the USPTO during its prosecution were for obviousness-type double patenting, including over the granted claims of the '781 patent. Exact

overcame these rejections by filing terminal disclaimers, effectively acknowledging that the claimed methods were obvious variants of the methods claimed in the '781 patent. EX1018; EX1019. The '746 patent issued on April 30, 2024.

VI. IDENTIFICATION OF THE CHALLENGE

Geneoscopy requests that the Board institute IPR of claims 1-4 and 12-19 of the '746 patent and find those claims unpatentable. This Petition should be granted, and trial instituted, because there is a reasonable likelihood that Geneoscopy will prevail with respect to at least one challenged claim.

Geneoscopy's challenge is based on the following references:

Exhibit	Description
EX1004	Lenhard *et al.,* 2005 "Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer" *Clinical Gastroenterology and Hepatology* 3:142-149 ("Lenhard")
EX1005	Vilkin *et al.,* 2005 "Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical Fecal Occult Blood Screening Test" *American Journal of Gastroenterology* 100:2519-2525 ("Vilkin")
EX1006	Itzkowitz *et al.,* 2007 "Improved Fecal DNA Test for Colorectal Cancer Screening" *Clinical Gastroenterology and Hepatology* 5:111-117 ("Itzkowitz")
EX1007	U.S. patent publication number US 2006/0216714 ("Kanaoka")
EX1008	International application publication number WO 2005/113769 ("Shuber")
EX1009	International application publication number WO 97/25925 ("Inbar")

Each reference above qualifies as prior art under pre-AIA 35 U.S.C. § 102(b) (pre-AIA law applies) because it published more than one year prior to the Priority Date.

Geneoscopy asserts the following grounds of unpatentability:

Ground	Statute	Claims	Prior Art
I	§103	1-4, 14-19	Lenhard, Vilkin, and Itzkowitz
II	§103	12 and 13	Lenhard, Vilkin, Itzkowitz, and Kanaoka
III	§103	1-4, 14-19	Shuber and Vilkin
IV	§103	12 and 13	Shuber, Vilkin, and Kanaoka
V	§102	1 and 2	Inbar
VI	§103	1-4, and 14-19	Inbar, Vilkin and Shuber
VII	§103	12 and 13	Inbar, Vilkin, Shuber, and Kanaoka

In support of the above Grounds, Geneoscopy submits with this Petition the declaration of Duncan Whitney, Ph.D., an expert in sample preparation and cancer diagnostics. EX1002; EX1003.

A. The Person of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") relevant to the '746 patent would have a Ph.D. in chemistry, biochemistry, biology, or a related field and at least five years of experience designing and performing diagnostic assays on fecal samples. EX1002 ¶9-13.

B. References in the Grounds

1. Lenhard (EX1004)

Lenhard is a 2005 publication that describes the combined analysis of DNA methylation and FOBT in stool samples to detect CRC. EX1004 p.143; EX1002 ¶¶113-119.

Lenhard tested for CRC by separating a patient's stool sample into two aliquots and then performing a gFOBT on one and a DNA methylation test on the other. EX1002 ¶¶114-118. Samples were collected from patients and sent to a diagnostic laboratory. EX1004 p.143. There, a portion of the sample was removed and tested using gFOBT. EX1004 pp.143, 145. The DNA was extracted from the remaining portion of the sample and tested for DNA methylation. EX1004 pp.143-144.

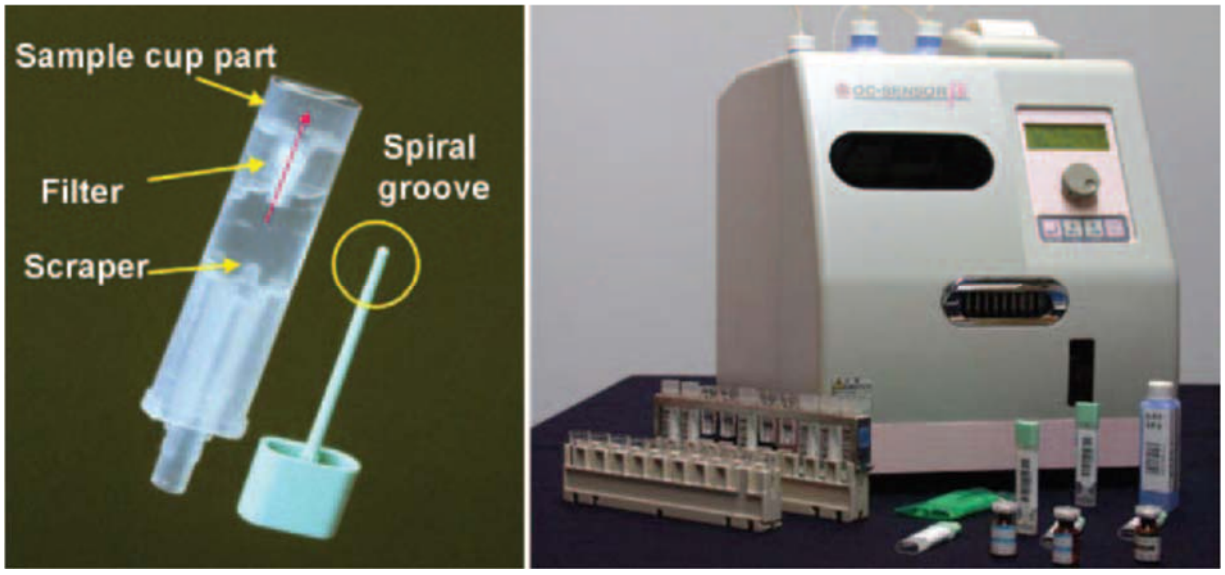
Lenhard found that "[t]he **combination of H1C1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs**." EX1004 pp.143, 147, emphasis added. Lenhard determined that, while HIC1 methylation alone detected 42% of CRCs and FOBT alone detected 35% of CRCs, the combination of the two tests detected 65% of CRCs. EX1004 Table 4, p.146. Lenhard also noted that "the combined test detected all localized cancers." EX1004 p.147.

2. Vilkin (EX1005)

Vilkin is a 2005 publication describing the use of an automated iFOBT to detect CRC. EX1002 ¶¶120-125.

In the iFOBT of Vilkin, an at-home patient uses a sampling device (shown in the left panel of Figure 1, reproduced below) to remove a portion of a fecal sample into a separate sealable container with a hemoglobin stabilizing buffer. EX1005 p.2520. The patient then ships the stabilized sample to a diagnostic laboratory without freezing. *Id*.

Vilkin Figure 1.



Once the laboratory receives the portion of the sample, it analyzes it on a desktop instrument (depicted in the right panel of Figure 1, above), which performs immunochemical detection of human Hb. EX1005 pp.2520-2521. Vilkin concludes

that there are numerous advantages of the described iFOBT over gFOBT. EX1005 p.2519.

3. Itzkowitz (EX1006)

Itzkowitz is a 2007 publication that discloses "version 2" of Exact's fecal DNA test for CRC. EX1002 ¶¶126-130. Thid version of the assay differs from the first version by using "improved DNA stabilization/isolation techniques and a new promoter methylation marker." EX1006 Abstract.

In Itzkowitz, patients collect stool samples at home by direct defecation into a sealable container. EX1006 p.112. Patients then add a DNA-stabilizing buffer to the sample. *Id*. Adding the DNA stabilizing buffer to the stool "was shown to prevent DNA degradation for several days," which improved the sensitivity of the test for detecting CRC. EX1006 pp.111, 116. The patients shipped the stabilized stool samples to a clinical laboratory at room temperature, where the samples were assayed for the presence of tumor-derived DNA. EX1006 p.112. Itzkowitz concluded that their "preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirms a very high degree of patient satisfaction." EX1006 pp.116-117.

4. Kanaoka (EX1007)

Kanaoka is a patent application published in 2006. EX1002 ¶¶131-133. Kanaoka describes a non-invasive CRC diagnostic assay that tests a stool sample for the presence of COX-2 RNA. EX1007 ¶¶0021-0026, 0055-0068.

In the assay disclosed in Kanaoka, a sample is collected, divided into separate tubes, and homogenized in the presence of an RNase inhibitor. EX1007 ¶¶0017, 0019. Kanaoka specifies that the samples are preferably feces, which can be "used as they are, or, in some cases, after frozen." EX1007 ¶¶0040-0041. RNA is extracted from the sample, subjected to RT-PCR, and detected. EX1007 ¶¶0021-0025. Among the advantages of the disclosed method is that it "has a higher detection sensitivity compared to the detection of gene mutation of APC, K-ras, or p53" and "it can save largely the time and effort needed for the detection." EX1007 ¶0076. Kanaoka also includes a working example in which stool samples from colon cancer patients and patients without colon cancer were tested for COX-2 RNA using RT-PCR and for hemoglobin using iFOBT. EX1007 ¶¶0056-0057, 0063.

5. Shuber (EX1008)

Shuber is a 2005 patent application filed by Exact that describes a method for preparing a fecal sample using a DNA stabilizing buffer. EX1008 6:2-20, 7:10-21; EX1002 ¶¶134-137. Shuber touts that the disclosed methods "do not require

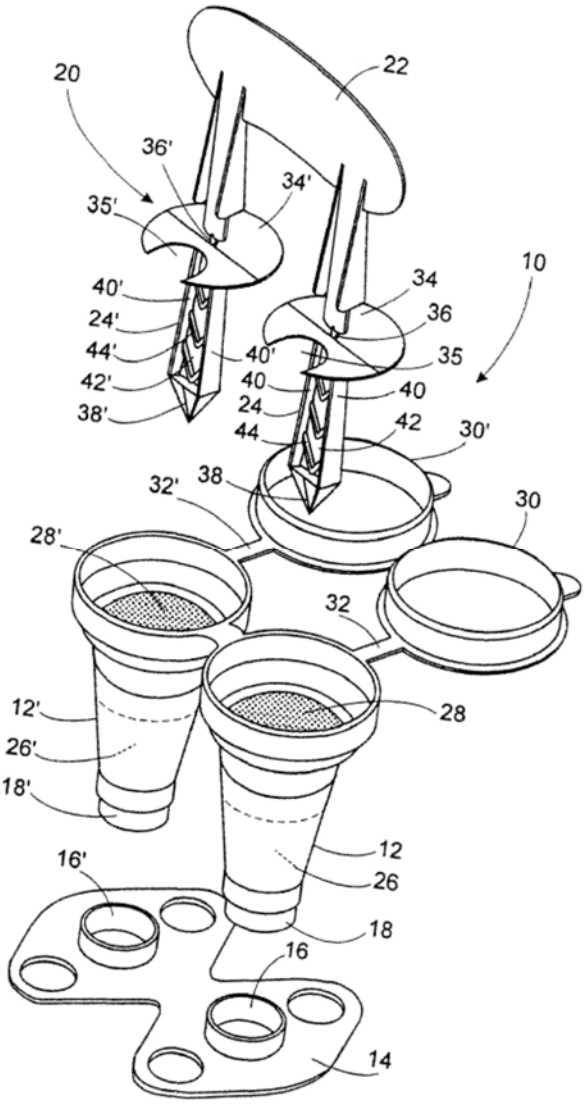
refrigeration or freezing." EX1008 7:10-21. Shuber teaches that "a stabilization solution may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center." EX1008 10:10-15. Shuber explains that the stabilized sample "can be characterized in a nucleic acid integrity analysis, multiple mutation assay, or methylation study." EX1008 8:27-31, 12:8-14, 13:21-14:16. Shuber describes the possibility of using multiple tests in combination to improve the test's sensitivity for detection of CRC. In particular, "aspects of the invention may be particularly useful for detecting indicia of adenoma and/or early-stage cancer" and "to avoid or reduce the number of false negative results in a screen of a population of individuals for one or more indicia of adenoma or early-stage cancer (e.g., using DNA integrity assay, a multiple mutation assay, a hypermethylation assay, **or any combination thereof**.)". EX1008 28:18-27, emphasis added.

6. Inbar (EX1009)

Inbar is a 1997 patent application disclosing a system for collecting multiple specimens from a stool sample into separate sealable containers, each containing its own preservation medium for preserving a chemical entity (such as cryptic blood) or living matter (such as bacteria or parasites), and then sealing the containers so that the separately preserved specimens can be shipped to a laboratory where different laboratory assays can be performed on each one.

EX1009 Abstract, 1:2-12, 3:48, 4:18-5:22; 9:7-30, Figures 1-4; EX1002 ¶¶138-142. An embodiment of the Inbar system is illustrated in Figure 1, reproduced below.

Inbar Figure 1.



VII. DETAILED EXPLANATION OF THE GROUNDS

A. Ground I: Lenhard in view of Itzkowitz and Vilkin

Lenhard, in view of Itzkowitz and Vilkin, renders obvious a method of processing a freshly collected fecal sample according to claims 1-4 and 14-19. Specifically, it would have been obvious for a POSA to use the iFOBT of Vilkin and the fecal collection and DNA stabilization process of Itzkowitz in the fecal screening method of Lenhard to arrive at the method of the challenged claims. EX1002 ¶¶144-219.

Lenhard discloses a method for noninvasive CRC detection in which a portion of a patient's stool sample is removed and tested for blood proteins using gFOBT and the remainder of the sample is tested for tumor-derived DNA using methylation of the HIC1 gene promoter as a biomarker. EX1004 pp.142, 144-145. Lenhard teaches that **"[t]he combination** of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs." EX1004 p.143, emphasis added. Detecting both tumor-derived DNA and fecal blood resulted in "increased detection rates for CRCs" and, in fact "detected all localized cancers." EX1004 p.147.

Lenhard therefore discloses a method of processing a fecal sample that includes collecting it from a subject, testing a first portion for cancer-specific DNA and testing a second portion for blood proteins. EX1002 ¶¶145-148. While

Lenhard does not disclose use of a stabilizing buffer that retains DNA integrity in the first portion, or use of a buffer to prevent degradation of blood proteins in the second portion, use of such buffers was routine in the art, as evidenced by Itzkowitz and Vilkin, respectively. EX1002 ¶¶148-166.

First, it would have been obvious for a POSA to replace the gFOBT of Lenhard with the iFOBT of Vilkin, in which a portion of a stool sample is stabilized in a buffer that prevents blood protein degradation so it can be sent to a diagnostic laboratory for automated analysis. EX1005 pp.2519-2520. A POSA would be motivated to modify Lenhard's assay to include Vilkin's iFOBT because Vilkin teaches numerous advantages of iFOBT over gFOBT, including that iFOBT (1) has a higher sensitivity than gFOBT, (2) eliminates the need for the diet restrictions associated with gFOBT, and (3) is quantitative, which allows a physician to choose the optimal fecal Hb threshold level for a patient. EX1005 pp.2519, 2524. Thus, a POSA would recognize Vilkin's iFOBT, including stabilization of blood proteins in a buffer during transit to the laboratory, as a superior alternative to the gFOBT used in Lenhard. EX1002 ¶149-153.

The advantages of iFOBT over gFOBT were well known by the Priority Date. *Id*. For example, a 2007 review article teaches that iFOBT technology "simplifies the testing process, removes the need for diet and drug restrictions, provides for preferred and more acceptable stool-sampling methods such as

brushes or probes rather than a wooden spatula, and is achieved while collecting fewer fecal samples." EX1020 p.29. It further notes that iFOBT "provide for an improved sensitivity/specificity ratio; in other words, they can achieve better sensitivity without an unacceptable deterioration in specificity." *Id.* It concludes that "[o]bviously, [iFOBT] overcome most of the disadvantages presented by GFOBT, are superior to GFOBT in terms of participation as well as performance and should replace GFOBT in two-step screening." EX1020 p.30. Another 2007 paper recognized these same advantages to iFOBT and concluded that "**it is time to give colorectal cancer screening a new future by using I-FOBT instead of G-FOBT**." EX1021 p.214, emphasis added.

Accordingly, based on the express teachings of Vilkin and the knowledge in the art, a POSA would be motivated to modify the diagnostic assay of Lenhard by replacing the gFOBT of Lenhard with the superior iFOBT of Vilkin, including its use of a stabilization buffer to permit at-home collection and shipment of the sample to a diagnostic laboratory. EX1002 ¶¶149-153.

Second, a POSA also would have been motivated to improve Lenhard's diagnostic assay by combining a portion of a stool sample with a DNA stabilizing buffer in a sealable container prior to its shipment to a diagnostic laboratory, as was done in Itzkowitz. EX1002 ¶154-168; EX1006 p.112.

Lenhard provides few details regarding sample collection beyond stating that samples were collected before cathartic preparation and then aliquoted by the laboratory. EX1004 p.143. However, a POSA would have been motivated by Itzkowitz's teachings to combine an at-home collected stool sample with a stabilizing buffer so it could be collected at a patient's home and then shipped to a diagnostic laboratory without freezing. *Id.* Itzkowitz states that addition of DNA stabilization buffer to stool "was shown to prevent DNA degradation for several days" which improved the sensitivity of both the DNA marker panel used and the DIA for detecting CRC. EX1006 pp.111, 116. Itzkowitz states that their "preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirms a very high degree of patient satisfaction." EX1006 pp.116-117.

By the Priority Date, the advantages of using DNA stabilizing buffer were well known. EX1002 ¶¶160-162. Olson, a 2005 paper cited by Itzkowitz, explains that "one of the central challenges [of DNA-based CRC assays] is to preserve the integrity of human DNA in the hostile stool environment, particularly during sample transport, to recover, amplify, and interrogate the DNA for known cancer-related abnormalities." EX1022 p.186. Olson states that "to maximize clinical sensitivity of fecal DNA assays, it is important to maximize the recovery of otherwise scarce amounts of human DNA." EX1022 p.190. Olson concludes that

"addition of stabilization buffer to samples upon collection should provide a robust means of storing (and transporting) samples at room temperature." *Id.*

A POSA therefore would be motivated to use the stool collection and DNA stabilization methods of Itzkowitz in Lenhard's assay to maintain DNA integrity in a portion of the fecal sample, allowing it to be collected at home and shipped to a diagnostic laboratory without freezing. EX1002 ¶¶159-164.

In summary, as of the Priority Date, a POSA would have been motivated to modify the CRC analysis method of Lenhard by replacing the gFOBT with the iFOBT of Vilkin and using the stool collection and stabilization methods of Itzkowitz. EX1002 ¶¶165-166. The result of these obvious improvements would be a method for processing a freshly-collected fecal sample in which a patient defecates into a sealable vessel (as described in Itzkowitz), removes a portion of the sample and combines it with a buffer that stabilizes blood proteins in a separate sealable container (as described in Vilkin), and then adds DNA stabilizing buffer to the remaining sample before sealing the original sealable vessel (as described in Itzkowitz). *Id.* The patient would then send both sealed containers to a diagnostic laboratory for a combination of DNA methylation and iFOBT analysis, which Lenhard teaches provides improved assay sensitivity compared to either test alone. *Id.*

A POSA would have a reasonable expectation that the resulting assay would be successful because it amounts to the routine performance, in combination, of two well-established prior art tests that already had been shown to work on fecal samples. EX1002 ¶167.As set forth below, the above-described assay meets all limitations of claims 1-4 and 14-19 of the '746 patent.

In IPR2024-00459, the Board instituted IPR and found Petitioner had shown a reasonable likelihood of prevailing in its assertion that the narrower claims of the '746 patent's parent were unpatentable as obvious based on the same art and arguments presented in Ground I herein. EX1033 pp.9-20.

1. Claim 1

a. "A method of processing a freshly-collected fecal sample without freezing, the method comprising:"

To the extent the claim 1's preamble is limiting, it is rendered obvious by Lenhard in view of Vilkin and Itzkowitz.

When the diagnostic assay of Lenhard is improved by incorporating the sample collection and stabilization methods of Itzkowitz and the iFOBT of Vilkin, as described above, the resulting assay produces two samples: a "first portion" in a DNA stabilizing buffer and a "second portion" in a blood protein stabilizing buffer, both of which are processed without freezing, as taught by both Itzkowitz and Vilkin. EX1006 p.112; EX1005 p.2520; EX1002 ¶¶170-173.

b. "a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;"

Vilkin and Itzkowitz both describe at-home sample collection by a human subject. EX1005 p.2520; EX1006 p.112. Itzkowitz notes that at-home collection is advantageous because "geographic access becomes less of a barrier, there is no loss of time from work, and no formal health care visit." EX1006 p.115. The at-home collection methods disclosed in Vilkin and Itzkowitz would be used in the method rendered obvious by Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶174-178; EX1005 p.2520; EX1006 p.112.

c. "b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel"

Lenhard describes an assay in which a first portion of a stool sample is tested for tumor-derived DNA and a second portion is tested for blood proteins using gFOBT. EX1004 pp.143-145.

A POSA would have been motivated to combine the DNA stabilizing buffer of Itzkowitz with the first portion of the fecal sample generated according to Lenhard in a sealable vessel to preserve the integrity of the DNA in that portion of the sample when it was shipped to a diagnostic laboratory for analysis. EX1006 p.112. Itzkowitz states that addition of the DNA stabilizing buffer to the stool "was shown to prevent DNA degradation for several days" which improved the

sensitivity of both the DNA marker panel used and the DIA for detecting CRC. EX1006 pp.111, 116. As Itzkowitz teaches that inclusion of a DNA stabilizing buffer resulted in an improved "second-generation fecal DNA test" EX1006 pp.111, 112, it would have been obvious to use this known approach similarly to improve the DNA test used in Lenhard in the same way. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

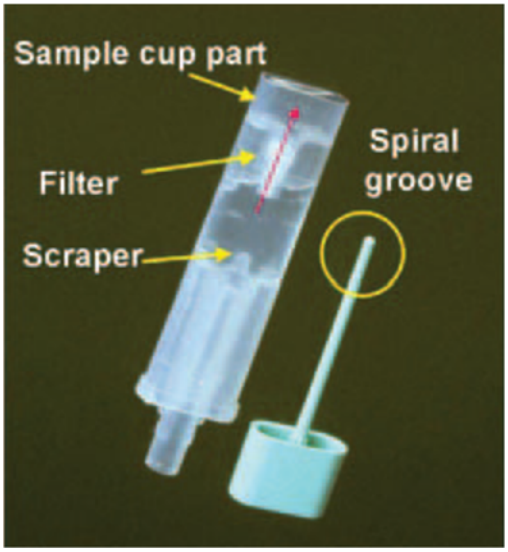
A POSA would also understand that the collection vessel containing the first portion of the fecal sample in DNA stabilizing buffer would be sealed prior to shipping so that the stabilizing buffer and sample are contained, and emanation of odors is prevented. EX1002 ¶185.

Accordingly, when the DNA stabilizing buffer used in Itzkowitz is incorporated into the assay of Lenhard, the result is a method that includes combining a first portion of the fecal sample in a sealable collection vessel with a stabilizing buffer, and sealing the collection vessel. EX1002 ¶¶179-186.

d. "c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container."

Lenhard discloses the testing of a second portion of the fecal sample for blood proteins using gFOBT. EX1004 pp.143-145. As discussed above, it would have been obvious to replace the gFOBT with the iFOBT of Vilkin in view of the

numerous advantages of iFOBT taught by Vilkin and known in the art. In the iFOBT described in Vilkin, the patient removes a portion of the fecal sample using a "fecal test device" shaped like a small test tube having a probe attached to the inner portion of the device's cap (illustrated below). EX1005 p.2520. The probe is "poked into the stool and then pushed back into the tube, past a scraper and through a membrane into the sample cup." *Id*. This results in sealing the fecal test sampling device with the tip "put in a closed amount of Hb stabilizing buffer." *Id*. Vilkin teaches that when the samples are in this buffer they "maintained their elevated fecal Hb levels for 21 or more days" when stored at 4°C. EX1005 p.2521.



Accordingly, when the gFOBT of Lenhard is replaced with the iFOBT of Vilkin, the resulting assay includes combining a second portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or

degradation of blood proteins found in a fecal sample, and sealing the sealable container. EX1002 ¶¶187-189.

In sum, when the fecal collection and DNA stabilization process of Itzkowitz, and the iFOBT and sample stabilization of Vilkin, are incorporated into the diagnostic method taught by Lenhard, the result is a method in which each step of claim 1 is performed. EX1002 ¶¶169-190. Claim 1 is therefore obvious over the prior art.

2. Claim 2: "The method of claim 1, further comprising delivering the sealable vessel… and the sealable container… to a medical diagnostics laboratory"

The above-described method rendered obvious by Lenhard in view of Vilkin and Itzkowitz includes delivering the sealed containers containing the first and second portions the fecal sample in their respective buffers to a medical diagnostics laboratory. Indeed, all three references include delivery of fecal samples to a medical diagnostics laboratory for testing and, therefore, render Claim 2 obvious. EX1002 ¶¶191-193; EX1004 p.143; EX1005 p.2520; EX1006 p.112.

3. Claim 3

a. "A method of processing a fecal sample, the method comprising:"

To the extent claim 3's preamble is limiting, it is rendered obvious by Lenhard in view of Vilkin and Itzkowitz. All three references disclose methods of processing fecal samples. EX1002 ¶195; EX1004; EX1005; EX1006.

b. "a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in the fecal sample, wherein the pair of portions are obtained by the method of claim 1;"

The above-described method, rendered obvious by Lenhard in view of Vilkin and Itzkowitz, includes receipt of the sealed containers containing the first portion and second portion of the fecal sample by technicians at a medical diagnostics laboratory, where the portions are then analyzed. All three references include delivery of fecal samples to a medical diagnostics laboratory and, as such, render this step obvious. EX1002 ¶¶196-198.

c. "b) extracting nucleic acid from the first portion of the fecal sample;"

Performance of the DNA methylation assay described in Lenhard includes isolation of DNA from the first portion of the stool sample. EX1004 p.143. Extraction of DNA from stool samples is a standard step performed when a stool sample is tested for DNA. EX1002 ¶199. Indeed, Itzkowitz extolls the advantages of an "enhanced DNA extraction" process on fecal DNA tests. EX1006 p.112. Extracting nucleic acid from the first portion of the fecal sample is performed in

both Lenhard and Itzkowitz and therefore would also be included in the method rendered obvious by Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶199-200.

d. "c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and"

Performance of the DNA methylation assay described in Lenhard includes testing the first portion of the fecal sample for an amount of methylated HIC1 promoter DNA. EX1004 p.144. The second-generation stool DNA test described in Itzkowitz tests the fecal sample for the presence of long DNA using a DIA and an amount of methylated vimentin DNA using a methylation assay. EX1006 p.112. Accordingly, testing for an amount of a human nucleic acid is performed in both Lenhard and Itzkowitz and would also be included in the method rendered obvious by Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶201-202.

e. "d) testing the second portion of the fecal sample for an amount of blood protein present in the second portion of the fecal sample."

As explained above, it would have been obvious to replace the gFOBT of Lenhard with the iFOBT of Vilkin at least because of the numerous known advantages of using the iFOBT. The Vilkin iFOBT is a quantitative test of the level of the human blood protein, hemoglobin (Hb), in a portion of a stool sample. EX1005 pp.2519, 2522, Table 1. When the gFOBT of Lenhard is replaced with the

iFOBT of Vilkin, the resulting assay therefore includes testing of a second portion of the sample for an amount of blood protein in that portion. EX1002 ¶¶203-207.

In sum, when the iFOBT of Vilkin and the fecal collection and DNA stabilization process of Itzkowitz are incorporated into the diagnostic method of Lenhard it results in a method in which each of the steps of claim 3 is performed, rendering the claim obvious. EX1002 ¶¶194-207.

4. Claim 4: "The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene."

Claim 4 of the '746 patent recites that the assay includes "determining expression from a human gene." The process of "determining expression of a human gene," in claim 4 must at least include testing for indirect indicators of gene expression, such as epigenetically-modified human DNA, as recited in claim 5, and methylated human DNA, as recited in claim 6. EX1002 ¶¶208-209. Both claims 5 and 6 depend from claim 4 and therefore narrow claim 4's scope. *E.g., Alcon Research, LTD. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012). Consistently, the '746 patent defines "epigenetic modification" as including any alteration in the DNA, **generally resulting in diminished gene expression**, which is mediated by mechanisms other than alterations in the primary nucleotide sequence of a gene." EX1001 12:48-52, emphasis added.

The fecal DNA assay disclosed in Lenhard includes testing the first portion of the sample for the presence of methylated human DNA, and therefore includes determining expression from a human gene in that portion of the sample. EX1004 p.144. Similarly, Itzkowitz discloses testing for methylation of the vimentin gene. EX1006 p.111. Accordingly, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz includes testing for expression from a human gene. EX1002 ¶¶208-211. Claim 4 is therefore obvious.

5. Claim 14: "The method of claim 3, wherein testing for an amount of blood protein present in the second portion comprises testing for a concentration of hemoglobin in the second portion, wherein a concentration of hemoglobin is indicative of a presence of blood in the fecal sample."

Claim 15: "The method of claim 14, wherein the testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin."

As explained above, it would have been obvious to replace the gFOBT of Lenhard with the iFOBT of Vilkin at least because of the numerous known advantages of iFOBT. Vilkin's iFOBT uses an immunochemical process to test for a concentration of hemoglobin in the second portion of the fecal sample, wherein the concentration of hemoglobin is indicative of a presence of blood in the fecal sample. EX1005 pp.2519, 2520-2522, Table 1. Accordingly, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz includes the immunochemical testing for a concentration of hemoglobin

that indicates the presence of blood in the fecal sample. EX1002 ¶¶212-215. Claims 14 and 15 are therefore obvious.

6. Claims 16-19: "The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the second portion is at least [5, 10, 20, or 50] ng/ml."

Claims 16-19 each recites a particular threshold hemoglobin concentration used when determining whether the removed portion of the fecal sample is considered positive for the presence of blood. Each of claims 16-19 is rendered obvious by Lenhard in view of Vilkin and Itzkowitz because selecting any of the claimed hemoglobin thresholds would have been a matter of routine optimization of a result-effective variable. *In re Applied Materials, Inc*., 692 F.3d 1289, 1295, 1297 (Fed. Cir. 2012).

Vilkin explains that one of the advantages of its test is that it "allows the physician to choose the optimal fecal Hb threshold level that triggers a follow-up colonoscopy." EX1005 p.2524. Such threshold selections "involve an evaluation of cost-benefit." *Id.* Selection of a lower threshold typically increases the sensitivity of the assay and decreases specificity of the assay, while selection of a higher threshold has the opposite effect. EX1002 ¶217. This is illustrated, for example, in Table 2 of Vilkin, which shows how different thresholds between 50 ng/ml and 200 ng/ml affect the sensitivity and specificity of the disclosed iFOBT. EX1005

p.2523. Use of lower hemoglobin thresholds was routine in the art. EX1002 ¶217; EX1005 p.2523; EX1021 p.210; EX1023 p.140. A POSA would therefore routinely optimize the threshold used by balancing the risk that a false-negative result fails to diagnose a patient's CRC against the risk that a false-positive result subjects a patient to an unnecessary colonoscopy. EX1002 ¶217.

The hemoglobin concentration measured in quantitative iFOBT is the concentration of hemoglobin in protein stabilizing buffer, not the amount of hemoglobin in the stool sample itself. EX1005 p.2520-2521. The concentration of hemoglobin in the buffer will depend both on how much stool is collected and what volume of buffer is used. EX1002 ¶218. The hemoglobin threshold will therefore be routinely optimized, in part, based on how the fecal sample was collected. *Id.*

Accordingly, the hemoglobin thresholds recited in claims 16-19 are result-effective variables that are the product of routine optimization and therefore are obvious. EX1002 ¶¶216-219.

B. Ground II: Lenhard in view of Itzkowitz and Vilkin, in further view of Kanaoka

1. Claim 12: "The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the human gene."

As set forth in Section VII(A), it would have been obvious to a POSA to improve the stool diagnostic assay of Lenhard by replacing the disclosed gFOBT with the iFOBT of Vilkin and incorporating the stool collection and DNA stabilization methods of Itzkowitz.

A POSA would also find it obvious to further modify the above-described method to incorporate the COX-2 RNA detection process disclosed in Kanaoka to arrive at the method of claim 12. EX1002 ¶¶220-224; EX1007 ¶¶021-026. Kanaoka states that the use of COX-2 RNA as a biomarker "has a higher detection sensitivity compared to the detection of gene mutation of APC, K-ras, or p53." EX1007 ¶0076. Indeed, in Example 1, Kanaoka reports that the disclosed fecal COX-2 RNA assay exhibited a sensitivity of 90% and a specificity of 100%. EX1007 ¶0065. A POSA therefore would have been motivated to use Kanaoka's mRNA detection assay either in place of or in addition to a DNA assay, like the one disclosed in Lenhard, to improve assay sensitivity. EX1002 ¶220-224.

Example 1 of Kanaoka provides further motivation to combine Kanaoka's assay with an iFOBT, like the one disclosed in Vilkin. EX1002 ¶222. In this

example, samples were tested using both an RNA assay and iFOBT. EX1007 ¶¶0055-0068. The iFOBT identified a CRC patient as positive who was missed by the RNA assay, while the RNA assay identified three CRC patients missed by iFOBT. EX1007 ¶¶0067-0068. A POSA would have been motivated to combine the Kanaoka RNA assay with iFOBT, such as the one disclosed in Vilkin, to increase the sensitivity of both assays. EX1002 ¶222.

A POSA would have had a reasonable expectation of successfully incorporating the RNA assay of Kanaoka into the fecal processing method rendered obvious by Lenhard, Vilkin and Itzkowitz. Example 1 of Kanaoka provides a working example of the successful combination of an RNA assay with iFOBT. EX1007 ¶¶0055-0068. A POSA would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because, by the Priority Date, the literature reported that "preserving fecal samples at room temperature for a duration of 5 days, in a medium ***suitable for DNA and RNA analysis is feasible***." EX1024 p.131, emphasis added. A POSA therefore would have a reasonable expectation of successfully using the Kanaoka fecal RNA assay in a method of processing a freshly-collected fecal sample, as set forth in the challenged claims. EX1002 ¶223.

As Kanaoka discloses detection of an amount of RNA expressed from a human gene, the method of processing a fecal sample rendered obvious by Lenhard

in view of Vilkin, Itzkowitz, and Kanaoka includes such a step. EX1002 ¶¶220-224. Claim 12 is therefore obvious.

2. Claim 13: "The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR)"

When the COX-2 RNA detection process of Kanaoka is incorporated into the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin, and Itzkowitz, the resulting method includes measuring an amount of RNA expressed from the gene using RT-PCR, which Kanaoka employs to detect RNA expression. EX1007 ¶¶0021-0025, 0047-0048, 0059. Accordingly, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin, Itzkowitz, and Kanaoka includes such a step. EX1002 ¶¶225-226. Claim 13 is therefore obvious.

C. Ground III: Shuber and Vilkin

Shuber and Vilkin render obvious a method of processing a freshly collected fecal sample according to claims 1-4, and 14-19 of the '746 patent. These claims are directed to the separation of a fecal sample into two portions so a pair of well-established assays—one detecting nucleic acids as disclosed in Shuber and the other detecting blood proteins as disclosed in Vilkin—can separately be performed on different portions of the same sample. It would have been obvious for a POSA

to combine the fecal DNA assay set forth in Shuber with the iFOBT of Vilkin to arrive at the method of the challenged claims.

As discussed above, Vilkin discloses an iFOBT in which a portion of a fecal sample is removed to a sealable container where it is mixed with hemoglobin stabilizing buffer. EX1005 p.2520. The sealed container is then transported to a diagnostic laboratory without freezing, where a benchtop instrument is used to quantitate the level of hemoglobin in the sample. EX1005 pp.2520-2521.

Shuber describes fecal DNA analysis in which a stool sample is deposited into a sealable container to which a stabilizing solution is added before it is sealed and shipped to a testing center. EX1008 29:8-19, 10:12-14. The stabilizing solution is added "to preserve a sample for analysis using a nucleic acid integrity assay along with a mutation detection assay (e.g., a multiple mutation panel assay), a hypermethylation assay, or both." EX1008 7:19-21. Shuber emphasizes that "[m]ethods of the invention do not require refrigeration or freezing." EX1008 7:12.

A POSA would have been motivated to combine a DNA-based stool test, such as those disclosed in Shuber, with a blood protein-based stool test, such as the iFOBT disclosed in Vilkin, to arrive at a CRC diagnostic test with improved sensitivity. EX1002 ¶227-239.

By the Priority Date, the advantages of combining such stool DNA and blood protein assays were well understood in the art. EX1002 ¶233-236. For

example, Nishikawa, a 2002 paper reporting a fecal DNA assay similar to those disclosed in Shuber, concluded that the disclosed assay "should provide a more sensitive and specific tool for mass screening of colorectal cancer than is currently available, **especially if used in combination with fecal occult blood testing**." EX1011 p.112, emphasis added.

That combining fecal DNA assays with FOBT increases sensitivity is further supported by Lenhard, which reported that "[t]he **combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs**." EX1004 p.143, emphasis added. Lenhard determined that while HIC1 methylation detected 42% of CRCs and FOBT detected 35% of CRCs, the combination of the two markers was able to detect 65% of CRCs. EX1004 p.147, Table 4. Lenhard also noted that "the **combined test** detected all localized cancers." EX1004 p.147, emphasis added.

Further evidencing the recognized value of combining DNA assays with FOBT, Kutzner examined "whether the analysis of three faecal DNA markers has the potential to complement or even to replace the FOBT and whether **the combined application of the two methods might increase the overall diagnostic reliability,**" and concluded that "[t]he **combined application** of FOBT and MD [a DNA methylation assay] **resulted in an overall sensitivity, which could not be achieved by any of the methods alone**." EX1012 p.34, abstract, emphasis added.

Indeed, before the Priority Date, the 2008 joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology proposed investigating whether "including a sensitive gFOBT or FIT at the time of testing would **improve sensitivity [of DNA-based assays] without adversely affecting specificity**." EX1013 p.1578, emphasis added.

Accordingly, a POSA would have been motivated to combine a fecal DNA test, such as disclosed in Shuber, with a fecal blood test, like the iFOBT disclosed in Vilkin, to improve sensitivity of CRC diagnosis. EX1002 ¶¶232-237. When the combined test was performed, a patient would: (1) collect a fecal sample in a sealable vessel at home (as in Shuber); (2) use a fecal test sampling device to remove a portion of the sample and combine it with hemoglobin stabilizing buffer (as in Vilkin); (3) add DNA stabilizing buffer to the remaining sample before sealing the vessel (as in Shuber); and (4) ship the sealed sampling device and sealed container to a diagnostic laboratory for testing (as in Vilkin and Shuber, respectively). *Id.* A POSA would recognize that separation of the sample by patients at home ensures that the relevant biomarker in each portion (hemoglobin in one, DNA in the other) is stabilized with an appropriate buffer prior to shipment, as taught by Vilkin and Shuber. *Id.*; EX1005 p.2520; EX1008 10:10-15, 29:8-19.

A POSA would have a reasonable expectation of successfully combining such assays because doing so requires no more that the use of routine methods to perform of a pair of well-established assays on separate portions of a fecal sample. EX1002 ¶238.

As set forth below, when the methods of Shuber and Vilkin are performed on a fecal sample, the result is the fecal processing method set forth in claims 1-4 and 14-19. EX1002 ¶¶227-271.

In IPR2024-00459, the Board instituted IPR and found Petitioner had shown a reasonable likelihood of prevailing in its assertion that the narrower claims of the '746 patent's parent were unpatentable as obvious based on the same art and arguments presented in Ground III herein. EX1033 pp.20-23.

1. Claim 1

a. "A method of processing a freshly-collected fecal sample without freezing, the method comprising:"

To the extent claim 1's preamble is limiting, it is rendered obvious by Shuber and Vilkin. As the processes of Shuber and Vilkin both include the processing of freshly-collected fecal samples without freezing, the obvious combination of the two assays would as well. EX1005 p.2520; EX1008 7:10-12; EX1002 ¶¶240-241.

b. "a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;"

Shuber and Vilkin both describe sample collection by a human subject at home. EX1008 29:8-19; EX1005 p.2520. Shuber suggests at-home collection, stating that stabilizing buffer "may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center." EX1008 10:12-14. The at-home collection methods disclosed in Shuber and Vilkin would be used in the method they render obvious. EX1002 ¶¶242-246 EX1008 29:8-19; EX1005 p.2520.

c. "b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel"

Shuber describes a fecal DNA analysis method in which DNA stabilizing buffer is combined with a stool sample "to preserve a sample for analysis using a nucleic acid integrity assay along with a mutation detection assay (e.g., a multiple mutation panel assay), a hypermethylation assay, or both." EX1008 7:19-21. Shuber states that the stool sample can be "directly deposited into a container (e.g., a sealable container)" to which the "stabilizing solution may be added." EX1008 29:8-19. The "container with sample and stabilization solution may be sealed for storage/shipping." *Id.*

Thus, performing the DNA test of Shuber and the iFOBT of Vilkin on a sample results in a first portion of the fecal sample being combined with a stabilizing buffer in a sealable vessel, which is sealed. EX1002 ¶247-248.

d. "c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container."

As discussed in Section VII(A)1c, when Vilkin's iFOBT is performed on a stool sample, a portion of the sample is obtained using a test device shaped like a small test tube having a probe attached to the inner portion of its cap. EX1005 p.2520. The probe is poked into stool to collect a portion of it, and then pushed back into the tube. *Id*. This results in sealing of the test device with the sample portion in hemoglobin stabilizing buffer. *Id.* Vilkin teaches that when samples are in this buffer they "maintained their elevated fecal Hb levels for 21 or more days" when stored at 4°C. EX1005 p.2521. Thus, the Vilkin iFOBT includes combining a portion of a fecal sample with a solution that prevents denaturation or degradation of hemoglobin in a sealable container, which is then sealed. EX1002 ¶¶249-250.

Thus, when the fecal DNA test of Shuber and the iFOBT of Vilkin are performed on a stool sample, a second portion of the fecal sample is combined with a solution that prevents denaturation or degradation of blood proteins found in the sample in a sealable container, which is then sealed. *Id*.

In sum, when the fecal DNA test of Shuber and the iFOBT of Vilkin are both performed on a stool sample, each of the steps of claim 1 is performed, rendering the claim obvious. EX1002 ¶¶249-251.

2. Claim 2: "The method of claim 1, further comprising delivering the sealable vessel… and the sealable container… to a medical diagnostics laboratory"

Both Shuber and Vilkin include delivery of the collected fecal samples to a medical diagnostics laboratory for testing. EX1008 10:10-15; EX1005 p.2520. Accordingly, when both tests are performed on a stool sample, this step would be performed on the resulting sealed containers as well. Claim 2, therefore, is obvious. EX1002 ¶¶252-254.

3. Claim 3

a. "A method of processing a fecal sample, the method comprising:"

To the extent claim 3's preamble is limiting, it is rendered obvious by Shuber and Vilkin, as both references are directed to methods of processing fecal samples. EX1008; EX1005.

b. "a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found

in the fecal sample, wherein the pair of portions are obtained by the method of claim 1;"

Obtaining the sealable containers generated according to the method of claim 1 is rendered obvious by Shuber and Vilkin, as both references disclose delivery of the collected fecal samples to a medical diagnostics laboratory for testing. EX1002 ¶¶256-257; EX1008 10:10-15; EX1005 p.2520.

c. "b) extracting nucleic acid from the first portion of the fecal sample;"

Performance of the fecal DNA assays described in Shuber includes purification of DNA from a portion of the sample. EX1008 15:18-16:17. Indeed, extraction of DNA from the stool sample is a standard step in an assay in which stool DNA is tested. EX1002 ¶258. Thus, performing the DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in extracting nucleic acid from the first portion of the fecal sample. *Id*.

d. "c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and"

Performance of the fecal DNA assay described in Shuber includes "analysis using a nucleic acid integrity assay along with a mutation detection assay (e.g., a multiple mutation panel assay), a hypermethylation assay, or both." EX1008 7:19-21. Each of these assays includes testing for an amount of a human nucleic acid. EX1002 ¶¶259-260. Thus, performing the DNA test of Shuber and the iFOBT of

Vilkin on a stool sample results in the extracted nucleic acid being tested for an amount of a human nucleic acid. *Id*.

e. "d) testing the second portion of the fecal sample for an amount of blood protein present in the second portion of the fecal sample."

The Vilkin iFOBT is a quantitative test of the level of human hemoglobin (Hb) in a portion of a stool sample. EX1005 pp.2519, 2522. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the testing of the second portion of the sample for an amount of blood protein in that portion. EX1002 ¶261-262.

In sum, when the fecal DNA test of Shuber and the iFOBT of Vilkin are both performed on a stool sample, each of the steps of claim 3 is performed, rendering the claim obvious. EX1002 ¶¶255-262.

4. Claim 4: "The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene."

Claim 4 of the '746 patent recites that the assay include "determining expression from a human gene." For the reasons explained in Section VII(A)4, as used in the '746 patent, testing a nucleic acid by determining expression from a human gene at least includes detection of a methylated human gene or promoter in the nucleic acid.

Shuber discloses fecal DNA assays that include testing nucleic acids for the presence of methylated human genes. EX1008 14:1-5. Thus, performing the DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in testing the extracted nucleic acid by determining expression from a human gene. EX1002 ¶¶263-265. Claim 4 is therefore obvious.

5. Claim 14: "The method of claim 3, wherein testing for an amount of blood protein present in the second portion comprises testing for a concentration of hemoglobin in the second portion, wherein a concentration of hemoglobin is indicative of a presence of blood in the fecal sample."

Claim 15: "The method of claim 14, wherein the testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin."

The iFOBT disclosed in Vilkin uses an immunochemical process to test for a concentration of hemoglobin in a portion of a fecal sample that is indicative of a presence of blood in the fecal sample. EX1005 pp.2519, 2520-2522, Table 1. Thus, performing the DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in use of an immunochemical process to test for a concentration of hemoglobin in the second portion. EX1002 ¶¶266-267. Claims 14 and 15 are therefore obvious.

6. Claims 16-19: "The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin

detected in the second portion is at least [5, 10, 20, or 50] ng/ml."

Claims 16-19 each recites a particular threshold hemoglobin concentration used to determine whether the removed portion of the fecal sample is considered positive for the presence of blood. Each of claims 16-19 is rendered obvious by Shuber and Vilkin. As explained in Section VII(A)6, selecting any of the claimed hemoglobin thresholds would have been a matter of routine optimization of a result-effective variable. *In re Applied Materials, Inc*., 692 F.3d 1289, 1295, 1297 (Fed. Cir. 2012). Accordingly, the hemoglobin thresholds recited in claims 16-19 are result-effective variables that are the product of routine optimization and are obvious. EX1002 ¶¶268-271.

D. Ground IV: Shuber and Vilkin, in further view of Kanaoka

1. Claims 12 "The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the human gene."

As set forth in Section VII(C), it would have been obvious to a POSA to combine the fecal DNA test of Shuber with the iFOBT of Vilkin to improve upon the sensitivity achieved by either assay alone. EX1002 ¶¶272-276. For the same reasons as set forth in Section VII(B)1, a POSA would have been motivated to use Kanaoka's RNA detection assay either in place of or in addition to a DNA assay, like those disclosed in Shuber, to improve assay sensitivity, and would have had a reasonable expectation of successfully doing so. *Id*. As Kanaoka discloses

detection of an amount of RNA expressed from a human gene, the method rendered obvious by Shuber, Vilkin, and Kanaoka includes such a step. *Id*. Claim 12 is therefore obvious.

2. Claim 13: "The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR)"

When the RNA detection process of Kanaoka is incorporated into the method rendered obvious by Shuber and Vilkin, as described above, the resulting method includes measuring RNA expression using RT-PCR, as done in Kanaoka. EX1007 ¶¶0021-0025, 0047-0048, 0059. Accordingly, the method of processing a fecal sample rendered obvious by Shuber, Vilkin, and Kanaoka includes such a step. EX1002 ¶277. Claim 13 is therefore obvious.

E. Ground V: Inbar

Inbar discloses a system for collecting multiple specimens from a stool sample into separate sealable containers, each containing its own medium for preserving a chemical entity or living matter, so that the multiple specimens can be shipped to a laboratory where different assays are performed on the separately preserved specimens. EX1002 ¶¶278-287; EX1009 Abstract, 1:2-12, 3:48, 4:18-5:22; 9:7-30, Figures 1-4.

Inbar explains that that "[c]ollection and transportation of a pasty material, such as stool… for the purpose of laboratory manipulation such as detection of

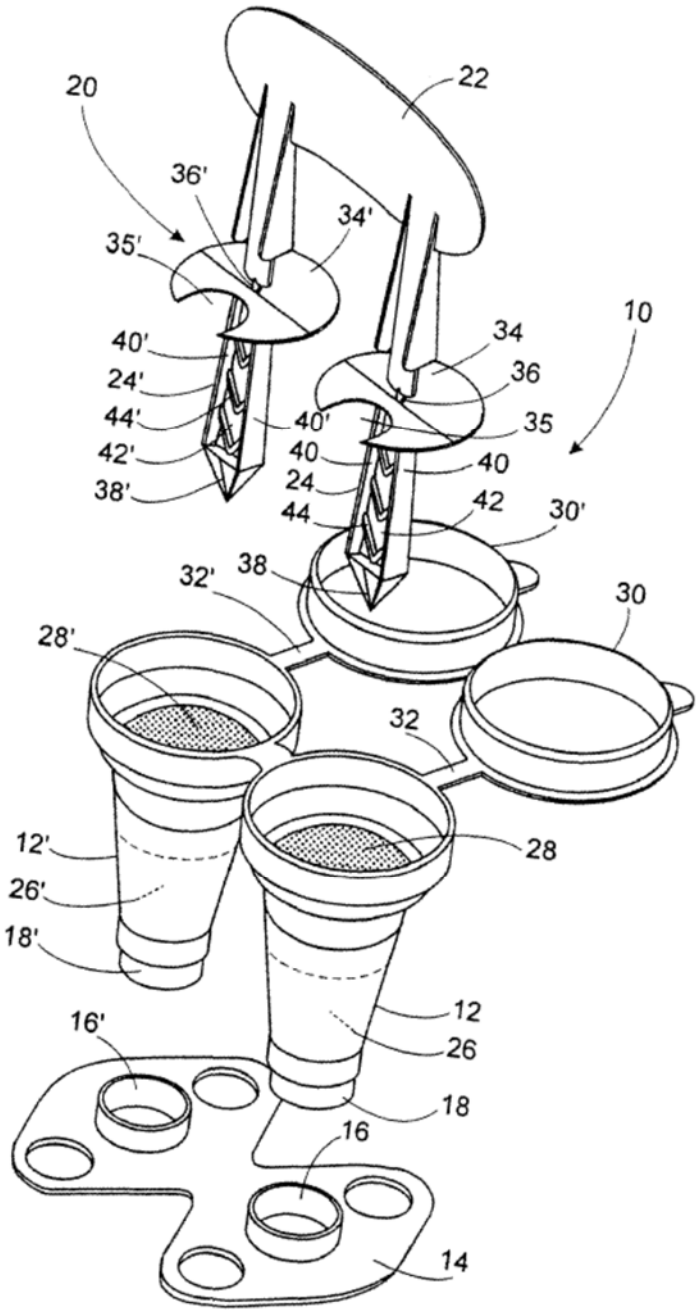
microorganism being bacteria or parasites, ***detection of cryptic blood***, preparation of a biochemical profile, etc., is an essential component of modern medicine…" EX1009 1:8-12, emphasis added. Inbar further states that when stool "is to be sampled for the purpose of two or more different laboratory assay… ***it would be preferable to provide a system for collection and transportation of pasty material which comprises two or more separate containers, each one holding a different transport or suspension medium***." EX1009 3:3-8, emphasis added. Inbar notes that "if the entity is a chemical substance, the medium will have composition which ensure the substance is preserved in a manner to avoid its deterioration." EX1009 4:4-6. Accordingly, "[w]ith appropriate preservation media, the samples may be stored for a lengthy period of time prior to assaying the chemical entity." EX1009 3:32-4:2.

In the Inbar system, stool is first excreted into a "stool collecting device" attached to a toilet seat. EX1009 6:18-32, Figures 6-8. This "device is fixed such that stool excreted by a person sitting on the toilet, falls into a sack-like collecting member… for later sampling by the sampling device." EX1009 10:11-12.

Next, multiple stool specimens are obtained from the collected stool and preserved in separate sealable containers using a system like the one illustrated in Figure 1, reproduced below. This system includes a "sampling device" (component 20), with two "collecting members" (components 24 and 24′), that are structured to

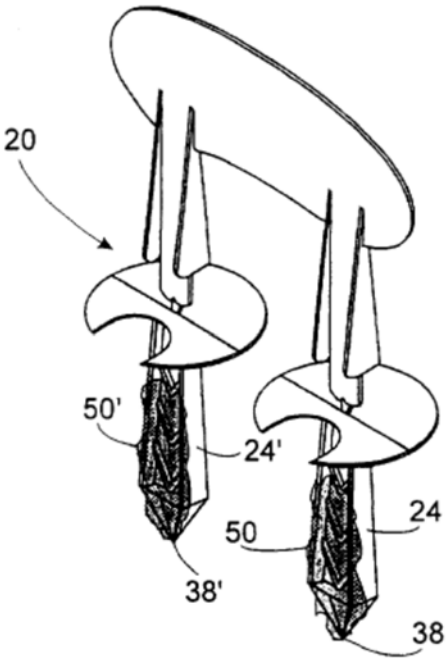
align with two sealable containers (components 12 and 12′), each containing a different “preservation medium” (components 26 and 26′). EX1009 3:20-23, 4:13-28, 5:1-23, 8:9-28. EX1009 3:48, 4:18-5:22.

Inbar Figure 1.



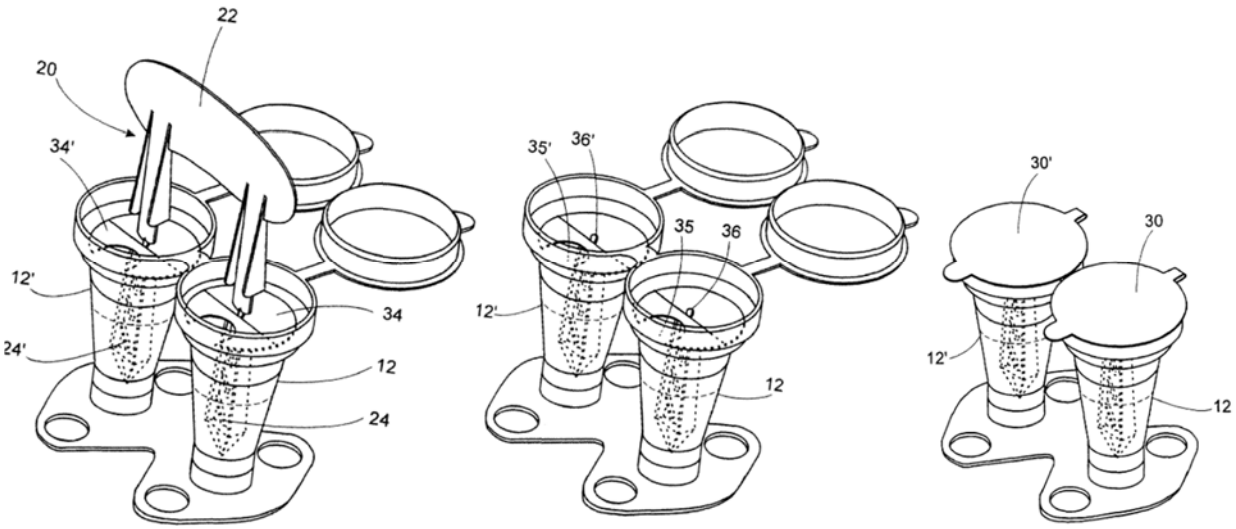
Stool specimens are collected by inserting the collecting members into stool, which results in separate stool specimens being retained on each collecting member, as shown in Figure 2. EX1009 9:7-11.

Inbar Figure 2



The stool-coated collecting members are then inserted into the preservation medium-containing containers, the top portion of the sampling device is broken off and the containers sealed. EX1009 9:13-26. These steps, illustrated in Figures 3-5, reproduced below, result in each stool specimen being combined with its own preservation medium in a separate sealed container, which is then transported to a laboratory for analysis. EX1009 1:13-16, 3:29-4:12, 6:4-17, 9:24-30.

Inbar Figures 3-5.



As explained in detail below, Inbar anticipates claims 1 and 2 of the '746 patent.

1. Claim 1

a. "A method of processing a freshly-collected fecal sample without freezing, the method comprising:"

Inbar discloses a method of processing a freshly-collected fecal sample. EX1002 ¶¶288-291; EX1009 6:18-32, 10:11-12. Inbar does not disclose freezing the samples, but rather teaches that "[w]ith appropriate preservation media, the samples may be stored for a lengthy time prior to assaying for the chemical entity." EX1009 1:2-4, 3:32-4:3; EX1002 ¶¶288-291. To the extent the claim 1's preamble is limiting, it is disclosed by Inbar. EX1002 ¶¶288-291.

b. "a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;"

Inbar discloses collection of a fecal sample from a human subject using a stool collection device that can be fixed to a toilet seat. EX1009 6:18-32, 10:1-15, Figures 6-8. A POSA would recognize that this fecal collection process would occur at a subject's home because Inbar states that specimens obtained from the fecal sample are combined with preservation medium in sealed containers and shipped to a laboratory for testing. EX1002 ¶¶292-294; EX1009 9:7-30.

c. "b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and

c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container."

Inbar teaches that multiple assay types can be performed on stool specimens, including detection of microorganisms like bacteria or parasites, and detection of cryptic blood, and explains that when stool "is to be sampled for the purpose of two or more different laboratory assay[s]… it would be preferable to provide a system for collection and transportation of [stool] which comprises two or more separate containers each one holding a different transport or suspension medium." EX1009 1:7-12, 3:3-8; EX1002 ¶¶295-304. To facilitate this, Inbar discloses use of

a two-pronged sampling device to transfer first and second stool specimens into a pair of sealable containers, each containing its own preservation medium, which are then sealed. EX1002 ¶¶ 295-304; EX1009 3:18-4:22, 8:2-9:30, Figures 2-5. Inbar therefore discloses combining first and second portions of a fecal sample with different stabilizing buffers in separate sealable vessels, which are then sealed. EX1002 ¶¶295-304.

Inbar teaches that, when testing a chemical substance (e.g., cryptic blood), the preservation medium "will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration." EX1009 4:2-8. A POSA would understand that, when one of the specimens is to be tested for cryptic blood, the medium used to preserve that specimen would prevent denaturation or degradation of blood proteins in that specimen. *Id*. The '746 patent admits that such buffers were "known in the art and commercially available" EX1001 18:33-37.

Inbar therefore discloses combining a first portion of the fecal sample with a stabilizing buffer in a sealable vessel, sealing the sealable vessel, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

Inbar discloses every element of, and therefore anticipates, claim 1. EX1002 ¶¶295-304.

2. Claim 2: "The method of claim 1, further comprising delivering the sealable vessel… and the sealable container… to a medical diagnostics laboratory"

Inbar discloses that after the two portions of the fecal sample are combined with their respective preservation media in sealed containers, "the containers are shipped to the laboratory… for laboratory testing." EX1009 9:24-30; EX1002 ¶305. Inbar therefore anticipates Claim 2.

F. Ground VI: Inbar, Shuber, and Vilkin

It would have been obvious to use the system of Inbar to prepare fecal specimens for testing using the DNA and blood protein assays of Shuber and Vilkin, respectively, to arrive at a method of processing a freshly collected fecal sample according to claims 1-4, and 14-19.

As described in Section VII(E), Inbar discloses a system for collecting multiple specimens from a stool sample into separate sealable containers, each containing its own preservation medium so that the specimens can be shipped to a laboratory and different assays performed on each separately preserved specimen. EX1002 ¶¶295-304; EX1009 Abstract, 1:2-12, 3:48, 4:18-5:22; 9:7-30, Figures 1-4. Inbar's system is specifically designed for the separate preservation of portions of a stool sample when different assays are to be performed each portion. EX1002 ¶¶306-308.

It would have been obvious to use Inbar's system to prepare specimens for performance of both a fecal DNA assay, as disclosed in Shuber, and an iFOBT, as disclosed in Vilkin. EX1002 ¶307; EX1008 7:19-21; EX1005 pp.2520-2521. A POSA would have been motivated to perform both a DNA assay and an iFOBT on a stool sample to arrive at a CRC diagnostic test with improved sensitivity, as explained in Section VII(C). EX1002 ¶¶232-236.

Inbar teaches that the system it provides is "for assaying a plurality of entities, which require different media" and that it therefore "comprises at least two containers, each holding a different preservation medium, each suitable for different entities." EX1009 4:16-18. Inbar further teaches that the preservation medium "will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration." EX1009 4:2-8. A POSA would therefore understand that Inbar's system would incorporate a DNA and blood protein stabilizing buffers, respectively, when it is being used to prepare specimens for a DNA test and an iFOBT, and would be motivated to do so. EX1002 ¶¶307-308; EX1008 7:19-2; EX1005 p.2520.

A POSA would have a reasonable expectation of successfully combining such assays using the Inbar system because doing so amounts to using the Inbar system for its intended purpose to facilitate performance of a pair of well-established assays on separate portions of a fecal sample. EX1002 ¶309.

As set forth below, when the system of Inbar is used to prepare fecal specimens for the assays of Shuber and Vilkin, the result is the fecal processing method set forth in claims 1-4, and 14-20. EX1002 ¶¶310-329.

1. Claim 1

a. "A method of processing a freshly-collected fecal sample without freezing, the method comprising:"

As set forth in Section VII(E)1, Inbar discloses a method of processing a freshly collected fecal sample without freezing. To the extent Inbar does not expressly state that the fecal sample is unfrozen, it is rendered obvious by Shuber and Vilkin, which both teach the processing of fecal samples without freezing. EX1005 p.2520; EX1008 7:10-12. EX1002 ¶311.

b. "a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;"

As set forth in Section VII(E)1, Inbar discloses collecting a fecal sample from a human subject at home. To the extent Inbar does not expressly state that the fecal sample is collected at home, it is rendered obvious in combination with Shuber and Vilkin, which both describe at-home sample collection. EX1008 29:8-19; EX1005 p.2520; EX1002 ¶312.

c. "b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel"

As set forth in Section VII(E)1, Inbar discloses combining a first portion of the fecal sample with a stabilizing buffer in a sealable vessel, and sealing the sealable vessel. Accordingly, when the Inbar system is used to prepare a specimen for a DNA assay, as set forth above, a DNA stabilizing buffer like the one disclosed in Shuber would be used as the preservation medium for that portion. EX1008 7:19-21; EX1002 ¶313. Inbar teaches that "if the entity [to be assayed] is a chemical substance [in this case, DNA], the medium will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration." EX1009 4:3-6;

Thus, use of the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin results in a first portion of the sample being combined with a stabilizing buffer in a sealable vessel, which is sealed. EX1002 ¶314.

d. "c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container."

As set forth in Section VII(E)1, Inbar discloses combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container. Thus, when the Inbar system is used to prepare a portion of a fecal sample for an iFOBT, as disclosed in Vilkin, a buffer that prevents denaturation or degradation of blood

proteins would be used as the preservation medium for that portion. Inbar states that "if the entity [to be assayed] is a chemical substance [in this case the blood protein hemoglobin], the medium will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration." EX1009 4:3-6. The '746 patent admits that buffers that prevent denaturation or degradation of blood proteins were "known in the art and commercially available." EX1001 18:33-37; EX1005 pp.2520-2521.

Thus, use of the Inbar system to prepare specimens for the assays of Shuber and Vilkin results in the combining a second portion of the sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample in a sealable container, which is then sealed. EX1002 ¶¶315-316.

In sum, when the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin, each of the steps of claim 1 is performed, rendering the claim obvious. EX1002 ¶¶306-317.

2. Claim 2: "The method of claim 1, further comprising delivering the sealable vessel… and the sealable container… to a medical diagnostics laboratory"

Each of Inbar, Shuber and Vilkin disclose delivery of the collected fecal samples to a medical diagnostics laboratory for testing. EX1009 9:24-30; EX1008 10:10-15; EX1005 p.2520. Accordingly, when the Inbar system is used to prepare

specimens for the assays of Shuber and Vilkin, this step would be performed. Claim 2, therefore, is obvious. EX1002 ¶318.

3. Claim 3

a. "A method of processing a fecal sample, the method comprising:"

To the extent claim 3's preamble is limiting, it is rendered obvious by Inbar, Shuber and Vilkin, which are all directed to methods of processing fecal samples. EX1002 ¶319; EX1009; EX1008; EX1005.

b. "a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in the fecal sample, wherein the pair of portions are obtained by the method of claim 1;"

Obtaining the sealable containers generated according to the method of claim 1 is rendered obvious by Inbar, Shuber and Vilkin, each of which discloses delivery of the collected fecal samples to a medical diagnostics laboratory for testing. EX1009 9:24-30; EX1008 10:10-15; EX1005 p.2520; EX1002 ¶320.

c. "b) extracting nucleic acid from the first portion of the fecal sample;"

Performance of the DNA assays described in Shuber includes purification of DNA from the stool sample. EX1008 15:18-16:17. Indeed, extraction of DNA

from stool samples is a standard step in an assay in which stool DNA is tested. EX1002 ¶321. Thus, when the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin, nucleic acid is extracted from the first portion of the fecal sample. *Id*.

d. "c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and"

Performance of the DNA assay described in Shuber includes "analysis using a nucleic acid integrity assay along with a mutation detection assay (e.g., a multiple mutation panel assay), a hypermethylation assay, or both." EX1008 7:19-21. Each of these assays includes the testing for an amount of a human nucleic acid. EX1002 ¶322. Thus, when the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin, this step is performed. *Id*.

e. "d) testing the second portion of the fecal sample for an amount of blood protein present in the second portion of the fecal sample."

The Vilkin iFOBT is a quantitative test of the level of hemoglobin in a portion of a stool sample. EX1005 pp.2519, 2522. Thus, when the Inbar system to prepare fecal specimens for the assays of Shuber and Vilkin, the second portion of the sample is tested for an amount of blood protein. EX1002 ¶323.

In sum, when the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin, each of the steps of claim 3 is performed, rendering the claim obvious. EX1002 ¶¶319-324.

4. Claim 4: "The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene."

Claim 4 of the '746 patent recites that the assay include "determining expression from a human gene." For the reasons explained in Section VII(A)4, as used in the '746 patent, testing a nucleic acid by determining expression from a human gene at least includes detection of a methylated human gene or promoter in the nucleic acid.

Shuber discloses fecal DNA assays that include testing nucleic acids for the presence of methylated human genes. EX1008 14:1-5. Thus, when the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin, the extracted nucleic acid is tested by determining expression from a human gene. EX1002 ¶¶325-326. Claim 4 is therefore obvious.

5. Claim 14: "The method of claim 3, wherein testing for an amount of blood protein present in the second portion comprises testing for a concentration of hemoglobin in the

second portion, wherein a concentration of hemoglobin is indicative of a presence of blood in the fecal sample."

Claim 15: "The method of claim 14, wherein the testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin."

The iFOBT disclosed in Vilkin uses an immunochemical process to test for a concentration of hemoglobin in a removed portion of a fecal sample that is indicative of a presence of blood in the fecal sample. EX1005 pp.2519, 2520-2522, Table 1. Thus, when the Inbar system is used to prepare specimens for the assays of Shuber and Vilkin, the second portion is tested for a concentration of hemoglobin using immunochemical detection. EX1002 ¶¶327-328. Claims 14 and 15 are therefore obvious.

6. Claims 16-19: "The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the second portion is at least [5, 10, 20, or 50] ng/ml."

Claims 16-19 each recite a particular threshold hemoglobin concentration used to determine whether the removed portion of the fecal sample is considered positive for the presence of blood. Each of claims 16-19 is rendered obvious by Inbar, Shuber and Vilkin. As explained in Section VII(A)6, selecting any of the claimed hemoglobin thresholds would have been a matter of routine optimization of a result-effective variable. *In re Applied Materials, Inc*., 692 F.3d 1289, 1295, 1297 (Fed. Cir. 2012). Accordingly, the hemoglobin thresholds recited in claims

16-19 are result-effective variables that are the product of routine optimization and are obvious. EX1002 ¶329.

G. Ground VII: Inbar, Shuber and Vilkin, in further view of Kanaoka

1. Claim 12 "The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the human gene."

As set forth in Section VII(F), it would have been obvious to a POSA to use the Inbar system to prepare fecal specimens for the assays of Shuber and Vilkin. EX1002 ¶330. For the reasons set forth in Section VII(B)1, a POSA would have been motivated to use Kanaoka's RNA detection assay in combination with the iFOBT of Vilkin and either in place of or in addition to Shuber's fecal DNA assay, and would have had a reasonable expectation of successfully doing so. EX1002 ¶¶220-226. A POSA would therefore find it obvious to further modify the above-described fecal processing method to also use the Inbar system to prepare specimens for the RNA detection process disclosed in Kanaoka to arrive at the method of claim 12. EX1007 ¶¶021-026; EX1002 ¶330. Claim 12 is therefore obvious.

2. Claim 13: "The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR)"

When the RNA detection process of Kanaoka is incorporated into the method rendered obvious by Inbar, Shuber and Vilkin, as described above, the

resulting method includes measuring an amount of RNA expressed from the gene using RT-PCR, which Kanaoka uses to detect RNA expression. EX1007 ¶¶0021-0025, 0047-0048, 0059. Accordingly, the method of processing a fecal sample rendered obvious by Inbar, Shuber, Vilkin, and Kanaoka includes such a step. EX1002 ¶331. Claim 13 is therefore obvious.

VIII. Secondary Considerations of Non-obviousness

"[S]econdary considerations of non-obviousness" are among the "underlying factual inquiries" considered in the obviousness analysis. *E.g.*, *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018). To accord substantial weight to secondary considerations, "the evidence of secondary considerations must have a 'nexus' to the claims." *Fox Factory, Inc. v. SRAM*, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2019).

Geneoscopy is unaware of any secondary consideration having a nexus with the challenged claims that points towards their non-obviousness. In particular, there is no nexus between the challenged claims and any secondary considerations related to Exact's commercial product, Cologuard®, which Exact launched in 2014—years before it acquired the '746 patent family from Oncomethylome in 2017. EX1025; EX1017.

The patentee bears the burden of proving a nexus exists. *Fox Factory*, 944 F.3d at 1373. Presuming nexus is only appropriate "when the patentee shows that

the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them." *Id.* "Conversely, when the thing that is commercially successful is not coextensive with the patented invention—for example, if the patented invention is only a component of a commercially successful machine or process, the patentee is not entitled to a presumption of nexus." *Id.*

Exact is not entitled to a presumption of nexus because Cologuard is not coextensive with the challenged claims. EX1002 ¶¶333-345. Cologuard is a complex multistep stool DNA test that includes performance of quantitative assays for (a) aberrant methylation in the NDRG4 and BMP3 genes; (b) mutations in the KRAS gene; (c) ACTB DNA levels; and (d) hemoglobin protein levels. EX1080 p.4; EX1081 pp. 7-46. EX1002 ¶¶335-345. The claimed process of dividing a stool sample into two portions in separate buffers is, at most, a minor component of Cologuard®. EX1002 ¶¶334-345.

Cologuard's lack of coextensiveness with the challenged claims is illustrated by the ***over 60 patents unrelated to the '746 patent that Exact has identified as covering components of Cologuard***. EX1002 ¶344; EX1026; EX1027. Distinct components of Cologuard claimed by these other patents include: (a) its stool collection containers; (b) its DNA stabilization buffer; (c) its DNA extraction process; (d) its DNA biomarkers; (e) its process for preparing DNA for

methylation assays; (f) the DNA methylation assay itself; (g) its DNA mutation assay; and (h) controls used in these assays. EX1002 ¶344.

There is also no nexus between Cologuard and the challenged claims. Geneoscopy is unaware of any secondary considerations related to Cologuard attributable to the invention of the challenged claims, as opposed to, for example, other Cologuard components, Exact's marketing of Cologuard, or the exclusivity afforded to Exact by the dozens of blocking patents covering Cologuard. EX1002 ¶¶344-348. *Merck & Co v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) ("Because market entry from others was precluded… the inference of non-obviousness… is week").

Indeed, during prosecution of an unrelated patent asserting a later priority date than the '746 patent, Exact attributed Cologuard's success not to the sample processing method claimed in the '746 patent, but rather to the later-invented "particular combination of markers and methods for extracting the marker DNA from stool." EX1028; EX1029 p.9; EX1002 ¶¶346-347. Exact noted that Cologuard "comprises the system components recited in the instant claims as amended: stool homogenization buffer, PVPP inhibitor adsorbant, spin filter and guanidine thiocyanate, and magnetic target-specific capture particles for capturing NDRG4, BMP3 and KRAS target human DNAs" (EX1029 pp.6-7) and argued that these components "addressed this long-felt need and succeeded where others had

failed, as evidenced by first-ever FDA approval for the product containing these components." *Id.* p.9.

Should Exact allege secondary considerations, Geneoscopy will respond in its Reply.

IX. Discretion under 35 U.S.C. § 325(d)

The Board should not exercise discretion to deny institution under § 325(d). While the asserted art appeared in an information disclosure statement (IDS) filed on January 16, 2024, the second prong of the *Advanced Bionics* framework—whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims—strongly favors institution, not denial. *Advanced Bionics, LLC v. Med-El Elekromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential).

When analyzing whether an examiner materially erred, the Board considers three non-exclusive factors: (1) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (2) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and (3) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. *Id.* at 9-10.

In this case, the prior art was listed in an IDS during prosecution but never

substantively evaluated during examination. The Board repeatedly has declined to discretionarily deny institution where, as here, the prior art in question was not the subject of Examiner or applicant discussion or evaluation. *E.g., Satco Products Inc. v. The Regents of the Univ. of California,* IPR2021-00662, Paper 13 at 25 (P.T.A.B. Nov. 8, 2021).

The Examiner's error in overlooking the asserted prior art is clear. *See* Section VII. After the '746 patent issued, the Board instituted IPR2024-00459, which challenged the claims of its parent, the '781 patent, as obvious on grounds that correspond to Grounds I-IV of this petition. EX1031; EX1033. The Board found there was "a reasonable likelihood … that the challenged claims would have been unpatentable as obvious" over the ***same prior art*** asserted in this petition. EX1033 at 19, 20. As the scope of the currently challenged claims is broader than, and completely encompasses, that of the corresponding claims of the '781 patent, the Board's holding in the '781 patent institution decision applies equally to the currently challenged claims. EX1030, EX1001, EX1002 ¶¶ 107-111. Indeed, during prosecution, the examiner held the claims of the '746 patent to be patentably indistinct from those of the '781 patent. EX1018 p.3; EX1019 p.6. The Board's decision to institute review of the '746 patent's patently indistinct parent based on the same art presented here establishes the Examiner's material error in disregarding that art.

Similarly, the Examiner materially erred by disregarding Inbar during examination of the ’746 patent. As set forth in Section VII(E), Inbar discloses every element, and therefore anticipates, claims 1 and 2. Moreover, as discussed in Section VII(F), challenged claims 3-4 and 12-14 amount to no more than the obvious use of the Inbar system according to its intended purpose of collecting, preserving and transporting stool specimens so they can be tested using well-known assays. The Examiner’s failure to reject the challenged claims over Inbar was an error material to the patentability of the claims.

Accordingly, *Advanced Bionics* favors institution.

X. Conclusion

Petitioner respectfully submits that the Board should institute IPR and determine that claims 1-4 and 12-19 of the ’746 patent are invalid by a preponderance of the evidence as required by 35 U.S.C. § 316(e).

Dated: August 20, 2024

Respectfully submitted,

/Brendan T. Jones/

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that the foregoing complies with the type-volume limitations of 37 C.F.R. § 42.24 because, according to the "word count" function of Microsoft Word, the Petition contains 13,979 words, excluding those portions exempted under 37 C.F.R. § 42.24(a)(1).

/Brendan T. Jones/
Brendan T. Jones, Reg. No. 65,077

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105, I hereby certify that on August 20, 2024, I caused the foregoing Petition for *Inter Partes* Review, Power of Attorney, Exhibit List, and the accompanying exhibits to be served on Patent Owner by depositing them for shipment with Federal Express, Standard Overnight delivery, to the following correspondence addresses of record listed on PAIR:

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562
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A courtesy electronic copy has also been sent to James M. Glass (jimglass@quinnemanuel.com), Sandra Haberny (sandrahaberny@quinemanuel.com), Jihong Lou (jihonglou@quineanuel.com), and Anastasia M. Fernands (anastasiafernands@quinnemanuel.com), counsel for Patent Owner in IPR2024-00459.

Dated: August 20, 2024

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