UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

Case No.: IPR2024-00459
U.S. Patent 11,634,781

PETITION FOR *INTER PARTIES* REVIEW OF U.S. PATENT 11,634,781

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TABLE OF AUTHORITIES

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Cases

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PETITIONER'S EXHIBIT LIST

Exhibit	Short Name	Description
EX1001	'781 patent	U.S. Patent No. 11,634,781.
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	Derks	Sarah Derks et al., "Promoter Methylation Precedes Chromosomal Alterations in Colorectal Cancer Development," *Cellular Oncology*, 28:247-257 (2006).
EX1009	Shuber	International Patent Application Publication Number WO2005/113769.
EX1010	Guittet	Lydia Guittet et al., "Comparison of A Guaiac Based And An Immunochemical Faecal Occult Blood

Exhibit	Short Name	Description
		Test In Screening For Colorectal Cancer In A General Average Risk Population," *Gut*, 56:210-214 (2007).
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	US2016/0194723	US Patent Publication No. US2016/0194723.
EX1018	US2012/0164238	US Patent Publication No. US2012/0164238.

Exhibit	Short Name	Description
EX1019	Final Office Action	USPTO Final Office Action for US Patent Publication No. US15/010,436 dated October 28, 2016.
EX1020	Nonfinal Office Action	USPTO Nonfinal Office Action for US Patent Publication No. US17/936,335 dated January 11, 2023.
EX1021	Request for *Ex Parte* Reexamination	Request for *Ex Parte* Reexamination of US Patent No. 11,634,781 dated May 22, 2023
EX1022	Order Granting Request for *Ex Parte* Reexamination	USPTO Order Granting Request for *Ex Parte* Reexamination of US Patent No. 11,634,781 dated June 29, 2023.
EX1023	Notice of Intent to Issue *Ex Parte* Reexamination Certificate	USPTO Notice of Intent to Issue *Ex Parte* Reexamination Certificate for US Patent No. 11, 634,781 dated Oct 18, 2023.
EX1024	Young 2007	GP Young et al., "New Stool Screening Tests for Colorectal Cancer," *Digestion*, 76:26-33 (2007).
EX1025	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).
EX1026	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).
EX1027	Lapidus '178	U.S. Patent No. 5,952,178
EX1028	Lapidus '650	U.S. Patent No. 5,741,650
EX1029	Hoepffner	N. Hoepffner et al., "Comparative Evaluation of a New Bedside Faecal Occult Blood Test in a Prospective Multicentre Study," *Alimentary*

Exhibit	Short Name	Description
		Pharmacology & Therapeutics, 23:145-154 (2006).
EX1030	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).
EX1031	Recorded Assignment	Recorded Assignment of US Patent No. 11,634,781 dated April 25, 2017.
EX1032	n/a	Intentionally Omitted
EX1033	Simon	JB Simon, "Occult Blood Screening for Colorectal Carcinoma: A Critical Review," *Gastroenterology*, 88:820-837 (1985).
EX1034	n/a	Intentionally Omitted
EX1035	Sidransky	D. Sidransky, "Identification of Ras Oncogene Mutations in the Stool of Patients with Curable Colorectal Tumors," *Science*, 256:102–105 (1992).
EX1036	n/a	Intentionally Omitted
EX1037	Müller	Hannes Müller et al., "Methylation Changes in Faecal DNA: A Marker for Colorectal Cancer Screening?" *Lancet*, 63:1283-1285 (2004).
EX1038	Schuebel	Kornel Schuebel et al., "Comparing the DNA Hypermethylome with Gene Mutations in Human Colorectal Cancer," *PLoS Genet*., 3:1709–1723 (2007).
EX1039	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).

Exhibit	Short Name	Description
EX1040	Tagore	K.S. Tagore et al. "Review Article: The Evolution to Stool DNA Testing for Colorectal Cancer," *Aliment Pharmacol. Ther.,* 19: 1225-1233 (2004).
EX1041	Derks Printout	Printout of *Clinical Oncology* from Pubmed.
EX1042	Grow	U.S. Patent No. 5,198,365.
EX1043	Imperiale	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).
EX1044	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).
EX1045	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).
EX1046	Van Engeland	International Patent Application Publication Number WO2008/084219.
EX1047	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).
EX1048	Ostrow	Donald Ostrow, "Tests for Fecal Occult Blood, in Clinical Methods: The History, Physical, and Laboratory Examinations." Boston: Butterworths; Chapter 98 (1990).

Exhibit	Short Name	Description
EX1049	Cleator	U.S. Patent No. 7,195,878.
EX1050	Kahi	Charles Kahi et al., "Screening, Surveillance, and Primary Prevention for Colorectal Cancer: A Review of the Recent Literature," *Gastroenterology,* 135: 380-399 (2008).
EX1051	White	Victoria White and Richard Miller, "Colorectal Cancer: Prevention and Early Diagnosis," *Medicine,* 35(6) 297-301 (2007).
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	Itzkowitz 2008	Steven Itzkowtiz, "A Simplified, Noninvasive Stool DNA Test for Colorectal Cancer Detection," *American Journal of Gastroenterology,* 103: 2862-2870 (2008).
EX1056	Boynton	Boynton et al., "DNA Integrity as a Potential Marker for Stool-based Detection of Colorectal Cancer," *Clinical Chemistry,* 49:7 1058–1065 (2003).
EX1057	Jessup	J. Milburn Jessup et al., "Diagnosing Colorectal Carcinoma: Clinical and

Exhibit	Short Name	Description
		Molecular Approaches," *A Cancer Journal for Clinicians,* 47(2):70-92 (1997).
EX1058	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).
EX1059	Li	L-C Li and R. Dahiya, "MethPrimer: Designing Primers for Methylation Pcrs," *Bioinformatics,* 18(11): 1427-1431 (2002).
EX1060	Jones Declaraton	Declaration of Brendan T. Jones
EX1061	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).
EX1062	Matsumura 1992	Y Matsumura and D Tarin "Significance of CD44 Gene Products for Cancer Diagnosis and Disease Evaluation," *Lancet*, 340: 1053-1058 (1992).
EX1063	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).
EX1064	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).

Exhibit	Short Name	Description
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	Mahon	Suzanne Mahon, " Prevention and Screening of Gastrointestinal Cancers," *Seminars in Oncology Nursing,* 25(1): 15-31 (2009).
EX1069	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).
EX1070	Inbar	International Patent Application Publication Number WO97/25925.
EX1071	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).
EX1072	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).
EX1073	Lenhard Printout	Printout of *Clinical Gastroenterology and Hepatology* Website.

Exhibit	Short Name	Description
EX1074	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).
EX1075	Beaulieu	U.S. Patent No. 9,891,223.
EX1076	Itzkowitz Printout	Printout of *Clinical Gastroenterology and Hepatology* Website.
EX1077	Itzkowitz Press Release	Exact Sciences and Mount Sinai School of Medicine Press Release issued December 13, 2006.

I. Introduction

The claims of United States Patent No. 11,634,781 ("the '781 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 it can be tested both for blood proteins and for nucleic acids is reported throughout the prior art, including in Lenhard (EX1004). The fecal tests for detecting blood protein and nucleic acids recited by the claims were known and routine, as confirmed by Vilkin (EX1005), Itzkowitz (EX1006), and Shuber (EX1009). The method claimed by the '781 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 obvious, and the claims directed to the method are invalid.

The Board should institute IPR based on Lenhard, Itzkowitz, Vilkin, Shuber, and the other references cited in the grounds herein and should cancel claims 1-20 of the '781 patent.

The Petitioner, Geneoscopy, Inc. ("Geneoscopy") is a life sciences company focused on transforming gastrointestinal health through innovative diagnostics, including through its work to develop a noninvasive, at-home screening test for colorectal cancer. With the goal of expanding cancer detection options and

improving outcomes for millions of at-risk patients, 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 ’781 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any ’781 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”) has asserted the ’781 patent against Geneoscopy in *Exact Sciences Corporation v. Geneoscopy, Inc.,* No.

23-cv-1319-MN (D. Del.) ("the Exact Litigation"). Geneoscopy was served with the complaint in the Exact Litigation on November 17, 2023.

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).

Lead Counsel	Backup Counsel
Brendan Jones (Reg. No. 65,077) Foley Hoag LLP 155 Seaport Boulevard Boston, MA 02210-2600 T: (617) 832-1267 F: (617) 832-7000 bjones@foleyhoag.com	David Shore (Reg. No. 75,183) Foley Hoag LLP 155 Seaport Boulevard Boston, MA 02210-2600 T: (617) 832-1714 F: (617) 832-7000 dshore@foleyhoag.com
	Donald R. Ware (*pro hac vice* admission to be requested) Foley Hoag LLP 155 Seaport Boulevard Boston, MA 02210-2600 T: (617) 832-1714 F: (617) 832-7000 dware@foleyhoag.com
	Sarah Burg (*pro hac vice* admission to be requested) Foley Hoag LLP 155 Seaport Boulevard Boston, MA 02210-2600 T: (617) 832-1249 F: (617) 832-7000 sburg@foleyhoag.com

Petitioner consents to service by email at bjones@foleyhoag.com, dshore@foleyhoag.com, dware@foleyhoag.com, sburg@foleyhoag.com, and geneoscopyIPR@foleyhoag.com.

IV. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR, 37 C.F.R. § 42.22(a)

Geneoscopy requests institution of IPR and cancellation of claims 1-20 of the ’781 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 ’781 patent; “the Priority Date”), fecal samples had been used in non-invasive diagnostic tests for colorectal cancer (CRC) for decades. EX1002 ¶¶49-59. Such tests generally involved obtaining a stool sample from a patient and testing it for one or more biomarkers associated with CRC. EX1002 ¶¶49, 60-65. The CRC biomarkers known to be present in feces included blood proteins, mutated DNA, long DNA fragments, hypermethylated DNA, and RNA. EX1002 ¶¶49-59. It was broadly recognized that increasing the number of biomarkers used in such a diagnostic test could improve the test’s sensitivity and/or specificity. EX1002 ¶¶30-33, 60-65.

Many fecal diagnostic assays require specialized equipment and/or expertise, and accordingly are usually performed in medical diagnostics laboratories.

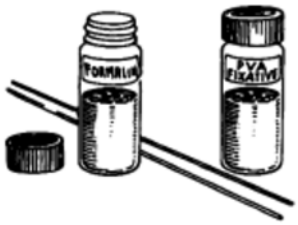
EX1002 ¶66. For such assays, patients typically collect their own stool sample at home using a specially-designed kit and then ship it to the laboratory for testing. EX1002 ¶¶66-72. To eliminate the need to freeze samples during shipment, scientists developed buffers that stabilize components of the fecal sample. EX1002 ¶¶73-81. For example, certain buffers prevent degradation of DNA, and are employed when DNA biomarkers are used. EX1002 ¶¶74-77. Other buffers stabilize proteins and are used when blood proteins are used as biomarkers. EX1002 ¶¶78-80.

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 ¶¶82-87. For example, such a process is illustrated in the below figure, from a 1985 laboratory manual, adapted from a 1949 publication. EX1002 ¶83; EX1026 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 di agnostic tests for CRC were based on the detection of small amounts of blood in a patient's stool. EX1002 ¶50. 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 samples. EX1002 ¶51. 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 ¶52. 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 also more sensitive than gFOBT. *Id.* Certain automated iFOBT also provided quantitative results, allowing physicians to select the threshold hemoglobin level above which a patient would undergo colonoscopy. *Id*.

3. Fecal Nucleic Acid Tests

By the 1990s it was known that fecal DNA biomarkers could be detected in the stool of people with CRC and used in diagnostics. EX1002 ¶54. CRC-associated DNA could be distinguished from normal DNA in several different

ways. EX1002 ¶¶53-59. CRC cells often die in a way that causes long DNA fragments to be released into a patient's stool. EX1002 ¶55. 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 to identify patients with CRC. EX1002 ¶54. CRC DNA can also be distinguished by detecting DNA methylation, an epigenetic DNA modification used by cancer cells to silence certain genes. EX1002 ¶¶57-58. Finally, by the Priority Date some scientists had begun detecting RNA biomarkers in stool as well. EX1002 ¶59.

By the Priority Date, it was recognized that diagnostic assay sensitivity could be improved by combining fecal nucleic acid tests with FOBT. EX1002 ¶¶60-65. 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 p.34, 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 '781 Patent

The '781 patent is part of a family of applications claiming priority to a provisional application filed on February 3, 2009 by the Belgian company OncoMethylome. EX1015. The '781 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 a fecal sample ("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, 6:40-67; EX1002 ¶98. The '781 patent acknowledges that such fecal protein tests and fecal DNA tests were known in the art, but asserts that "[t]o date, 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 April 2017, the OncoMethylome family was assigned to Exact. EX1031. Up to this point, all claims prosecuted in the family related to detection of epigenetically-modified DNA. EX1014; EX1017; EX1018. At the time of Exact's acquisition, no patents had issued from the family, and the claims of the only pending case were subject to a final rejection. EX1019.

Exact filed the application that gave rise to the '781 patent on September 28, 2022. The only rejection issued by the USPTO during its prosecution was for obviousness-type double patenting, which Exact overcame by filing a terminal disclaimer. EX1020. The '781 patent issued on April 25, 2023. It was the first patent in its family to issue.

On May 22, 2023, Petitioners filed a request for *ex parte* reexamination of the '781 patent, which was granted on June 29, 2023. EX1021; EX1022. The reexamination request was based on different prior art and arguments than those being presented in this petition. On October 18, 2023, the USPTO issued a Notice of Intent to Issue an *Ex Parte* Reexamination Certificate, upholding the claims as granted. EX1023. The USPTO's stated basis for upholding the claims was that "[n]one of the references of record reasonably suggest collection at home with each of the fecal portions sealed in separate containers, each with a buffer therein as required by independent claim 1." EX1023 p.3. The below grounds of

unpatentability bring to the PTAB's attention other prior art references and specifically set forth why they render such a process obvious.

VI. IDENTIFICATION OF THE CHALLENGE, 37 C.F.R. § 42.104(b)

Geneoscopy requests that the Board institute IPR of claims 1-20 of the '781 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. 35 U.S.C. § 314(a).

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	Derks *et al.,* 2006 "Promoter methylation precedes chromosomal alterations in colorectal cancer development" *Cellular Oncology 28*:247-257 ("Derks")
EX1009	International application publication number WO 2005/113769 ("Shuber")

Each of the above references 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 specific grounds of unpatentability:

Ground	Statute	Claims	Prior Art
I	§103	1-9, 11, 14-20	Lenhard, Vilkin, and Itzkowitz
II	§103	12 and 13	Lenhard, Vilkin, Itzkowitz, and Kanaoka
III	§103	10	Lenhard, Vilkin, Itzkowitz, and Derks
IV	§103	1-9, 11, 14-20	Shuber and Vilkin
VI	§103	12 and 13	Shuber, Vilkin, and Kanaoka
VII	§103	10	Shuber, Vilkin, and Derks

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.

A. The Person of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") relevant to the '781 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 ¶9-12.

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 ¶¶109-115.

In Lenhard, stool samples were collected from patients before they underwent an endoscopy. EX1004 p.143. Samples were sent to a diagnostic laboratory within 10 hours of defecation. *Id*. There, a portion of the sample is removed and tested for the presence of fecal blood using a guaiac FOBT (gFOBT). EX1004 pp.143, 145. The remaining portion of the sample was then frozen, and then later tested for promotor methylation. EX1004 p.143.

Lenhard used methylation of the promoter of the HIC1 gene as a biomarker of CRC. *Id*. The HIC1 promoter had previously been found to be methylated in CRC, but not in normal colonic tissue. *Id*. To analyze HIC1 promoter methylation, the remaining portion of the sample was thawed, and DNA was isolated and purified. EX1004 pp.143-144. A process called methylation-specific polymerase chain reaction (PCR) (MSP) was then performed. EX1004 p.142. In the MSP assay, purified DNA was treated with sodium bisulfite to modify it, and then PCR amplification was performed using primers that distinguished methylated DNA from unmethylated DNA. EX1004 pp.143-144.

In short, by this method of sample processing, Lenhard tested for CRC by separating the patient's stool sample into separate aliquots and then performing a gFOBT on one and a DNA methylation test on the other. EX1002 ¶114.

Lenhard's results demonstrated that the ***combination*** of the DNA methylation assay with FOBT detected CRC with greater sensitivity than either assay alone. EX1004 pp.143, 147. 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.147. 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 ¶¶116-121. Vilkin explains that the described iFOBT has several advantages over gFOBT. For example, Vilkin explains that gFOBT "is faulted for its low sensitivity for significant colorectal neoplasia, and low specificity due to nonspecificity for human hemoglobin (Hb)" as well as "by the possibility of inaccurate development and evaluation by inadequately trained personnel." EX1005 p.2519. In contrast, "[t]he automated-developed and

quantitative I-FOBT is human Hb specific, eliminates the need for diet restrictions and the Hb quantification allows selection of a suitable threshold for follow-up colonoscopy." *Id*.

In the iFOBT of Vilkin, the at-home patient uses a fecal test 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:

> The fecal test sampling device is shaped like a small test tube with the fecal probe inserted into it **and sealing it**. **The probe has a serrated tip, which is poked into the stool and then pushed back into the tube**, past a scrapper, and through a membrane into the sample cup. These remove most of the excess feces and leave the stool collected (about 10 mg) into the serrations (Fig. 1). **The tip is then put in a closed amount of Hb stabilizing buffer**.

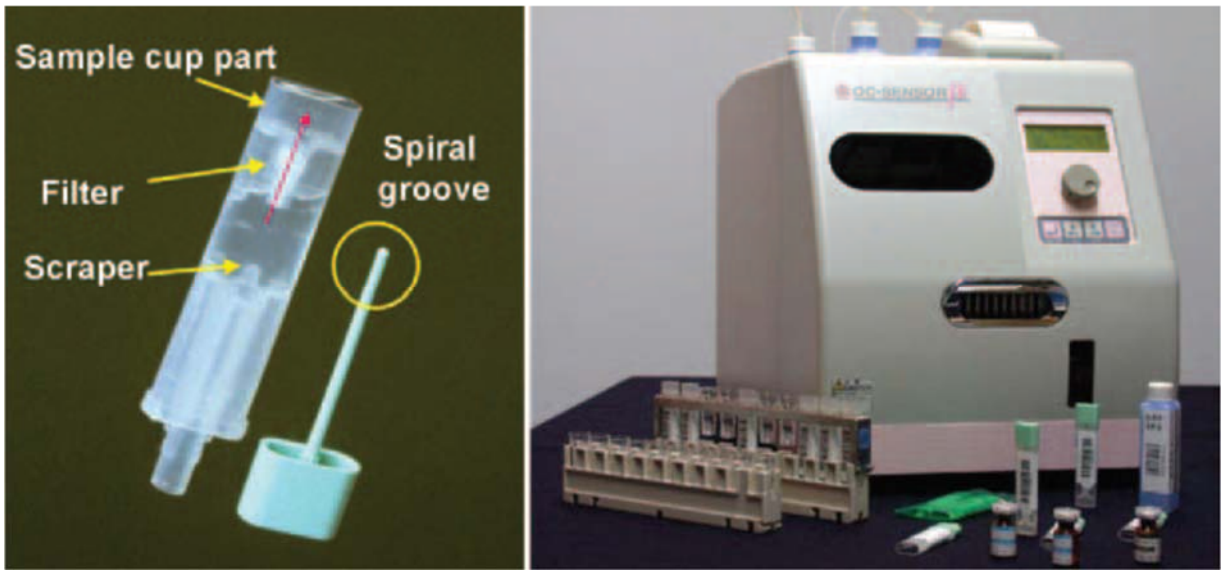
EX1005 p.2520, emphasis added.

The at-home patient then ships the stabilized sample to the diagnostic laboratory without freezing. *Id*. When stored in the stabilizing buffer at 4°C, all fecal samples "maintained their elevated fecal Hb levels for 21 or more days." EX1005 p.2521.

Once the testing laboratory receives the removed portion of the sample from the patient, it analyzes the sample on a desktop instrument (depicted in the right

panel of Figure 1, below), which performs immunochemical detection of human Hb. EX1005 pp.2520-2521.

Vilkin Figure 1.



Vilkin concludes that they "found this desktop, automated-developed and quantified Hb version of the immunochemical occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with an acceptable specificity and consequent high negative predictive value." EX1005 p.2524.

3. Itzkowitz (EX1006)

Itzkowitz is a 2007 publication that discloses "version 2" of Exact's fecal DNA test for CRC. EX1002 ¶¶122-126. The second 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 a stool sample at home by direct defecation into a sealable container ("each subject provided a single stool sample" using "a special stool collection kit that is mounted on the toilet bowl"). EX1006 p.112. Itzkowitz explains that "[i]mmediately after defecation, subjects added 250 mL of a DNA-stabilizing buffer to a stool specimen of at least 50 g." *Id*. Adding 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. The patients shipped the stabilized stool samples to the 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. They also concluded that the disclosed method of stabilizing DNA during specimen transport contributed to increasing assay sensitivity from 52% to 72.5%. EX1006 p.116.

4. Kanaoka (EX1007)

Kanaoka is a patent application published in 2006. EX1002 ¶¶127-129. 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 5 ml tubes, and thereafter homogenized in the presence of an RNase inhibitor. EX1007 ¶¶0017, 0019. Kanaoka specifies that the biological 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 homogenized fecal sample and then reverse transcribed to make cDNA, which is amplified (e.g., using PCR) and detected. EX1007 ¶¶0021-0025. Kanaoka provides various RNA CRC markers that can be used in the claimed method, but states that the marker is preferably COX-2. EX1007 ¶0044. 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 includes a working example in which thirty stool samples from colon cancer patients and 22 stool samples from patients without colon cancer were tested for the presence of COX-2 mRNA using RT-PCR. EX1007 ¶¶0056, 0063. In addition, "human hemoglobin (Hb) in the feces of each sample was measured by immunological fecal occult blood test." EX1007 ¶0057. Kanaoka notes that "[a]mong three COX-2 negative colon cancer cases, one was positive in the immunological fecal occult blood test" and also that "COX-2 was detected in 3 among 5 colon cancer cases negative to the immunological fecal occult blood test,"

indicating that the combination of the two tests had a higher sensitivity than either test alone. EX1002 ¶129; EX1007 ¶¶0067-0068.

5. Derks (EX1008)

Derks is a 2006 publication examining methylation of certain gene promotors during the development of CRC. EX1002 ¶¶130-132. Derks reports that the promoters of several genes, including GATA-4, are more highly methylated in colorectal adenomas and carcinomas than in normal tissues. EX1008 Abstract. In particular, the GATA-4 promoter was methylated in 94.4% of carcinoma tissue, but only 16.7% of paired normal tissue. EX1008 Table 3b. Derks states that their results are "highly relevant for methylation-marker based colorectal cancer screening." EX1008 p.255.

6. Shuber (EX1009)

Shuber is a 2005 patent application filed by Exact that describes a method for preparing a fecal sample using a nucleic acid stabilizing buffer. EX1009 6:2-20, 7:10-21; EX1002 ¶¶133-136. Shuber touts that the disclosed methods "do not require refrigeration or freezing." EX1009 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." EX1009 10:10-15. Shuber explains that the stabilized sample "can be characterized in a nucleic acid integrity analysis, multiple mutation assay, or methylation study." EX1009 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 early stage cancer (e.g., using DNA integrity assay, a multiple mutation assay, a hypermethylation assay, **or any combination thereof**.)". EX1009 28:18-27, emphasis added.

Shuber states that the stool sample "may be directly deposited into a container (e.g., a sealable container) that already contains stabilization solution," or "stabilization solution may be added to a container when (e.g., at the same time, immediately after, or within minutes, hours or a day) a biological sample (e.g., a stool sample) is deposited in the container." EX1009 29:8-19. The "container with sample and stabilization solution may be sealed for storage/shipping." *Id*.

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 1-9, 11, and 14-20 of the '781 patent. 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.

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 then 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 a fecal sample from the subject, removing a portion of it to test for blood proteins and then testing the remaining portion for cancer-specific DNA. EX1002 ¶142. While Lenhard does not expressly disclose use of a buffer to prevent degradation of blood proteins in the removed portion or use of a stabilizing buffer that retains DNA integrity in the remaining portion, use of such buffers was routine in the art, as evidenced by Vilkin and Itzkowitz, respectively. *Id*.

First, it would have been obvious for a POSA to replace the gFOBT used in Lenhard with the iFOBT disclosed in Vilkin, in which a removed 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 ¶143-144.

The advantages of iFOBT over gFOBT were well known by the Priority Date. EX1002 ¶145-146. 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." EX1024 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." EX1024 p.30.

Similarly, another 2007 paper concluded:

> I-FOBT tests have no dietary or medication restrictions. These tests have superior sensitivity and specificity, the gain being more important for high risk adenomas than for cancers. They also have a higher compliance rate and the automated reading technology allows the choice of the ideal positivity rate. **As suggested in recent reviews, it is time to give colorectal cancer screening a new future by using I-FOBT instead of G-FOBT**.

EX1010 p.214, emphasis added.

Accordingly, based on the express teachings of Vilkin and the general 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 ¶¶143-147.

Second, a POSA also would have been motivated to improve Lenhard's diagnostic assay by collecting the stool sample by direct defecation into a sealable container followed by addition of a DNA stabilizing buffer, as was done in Itzkowitz. EX1002 ¶148-158; EX1006 p.112.

Lenhard provides few details regarding sample collection beyond stating that "[s]tool samples were collected before cathartic preparation for scheduled surgery or colonoscopy" and then aliquoted by the laboratory. EX1004 p.143. However, a POSA would recognize that directly defecating into a sealable container, as was done in Itzkowitz, was a common and practical collection method that would be obvious to use in Lenhard's assay. EX1002 ¶148-152; EX1006 p.112. Indeed, direct defecation into a sealable container had been used for stool collection for decades by the Priority Date. EX1002 ¶¶150-151.

Once the sample was collected, a POSA would have been motivated by Itzkowitz's teachings to add a stabilization buffer to a sample so it could be shipped to a diagnostic laboratory without freezing. EX1002 ¶153-158; EX1006 p.112. Itzkowitz states that addition of 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. 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 ¶¶154-156. 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." EX1025 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." EX1025 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 sample collection and DNA stabilization methods described in Itzkowitz in Lenhard's assay to maintain DNA integrity in the remaining portion of the fecal sample, allowing it to be collected at home and shipped to a diagnostic laboratory at room temperature. EX1002 ¶¶153-158.

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 ¶¶159-160. The result of these obvious improvements would be a method for processing a freshly-collected fecal sample in which a patient defecates directly into a sealable container (as described in Itzkowitz), removes a portion of the stool sample and combines it with a buffer that stabilizes blood proteins in a separate sealable container (as described in Vilkin), and then adds

DNA stabilization buffer to the remaining fecal sample before sealing the original sealable container (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, at least 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 ¶161.

As set forth below, the above-described assay meets all limitations of claims 1-9, 11 and 14-20 of the ’781 patent.

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 incorporation of the sample collection stabilization method of Itzkowitz and the iFOBT of Vilkin, as described above, the resulting assay produces two samples: a “removed portion” in a blood protein stabilizing buffer that is “kept in the refrigerator until returned to

the developing laboratory where they are also kept at 4°C until development," EX1005 p.2520, and a "remaining portion" in a DNA stabilizing buffer that is "shipped at room temperature overnight." EX1006 p.112.

Accordingly, both Vilkin and Itzkowitz teach processing fecal samples without freezing, which would also be a characteristic of the method rendered obvious by Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶164-167.

b. "a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;"

Itzkowitz describes sample collection by a human subject directly defecating into a sealable container at home, stating that "[s]ubjects were given detailed instructions and a special stool collection kit that is mounted on the toilet bowl." EX1006 p.112. As the sample was subsequently "shipped at room temperature," to the diagnostic laboratory, a POSA would recognize that the sample was collected at home and in a container that must have been sealable. EX1002 ¶169; 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.

Confirming the obviousness of this step, direct defecation into a sealable container had been a standard method for collecting stool samples for decades

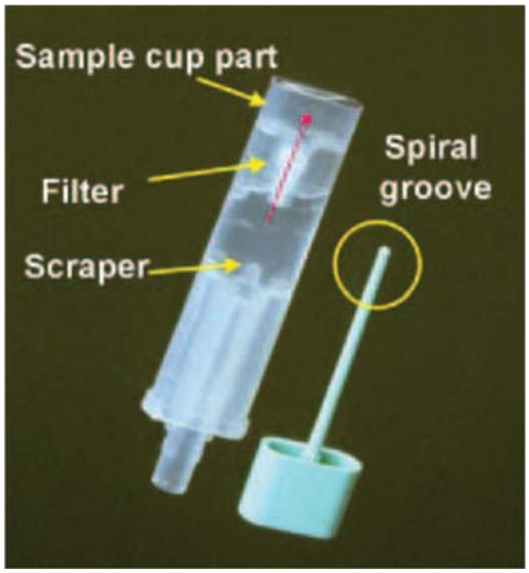
before the Priority Date. EX1002 ¶¶170-171. For example, a laboratory manual from 1985 recommends collecting fecal samples in a sealable container and that "[f]eces should be passed directly into the container." EX1026 p.2. Similarly, in a patent filed by Exact in 1994, Exact states that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." EX1028 7:45-49, Figure 2.

Accordingly, by the Priority Date, a POSA would have recognized direct defecation into a sealable collection vessel described in Itzkowitz as a routine and convenient at-home stool collection method that would be used in the method rendered obvious by Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶168-172; EX1006 p.112.

c. "b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;"

Lenhard describes an assay in which a portion of a patient's stool sample is removed and tested for the presence of blood proteins using gFOBT, after which the remainder of the sample is tested for the presence of tumor-derived DNA. EX1004 pp.143-145. Lenhard therefore discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample.

Lenhard does not expressly state that the removed portion of the sample was removed to a separate sealable container. However, as discussed above, it would have been obvious to replace the disclosed gFOBT with the iFOBT of Vilkin in view of the numerous advantages to iFOBT over gFOBT taught in 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 of the fecal test sampling device with the tip of the probe being in a closed amount of hemoglobin stabilizing buffer. *Id*.



Accordingly, when the gFOBT of Lenhard is replaced with the iFOBT of Vilkin the resulting assay includes removing a portion of the fecal sample to a separate sealable container to produce both a removed portion and a remaining portion of the fecal sample. EX1002 ¶¶173-176.

d. "c) combining the removed 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; and"

For the reasons set forth above, it would have been obvious to replace the gFOBT described in Lenhard with the iFOBT of Vilkin at least because of the recognized advantages of iFOBT. In the iFOBT described in Vilkin, a probe attached to the cap of the "fecal test sampling device" is "poked into the stool and then pushed back into device, past a scraper and through a membrane into the sample cup." EX1005 p.2520. This results in sealing of 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 the removed 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 ¶¶177-178.

e. "d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the collection vessel"

A POSA would have been motivated to combine the DNA stabilizing buffer of Itzkowitz with the remaining portion of the fecal sample generated according to Lenhard 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. 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. 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 remaining portion of the fecal sample and the 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 ¶181.

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

In sum, when the iFOBT and sample stabilization of Vilkin, and the fecal collection and DNA stabilization process of Itzkowitz, are incorporated into the diagnostic method taught by Lenhard, the result is a method in which each of the steps of claim 1 is performed. EX1002 ¶¶163-183. Claim 1 is therefore obvious over the prior art.

2. Claim 2: "The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer 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 removed portion and remaining portion of the fecal sample to a medical diagnostics laboratory. Indeed, all three references include delivery of fecal samples to a

medical diagnostics laboratory for testing and, as such, they render Claim 2 obvious. EX1002 ¶¶184-186; 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 are directed to methods of processing fecal samples. 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 container containing a removed portion of a fecal sample and a buffer; and ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions 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 removed portion and remaining 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 for testing and, as such, render the step of obtaining such samples by the technicians at the laboratory obvious. EX1002 ¶¶189-191.

c. "b) testing the removed portion of the fecal sample for an amount of blood protein present in the removed portion;"

As explained above, it would have been obvious to replace the gFOBT described in 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 removed 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 the removed portion of the sample for an amount of blood protein in that portion. EX1002 ¶¶192-194.

d. "c) extracting nucleic acid from the remaining portion of the fecal sample;"

Performance of the DNA methylation assay described in Lenhard includes isolation of DNA from the remaining portion of the stool sample ("DNA was isolated using the QiaAmp DNA Stool Mini-Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions."). EX1004 p.143. Extraction of DNA from the stool sample is a standard step performed when a stool sample is tested for DNA. EX1002 ¶195. Indeed, Itzkowitz extolls the advantages of an "enhanced DNA extraction" process on fecal DNA tests. EX1006 p.112. Extracting nucleic acid from the remaining 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 ¶¶195-196.

e. "d) testing the nucleic acid for an amount of a human nucleic acid"

Performance of the DNA methylation assay described in Lenhard includes testing the remaining 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 ¶197.

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 ¶¶187-198.

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

Claim 4 of the '781 patent recites that the assay include "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 ¶194. Both claims 5 and 6 depend from claim 4 and must therefore narrow claim 4's scope. *E.g., Alcon Research, LTD. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("It is axiomatic that a dependent claim cannot be broader than the claim from which it depends."). Consistently, the '781 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 12:35-39, emphasis added.

The fecal DNA assay disclosed in Lenhard includes testing the remaining portion of the fecal 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. Lenhard explains that "[m]ethylation of CpG islands of promoters leads to silencing of transcription of the affected gene." EX1004 p.142. Similarly, Itzkowitz discloses testing for methylation of the vimentin gene.

EX1006 p.111. Accordingly, testing for expression from a human gene is performed in both Lenhard and Itzkowitz and would also be included in the method of Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶199-202. Claim 4 is therefore obvious.

5. Claim 5: "The method of claim 4, wherein determining expression from the human gene comprises testing the nucleic acid for the presence of human DNA having an epigenetic modification."

As discussed above, the DNA assay disclosed in Lenhard includes testing the remaining portion for methylated HIC1 promoter. HIC1 promotor methylation is an epigenetic marker. EX1004 p.142. The stool DNA assay disclosed in Itzkowitz also includes testing an epigenetic marker—the methylation of the vimentin gene. EX1006 p.111. Accordingly, testing for expression from a human gene by detecting an epigenetic marker is performed in both Lenhard and Itzkowitz and would also be included in the method of Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶203-204. Claim 5 is therefore obvious.

6. Claim 6: "The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises measuring an amount of a methylated human DNA."

As discussed above, the assay disclosed in Lenhard includes testing the remaining portion of the stool sample for methylated HIC1 promoter DNA, while the assay disclosed in Itzkowitz includes testing for vimentin gene methylation.

Accordingly, testing for expression from a human gene by measuring an amount of methylated human DNA 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 ¶¶205-206. Claim 6 is therefore obvious.

7. Claim 7: "The method of claim 5, wherein the epigenetic modification comprises aberrant methylation."

The '781 patent defines aberrant methylation as at least including hypermethylation ("aberrant methylation, which may be referred to as hypermethylation of the gene or genes."). EX1001 12:47-49. The assay disclosed in Lenhard includes testing the remaining portion of the stool sample for hypermethylated HIC1 promoter DNA. EX1004 pp.142, 143. Similarly, the assay disclosed in Itzkowitz includes testing for vimentin gene hypermethylation. EX1006 p.115. Accordingly, testing for expression from a human gene by detecting aberrant methylation 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 ¶¶207-208. Claim 7 is therefore obvious.

8. Claim 8: "The method of claim 7, wherein the aberrant methylation comprises hypermethylation."

As discussed above, the assays disclosed in both Lenhard and Itzkowitz include detection of hypermethylated DNA. Accordingly, testing for expression from a human gene by detecting hypermethylation 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 ¶¶209-210. Claim 8 is therefore obvious.

9. Claim 9: "The method of claim 7, wherein the human DNA having an epigenetic modification comprises a gene and/or a promoter region of a gene."

As discussed above, the assay disclosed in Lenhard includes testing the remaining portion of the stool sample for the presence of HIC1 promoter methylation (an epigenetic modification to a promoter region of a gene), while the assay of Itzkowitz includes testing for vimentin gene methylation (an epigenetic modification to a gene). EX1004 p.142; EX1006 p.115. Accordingly, testing for an epigenetic modification in a gene and/or a promoter region of a gene 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 ¶¶211-212. Claim 9 is therefore obvious.

10. Claim 11: "The method of claim 5, wherein testing the nucleic acid for presence of human DNA having an epigenetic modification comprises modifying the nucleic

acid with bisulfate[1] ions under conditions wherein unmethylated cytosine is converted to uracil."

As discussed above, the assay disclosed in Lenhard includes testing the remaining portion of the stool sample for HIC1 promoter methylation, while the stool DNA test of Itzkowitz includes the testing for vimentin gene methylation. In both cases, DNA methylation is detected using "bisulfite conversion," a process in which bisulfite ions are used to convert unmethylated cytosine to uracil. EX1002 ¶214; EX1004, p.144; EX1006 p.112. Accordingly, bisulfite conversion is used in both Lenhard and Itzkowitz and would also be included in the method rendered obvious by Lenhard in view of Vilkin and Itzkowitz. EX1002 ¶¶213-215. Claim 11 is therefore obvious.

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

As explained above, it would have been obvious to replace the gFOBT described in Lenhard with the iFOBT of Vilkin at least because of the numerous known advantages of using the iFOBT. The Vilkin iFOBT tests for a concentration of hemoglobin in the removed portion of the fecal sample. EX1005 pp.2519, 2522,

[1] The reference to "bisulfate" instead of "bisulfite" in claim 11 appears to be a typographical error. EX1002 ¶¶105, 213.

Table 1. Accordingly, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz includes the testing for a concentration of hemoglobin. EX1002 ¶¶216-217. Claim 14 is therefore obvious.

12. 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 described in Lenhard with the iFOBT of Vilkin. The iFOBT disclosed in Vilkin uses an immunochemical process to detect hemoglobin. EX1005 pp.2519, 2520-2521. Accordingly, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz includes immunochemical detection of hemoglobin. EX1002 ¶¶218-219. Claim 15 is therefore obvious.

13. Claims 16-20: "The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least [5, 10, 20, 50, or 200] ng/ml."

Claims 16-20 each depend from claim 14 and 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 16-20 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 ¶221. 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. Vilkin tested a range of thresholds from 50 ng/ml to 200 ng/ml (including the claimed 50 ng/ml and 200 ng/ml thresholds), and use of lower hemoglobin thresholds was routine in the art. EX1002 ¶221; EX1005 p.2523; EX1010 p.210; EX1029 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 colorectal cancer against the risk that a false-positive result subjects a patient to an unnecessary colonoscopy. EX1002 ¶221.

Notably, the hemoglobin concentration being measured in quantitative iFOBT is the concentration of hemoglobin in the hemoglobin stabilizing buffer, not in the amount of hemoglobin in the stool sample itself. EX1005 p.2520-2521,

noting that 50-2000 ng/ml hemoglobin in the buffer is approximately equivalent to 40-400 µg/g hemoglobin in the feces. A POSA would therefore recognize that the concentration of hemoglobin in the stabilizing buffer will depend both on how much stool is collected and what volume of buffer is used. EX1002 ¶222. A POSA would understand that the hemoglobin threshold will be routinely optimized, in part, based on the specific way the fecal sample was collected. *Id.*

Accordingly, the hemoglobin thresholds recited in claims 16-20 are result-effective variables that are the product of routine optimization and therefore are obvious. EX1002 ¶¶220-223.

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 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 fecal processing method to incorporate the COX-2 RNA detection process disclosed in Kanaoka to arrive at the method of claim 12. EX1002 ¶224-228;

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 Lenhard's HIC1 promoter methylation assay to improve assay sensitivity. EX1002 ¶224-228.

Example 1 of Kanaoka provides further motivation to combine Kanaoka's COX-2 RNA assay with an iFOBT, like the one disclosed in Vilkin. EX1002 ¶226. In this example, samples were tested using both a COX-2 RNA assay and an iFOBT. EX1007 ¶¶0055-0068. The iFOBT identified a CRC patient as positive who was missed by the COX-2 RNA assay, while the COX-2 RNA assay identified three CRC patients missed by the iFOBT. EX1007 ¶¶0067-0068. A POSA would have been motivated to combine the Kanaoka fecal COX-2 RNA assay with an iFOBT, such as the one disclosed in Vilkin, to increase the sensitivity of both assays. EX1002 ¶226.

A POSA would have had a reasonable expectation of successfully incorporating the COX-2 fecal RNA assay of Kanaoka into the fecal processing method rendered obvious by Lenhard, Vilkin and Itzkowitz. EX1002 ¶227.

Example 1 of Kanaoka provides a working example of the successful combination of a COX-2 RNA assay with an 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***." EX1002 ¶227; EX1030 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 ¶227.

As Kanaoka discloses detection of an amount of RNA expressed from a COX-2 gene, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin, Itzkowitz, and Kanaoka includes such a step. EX1002 ¶¶224-228. 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 expressed from the COX-2 gene. 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 ¶¶229-230. Claim 13 is therefore obvious.

C. Ground III: Lenhard in view of Itzkowitz and Vilkin, in further view of Derks

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.

Based on Derks, it would have been obvious to a POSA also to test the remaining portion of the stool sample for methylation of the GATA-4 gene in addition to the HIC1 promoter, to arrive at the method of claim 10.

Lenhard suggests adding additional methylated DNA biomarkers to the disclosed assay, stating that "[c]ombination of HIC1 with a few other sensitive and specific methylation markers may allow for highly sensitive and specific stool-based detection of CRCs and adenomas." EX1004 p.148. Derks identifies GATA-4 methylation as such a biomarker. EX1008 p.250. Indeed, Derks reports that the GATA-4 gene is methylated in 94.4% of CRC tissue but only in 16.7% of normal tissue. EX1008 p.252, Table 3b.

A POSA therefore would have been motivated to include detection of GATA-4 methylation, as disclosed by Derks, to the fecal processing method rendered obvious by Lenhard, Vilkin and Itzkowitz to further improve the assay's sensitivity. EX1002 ¶¶231-234. Claim 10 is therefore obvious.

D. Ground IV: Shuber and Vilkin

Shuber and Vilkin render obvious a method of processing a freshly collected fecal sample according to claims 1-9, 11 and 14-20 of the '781 patent. These challenged claims are directed to the separation of a fecal sample into two portions so a pair of well-established assays—one detecting blood proteins as disclosed in Vilkin and the other detecting nucleic acids as disclosed in Shuber—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 methods of the challenged claims.

As discussed above, Vilkin discloses a quantitative 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 automatically quantitate the level of hemoglobin in the sample. EX1005 pp.2520-2521.

Shuber describes a fecal DNA analysis method in which a stool sample is "directly deposited into a container (e.g., a sealable container)" to which the "stabilizing solution may be added" Before shipment to a testing center. EX1009 29:8-19, 10:12-14. The stabilizing solution is added to 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." EX1009 7:19-21. The "container with sample and stabilization solution may be sealed for storage/shipping." EX1009 29:8-19. Shuber emphasizes that "[m]ethods of the invention do not require refrigeration or freezing." EX1009 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 ¶235-245.

By the Priority Date, the advantages of combining such stool DNA and blood protein assays were well understood in the art. EX1002 ¶241-244. For example, Nishikawa, a 2002 paper reporting a fecal DNA assay similar to the ones 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 had 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 [another acronym for iFOBT] 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 the sensitivity of CRC diagnosis. EX1002 ¶¶240-245. When the combined test was performed, a patient would: (1) directly defecate into a sealable container 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 the DNA stabilizing buffer of Shuber to the remaining sample before sealing the container (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; EX1009 10:10-15, 29:8-19. A POSA would also recognize that it is more convenient for patients to use the Vilkin sampling device before the fecal sample is immersed in buffer. EX1002 ¶245.

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 ¶246.

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 1-9, 11, and 14-20. EX1002 ¶¶235-247.

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. Both Shuber and Vilkin teach the processing of freshly-collected fecal samples without freezing. EX1005 p.2520; EX1009 7:10-12. Accordingly, the obvious combination of the two assays would also involve processing a fresh fecal sample without freezing. EX1002 ¶¶248-249.

b. "a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;"

Collection of a fecal sample at home by defecation directly into a sealable collection vessel is rendered obvious by Shuber and Vilkin. Shuber describes sample collection by direct defecation into a container by a human subject, stating that the stool sample can be "directly deposited into a container (e.g., a sealable container)" to which the "stabilizing solution may be added." EX1009 29:8-19.

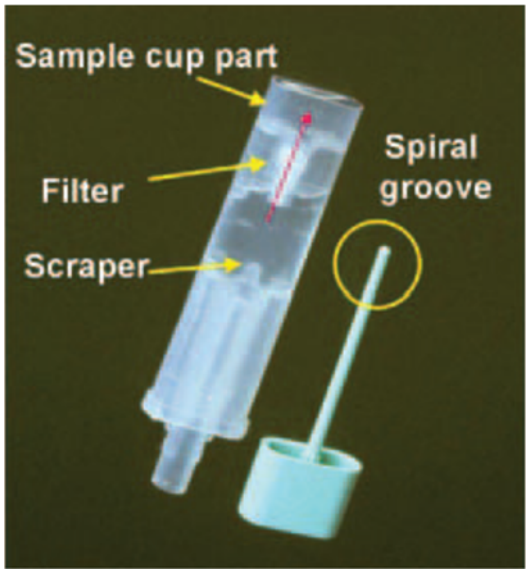
Shuber suggests at-home collection, stating that stabilizing buffer "may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center." EX1009 10:12-14.

Further supporting the obviousness of this step, as explained in section VII(A)1(c), direct defecation into a sealable container had been a standard method for collecting stool samples at home for decades. EX1002 ¶252-253.

Accordingly, by the Priority Date, a POSA would have recognized direct defecation into a sealable collection vessel, as described in Shuber, as a routine method for at-home collection of a stool sample. It therefore would have been obvious to use such a collection method when performing the assays of Shuber and Vilkin. EX1002 ¶¶251-254.

c. "b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;"

When the Vilkin iFOBT is performed on the stool sample, a portion of the fecal sample is obtained 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 the creation of a removed portion and a remaining portion of the fecal sample. EX1002 ¶255.



Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the removal of a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample. EX1002 ¶¶255-256.

d. "c) combining the removed 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; and"

When using the Vilkin iFOBT, a probe on the cap of the "fecal test sampling device" is "poked into the stool and then pushed back into device, past a scraper and through a membrane into the sample cup." EX1005 p.2520. This results in sealing of the fecal test sampling device with the tip "put in a closed amount of Hb

stabilizing buffer." *Id.* This facilitates the convenient shipment of the at-home collected sample to a diagnostic laboratory for analysis. *Id.*

Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the removed portion of the fecal sample being combined in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, as well as sealing of the sealable container. EX1002 ¶¶257-258.

e. "d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the collection vessel"

Shuber describes a fecal DNA analysis method in which a DNA stabilizing buffer is added to 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." EX1009 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." EX1009 29:8-19. The "container with sample and stabilization solution may be sealed for storage/shipping." *Id.*

Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the remaining portion of the fecal sample being combined

with a stabilizing buffer in the sealable collection vessel and the collection vessel being sealed. EX1002 ¶260.

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 ¶¶259-261.

2. Claim 2: "The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory"

Both Shuber and Vilkin include delivery of the collected fecal samples to a medical diagnostics laboratory for testing. EX1009 10:10-15; EX1005 p.2520. Accordingly, when the fecal DNA test of Shuber and the iFOBT of Vilkin are both performed on a stool sample, this step would be performed on the resulting sealed containers as well. Claim 2, therefore, is obvious. EX1002 ¶¶262-264.

3. Claim 3

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

To the extent claim 3's preamable is limiting, it is rendered obvious by Shuber and Vilkin, as both references are directed to methods of processing fecal samples. EX1009; 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 container containing a removed portion of a fecal sample and a buffer; and ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions 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. Both references disclose delivery of the collected fecal samples to a medical diagnostics laboratory for testing. EX1009 10:10-15; EX1005 p.2520. Accordingly, when the fecal DNA test of Shuber and the iFOBT of Vilkin are both performed on a stool sample, sealed containers containing the pair of portions of the fecal sample in their respective buffers will be obtained by a medical diagnostics laboratory. EX1002 ¶¶266-267.

c. "b) testing the removed portion of the fecal sample for an amount of blood protein present in the removed portion;"

The Vilkin iFOBT is a quantitative test of the level of human hemoglobin (Hb) in a removed 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 removed portion of the sample for an amount of blood protein in that portion. EX1002 ¶268.

d. "c) extracting nucleic acid from the remaining portion of the fecal sample;"

Performance of the fecal DNA assays described in Shuber includes purification of DNA from the remaining portion of the stool sample. EX1009 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 ¶269. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in extracting nucleic acid from the remaining portion of the fecal sample. *Id*.

e. "d) testing the nucleic acid for an amount of a human nucleic acid"

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." EX1009 7:19-21. Each of these assays includes the testing for an amount of a human nucleic acid. EX1002 ¶270. Thus, performing the fecal 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*.

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 ¶¶270-271.

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

Claim 4 of the '781 patent requires that testing of the nucleic acid extracted from the remaining portion include determining expression from a human gene. For the reasons explained in section VII(A)4, as used in the '781 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 ("assays are performed to detect hypermethylation at one or both of HLTF and V29 loci."). EX1009 14:1-5. Thus, performing the fecal 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 ¶¶272-274. Claim 4 is therefore obvious.

5. Claim 5: "The method of claim 4, wherein determining expression from the human gene comprises testing the nucleic acid for the presence of human DNA having an epigenetic modification."

As explained above, the fecal DNA assays disclosed in Shuber include testing for the presence of an epigenetic modification of methylated human DNA. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the extracted nucleic acid being tested for the presence of human

DNA having an epigenetic modification. EX1002 ¶275. Claim 5 is therefore obvious.

6. Claim 6: "The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises measuring an amount of a methylated human DNA."

As explained above, the stool DNA assay disclosed in Shuber includes testing for the presence of methylated human DNA. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in measuring an amount of a methylated human DNA. EX1002 ¶276. Claim 6 is therefore obvious.

7. Claim 7: "The method of claim 5, wherein the epigenetic modification comprises aberrant methylation."

The '781 patent defines aberrant methylation as including at least hypermethylation. EX1001 12:47-49. The stool DNA assay disclosed in Shuber includes testing for the presence of hypermethylated DNA. EX1009 14:1-5. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in detecting aberrant methylation. EX1002 ¶277. Claim 7 is therefore obvious.

8. Claim 8: "The method of claim 7, wherein the aberrant methylation comprises hypermethylation."

The fecal DNA assays disclosed in Shuber include testing for the presence of hypermethylated DNA. EX1009 14:1-5. Thus, performing the fecal DNA test of

Shuber and the iFOBT of Vilkin on a stool sample results in detecting hypermethylation. EX1002 ¶278. Claim 8 is therefore obvious.

9. Claim 9: "The method of claim 7, wherein the human DNA having an epigenetic modification comprises a gene and/or a promoter region of a gene."

The fecal DNA assays disclosed in Shuber include testing for the presence of methylated human genes, which is an epigenetic modification of a gene and/or a promotor region of a gene. EX1009 14:1-5. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the extracted nucleic acid being tested by detecting an epigenetic modification of a gene and/or a promoter of a gene. EX1002 ¶279. Claim 9 is therefore obvious.

10. Claim 11: "The method of claim 5, wherein testing the nucleic acid for presence of human DNA having an epigenetic modification comprises modifying the nucleic acid with bisulfate[2] ions under conditions wherein unmethylated cytosine is converted to uracil."

As discussed above, the fecal DNA assays disclosed in Shuber include testing for the presence of DNA methylation (an epigenetic modification). EX1009 14:1-5. As of the Priority Date, the standard method for testing for DNA methylation used "bisulfite conversion," in which bisulfite ions are used to convert

[2] The reference to "bisulfate" instead of "bisulfite" in claim 11 appears to be a typographical error. EX1002 ¶¶180, 213.

unmethylated cytosine to uracil. EX1002 ¶281. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the use of bisulfite conversion to detect DNA methylation. EX1002 ¶¶280-282. Claim 11 is therefore obvious.

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

The iFOBT disclosed in Vilkin tests for a concentration of hemoglobin in a removed portion of a fecal sample. EX1005 pp.2519, 2522, Table 1. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in testing for a concentration of hemoglobin in the removed portion. EX1002 ¶283. Claim 14 is therefore obvious.

12. 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 detect hemoglobin. EX1005 pp.2519, 2520-2521. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in testing for a concentration of hemoglobin by immunochemical detection of hemoglobin. EX1002 ¶284. Claim 15 is therefore obvious.

13. Claims 16-20: "The method of claim 14, wherein the removed portion of the fecal sample is considered positive

for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least [5, 10, 20, 50, or 200] ng/ml."

Claims 16-20 each depend from claim 14 and 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 16-20 is rendered obvious by Shuber and Vilkin. As explained in section VII(A)12, 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 16-20 are result-effective variables that are the product of routine optimization and are obvious. EX1002 ¶285-288.

E. Ground V: 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 gene."

As set forth in section VII(D), 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 ¶289.

A POSA would find it obvious to further modify the above-described fecal processing method to incorporate the COX-2 RNA detection process disclosed in Kanaoka to arrive at the method of claim 12. EX1002 ¶290; EX1007 ¶¶021-026.

Kanaoka states that 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 Shuber's fecal DNA assays to improve assay sensitivity. EX1002 ¶290.

Example 1 of Kanaoka provides further motivation to combine Kanaoka's COX-2 RNA assay with an iFOBT, like the one disclosed in Vilkin. EX1002 ¶291. In this example, samples were tested using both a COX-2 RNA assay and iFOBT. EX1007 ¶¶0055-0068. The iFOBT identified a CRC patient as positive who was missed by the COX-2 RNA assay, while the COX-2 RNA assay identified three CRC patients missed by the iFOBT. EX1007 ¶¶0067-0068. A POSA therefore would have been motivated to combine the Kanaoka fecal COX-2 RNA assay with an iFOBT, such as the one disclosed in Vilkin, to increase the sensitivity of both assays. EX1002 ¶291.

A POSA would have had a reasonable expectation of successfully incorporating the COX-2 fecal RNA assay of Kanaoka into the fecal processing method rendered obvious by Shuber and Vilkin. EX1002 ¶292. Example 1 of Kanaoka provides a working example of the successful combination of a COX-2

RNA assay with an 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 it had been 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***." EX1002 ¶292; EX1030 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 ¶292.

As Kanaoka discloses detection of an amount of RNA expressed from a COX-2 gene, the method rendered obvious by Shuber, Vilkin, and Kanaoka includes such a step. EX1002 ¶¶289-293. 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 rendered obvious by 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 expressed from the COX-2 gene. 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 ¶294. Claim 13 is therefore obvious.

F. Ground VI: Shuber and Vilkin, in further view of Derks

As set forth in section VII(D), 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.

The fecal DNA assays disclosed in Shuber include hypermethylation assays. EX1009 7:19-21. Derks identifies GATA-4 methylation as a biomarker of CRC, reporting that methylation of GATA-4 "occurred significantly more frequent in the carcinomas when compared to corresponding normal mucosa." EX1008 p.250. Indeed, Derks reports that the GATA-4 gene is methylated in 94.4% of CRC tissue but only 16.7% of normal tissue. EX1008 p.252, Table 3b.

A POSA therefore would have been motivated to detect GATA-4 methylation, in the hypermethylation assays disclosed in Shuber, to arrive at the method of claim 10. EX1002 ¶¶295-297. Claim 10 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). Geneoscopy is unaware of any such considerations having the required nexus with the challenged claims that point towards their non-obviousness. Exact did not assert secondary considerations during prosecution and there is not a nexus between the challenged claims and

Exact's commercial product, Cologuard®. Should Exact allege any secondary considerations following institution, 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) based on prior art or arguments previously presented to the Office. Of the references in the Grounds, Itzkowitz, Vilkin, Derks, and Kanaoka were not before the Examiner during prosecution or reexamination of the '781 patent. The other references, Lenhard and Shuber, appeared in an information disclosure statement (IDS) filed on September 28, 2022, but neither the Examiner nor the Applicant discussed or otherwise cited either one during prosecution or reexamination of the '781 patent.

The *Advanced Bionics* factors used to evaluate whether to deny institution as a matter of discretion under § 325(d) favor 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). Those factors are "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Id.*

The arguments and relied-upon combinations of art in the Grounds are substantively different from any presented to the Office during prosecution or in subsequent reexamination proceedings. As noted above, none of Itzkowitz, Vilkin, Kanaoka, or Derks was of record during prosecution or reexamination. With respect to Lenhard and Shuber, the Board repeatedly has declined to discretionarily deny institution where the prior art in question merely was listed in an IDS and was not the subject of Examiner or applicant discussion. *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). This is precisely the case with Lenhard and Shuber. Although Lenhard and Shuber were listed in an IDS, neither the Examiner nor the applicant discussed or otherwise cited either reference during prosecution of the ’781 patent. Although Shuber was cited as a secondary reference in an obviousness rejection during prosecution of U.S. patent application number 15/634,607 (the parent of the ’781 patent), that rejection was based on different secondary references and different arguments than the grounds presented in this petition.

Accordingly, the *Advanced Bionics* factors favor institution.

X. Conclusion

Petitioner respectfully submits that the Board should institute IPR and determine that claims 1-20 of the ’781 patent are invalid by a preponderance of the evidence as required by 35 U.S.C. § 316(e).

Dated: January 11, 2024

Respectfully submitted,

/Brendan T. Jones/
Brendan T. Jones, Reg. No. 65,077
Foley Hoag LLP
155 Seaport Boulevard
Boston, MA 02210
Tel: (617) 832-1000
Email: bjones@foleyhoag.com
Counsel for Geneoscopy, Inc.

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 13,876 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 January 11, 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
UNITED STATES

Dated: January 11, 2024

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