

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

EXACT SCIENCES CORPORATION,

Plaintiff,

v.

GENEOSCOPY, INC.,

Defendant

Civil Action No. 23-cv-1319-MN

DECLARATION OF DUNCAN WHITNEY, Ph.D.



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List of Exhibits

- Exhibit A:** *Curriculum vitae* of Dr. Duncan Whitney
- Exhibit B:** List of materials considered
- Exhibit C:** U.S. Patent No. 11,634,781 (“781 patent”)
- Exhibit D:** U.S. Patent No. 11,970,746 (“746 patent”)
- Exhibit 1:** IPR2024-00459 Petition
- Exhibit 2:** IPR2024-00459 Institution Decision
- Exhibit 3:** IPR2024-01330 Petition
- Exhibit 4:** 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) (“Lenhard”)
- Exhibit 5:** 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). (“Vilkin”)
- Exhibit 6:** Steven Itzkowitz et al., “Improved Fecal DNA Test for Colorectal Cancer Screening,” *Clinical Gastroenterology and Hepatology*, 5:111-117 (2007) (“Itzkowitz”)
- Exhibit 7:** International Patent Application Publication Number WO2005/113769 (“Shuber”)
- Exhibit 8:** 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) (“Olson”)
- Exhibit 9:** LinkedIn Page of Joost Louwagie
- Exhibit 10:** Exact Science’s webpage regarding the Cologuard test as obtained from <https://www.exactsciences.com/our-tests/cologuard> on August 15, 2024.
- Exhibit 11:** Cologuard Physician Brochure
- Exhibit 12:** Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use
- Exhibit 13:** Exact Sciences’ “Patents and Trademarks” page from their website, as visited on August 9, 2024.
- Exhibit 14:** Exact Sciences’ “Patents and Trademarks” page from their website as of December 6, 2014. Downloaded from Wayback Machine on August 9, 2024.

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Exhibit 15: U.S. Patent No. 9,163,278

Exhibit 16: Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of '278 patent

Exhibit 17: Feiger, Chase, "How This CEO Consumerized Cancer Into a \$13B Enterprise" Forbes, April 8, 2024.

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I. INTRODUCTION

1. I have been retained by counsel for Geneoscopy, Inc. (“Geneoscopy”) as a technical expert in the above-captioned litigation, as well as related *Inter Partes* Review (IPR) proceedings at the United States Patent and Trademark Office (USPTO). I understand that Exact Sciences (“Exact”) has asserted that Geneoscopy infringes U.S. Patent No. 11,634,781 (“the ’781 patent”) and U.S. Patent No. 11,970,746 (“the ’746 patent”) (collectively, “the Asserted Patents”). I further understand that Exact has filed a motion for preliminary injunction (“PI Motion”) seeking to enjoin Geneoscopy from selling their recently FDA-approved ColoSense™ colorectal cancer (CRC) screening test based on the supposed infringement of claim 1 of the ’781 patent and claim 3 of the ’746 patent (collectively, “the Asserted Claims”).

2. In connection to Geneoscopy’s opposition to Exact’s PI Motion, I have been asked to provide independent expert opinions concerning the validity of the Asserted Claims. I have previously submitted declarations concerning the validity of these claims in connection with two IPR proceedings: IPR2024-00459 (filed January 11, 2024, instituted July 26, 2024) and IPR-2024-01330 (filed August 20, 2024, institution decision pending).

II. QUALIFICATIONS AND EXPERIENCE

1. My current Curriculum Vitae is attached as Exhibit A. I have summarized my educational and professional background below.

2. I received a B.A. in Chemistry from Colby College in 1981, and a Ph.D. in Materials Sciences and Engineering from Massachusetts Institute of Technology in 1987. My research advisor was Professor Gary Wnek.

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3. I have held leadership positions in several companies developing clinical diagnostics tests, with multiple responsibilities including clinical trial design; conception of strategic research plans and specific research approaches to address clinical unmet needs; scoping of analytical and clinical experiments and data-generation plans, including review and interpretation of data; recruiting, training and management of research staff; and working with other functional areas to gain regulatory and reimbursement approvals as part of the test commercialization process. I have authored or co-authored multiple peer-reviewed publications associated with this work.

4. My current position is Chief Scientific Officer (CSO) of Gregor Diagnostics (Madison, WI), since February of 2022. The company focuses on development of improved clinical diagnostics tests for risk-management of patients with prostate cancer. The company's research has included recruitment of patients in a multicenter study to collect specimens and clinical data, which have been used to discover novel biomarkers using various DNA and RNA-based sequencing methodologies. Prior to 2022, I held the position of Vice President (VP) of Early Detection, within the Lung Cancer Initiative at Johnson & Johnson (Boston, MA and New Brunswick, NJ) for 3 years, leading research and clinical studies to advance ways to diagnose and manage subjects with lung cancer.

5. I held the position of VP of Research & Development (R&D) at Allegro Diagnostics Corp. (Boston, MA) from 2009 to 2014. The goal of the company was to develop novel diagnostics for pulmonary diseases, including lung cancer. I led research programs to discover gene-expression biomarkers from subjects at risk of lung cancer. A trial was completed recruiting approximately 2000 subjects with indeterminate

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bronchoscopy procedures, where normal-appearing bronchial epithelial cells were collected, RNA was isolated, and the RNA was then profiled using microarrays.

Regression analysis of top genes, found to be differentially expressed between subjects with and without cancer was validated and published in top-tier, peer-reviewed journals, and was ultimately commercialized as a clinical diagnostic test by Veracyte, Inc.

6. I was involved in the sale of the company Allegro to Veracyte, Inc. (South San Francisco, CA) in 2014, which then hired me as VP of Discovery R&D. In addition to completing studies to demonstrate analytical and clinical validity of the lung cancer diagnostic test, initially developed by Allegro, I also led a team to develop a second-generation thyroid cancer diagnostic test using an RNA-sequencing methodology.

7. My initial professional experience developing clinical diagnostics was at Exact Sciences Corporation, where I was employed for 5 years (2000-2005). I was initially hired as the Director of Technology Development in the R&D group focusing on developing and optimizing methods for isolation of human DNA from stool samples. I was subsequently promoted to VP of Technology Development.

8. I have authored 23 peer-reviewed publications spanning my work conducted as part of my professional experiences. This includes five publications from studies conducted while I was employed at Exact, focused on stabilization of stool samples and recovery of human DNA from the samples for non-invasive detection of colorectal cancer ("CRC"), and development of CRC detection tests and technologies. I am also a named inventor on numerous patents and patent applications, some of which originate from studies I conducted while employed at Exact that focused on methods to

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improve recovery of DNA from stool samples for applications in non-invasive detection of CRC.

9. I am being compensated at my usual rate of \$400 per hour plus expenses for my work in connection with this litigation. My compensation in no way depends on the outcome of this proceeding or on the opinions I express. The opinions and conclusions I express herein are based on my review of the materials cited herein, including those listed in Exhibit B, as well as on (1) my general knowledge of clinical diagnostic tests, including stool-based diagnostic tests and sample handling processes, and (2) my years of experience acquired working in this field. I reserve the right to supplement or amend my opinions in response to opinions expressed by other experts, or in light of any additional evidence, testimony, or other information that may be provided to me after that date of this declaration.

III. OVERVIEW OF OPINIONS

10. It is my opinion that the methods of the Asserted Claims are obvious and that the claims directed to the methods are invalid. The Asserted Claims 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 was reported throughout the prior art well before February 3, 2009, the priority date asserted by the Asserted Patents (“the Priority Date”). By that date, the fecal tests for detecting blood protein and nucleic acids recited by the claims were known and routine.

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11. It is my opinion that the Asserted Claims are invalid as obvious over at least two combinations of references: (a) Lenhard,¹ Vilkin,² and Itzkowitz³ and (b) Shuber⁴ and Vilkin. I have previously set forth these opinions in the declarations I submitted in IPR2024-00459 (with respect to the '781 patent) and IPR-2024-01330 (with respect to the '746 patent). I understand that the United States Patent Trials and Appeals Board (PTAB) has instituted IPR2024-00459, finding that there was "a reasonable likelihood... that the challenged claims [of the '781 patent] would have been unpatentable as obvious."⁵ While the institution decision IPR2024-01330 is still pending, the claims of the '746 patent are nearly identical to those of the '781 patent, and the PTAB's reasons for finding it likely that the claim of the '781 patent are obvious apply equally to the claims of the '746 patent.

12. I have reviewed the Declaration that Dr. Bruce K. Patterson submitted in support of Exact's PI Motion, including the portions concerning his opinion that Exact's Cologuard products embody the invention claimed in the Asserted Patents and provide secondary considerations of nonobviousness (also referred to as objective indicia of nonobviousness).⁶ I disagree with Dr. Patterson's assertions. In my opinion, the supposed

¹ 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), ("Lenhard").

² 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), ("Vilkin").

³ Steven Itzkowitz et al., "Improved Fecal DNA Test for Colorectal Cancer Screening," *Clinical Gastroenterology and Hepatology*, 5:111-117 (2007), ("Itzkowitz").

⁴ International Patent Application Publication Number WO2005/113769, ("Shuber").

⁵ IPR-2024-00459 Institution Decision.

⁶ Patterson Declaration, at ¶¶321-344.

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secondary considerations asserted by Dr. Patterson should be accorded little or no weight because there is no nexus between the Cologuard products and the methods of the Asserted Claims.

13. It is also my opinion that the common specification of the Asserted Patents, which is directed to the stabilization, extraction and testing of *DNA*, does not convey that the inventor was in possession of the full scope of the methods of the Asserted claims, which cover the stabilization extraction and testing of *any nucleic acid, including RNA*. Similarly, is also my opinion that the common specification does not enable the full breadth of the Asserted Claims.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

14. I have been informed that the person of ordinary skill in the art (“POSA”) is a hypothetical person who is presumed to have known all of the relevant art as of the priority date of the Asserted Patents patent and is the person to whom the subject matter of the Challenged Patents is directed.

15. I have been asked to opine as to the qualifications of the POSA to which the claims of the Asserted Patents are directed. For the purpose of rendering an opinion on this question, I have further been instructed to assume that the priority date of the Asserted Patents to be February 3, 2009 (the “Priority Date”).

16. I have been informed that factors that may be considered in determining the level of ordinary skill may include: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field. I have further been informed that

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the POSA may possess the education, skills, and experience of multiple actual people who would work together as a team to solve a problem in the field.

17. In my opinion, a POSA relevant to the Asserted Patents 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. I have applied this understanding in offering my present opinions.

18. I am aware that in its PI Motion, Exact argued that a POSA relevant to the Asserted Patents would have a doctoral degree in medicine, chemistry, biochemistry, biology, or a related field and 1-2 years of experience in the processing and analysis of biological samples, including fecal samples, where the POSA could have been an individual or a member of a team of scientists addressing fecal sample processing and analysis. My opinions offered here would not change if I applied Exact's definition of a POSA in place of my own.

V. TECHNICAL BACKGROUND

19. The Asserted Claims are directed to a method of processing a fecal sample, wherein the sample is collected at home and divided in two portions: a first portion that is combined with a stabilizing buffer; and a second portion that is combined with a buffer that prevents denaturation or degradation of blood proteins. Nucleic acid is extracted from the first portion and then tested for an amount of a human nucleic acid, such as methylated DNA. The second portion is tested for the presence of an amount of a blood protein, such as hemoglobin.

20. As set forth in section V(A), methods for processing fecal samples to detect methylated DNA and hemoglobin were routine in the art well before the Priority Date. Moreover, as I explain in sections V(B) and V(C), below, separating a fecal sample

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so that it can be tested for both had been reported throughout the prior art. The method of the Asserted Claims amounts to no more than the routine performance of standard methods to prepare a fecal sample for performance of well-established, complementary diagnostic assays.

A. Fecal Assays for Detecting CRC

21. By the Priority Date, fecal samples had been used in non-invasive diagnostic tests for CRC for decades. Such tests generally involved obtaining a stool sample from a patient and testing it for one or more indicators of CRC (referred to as “biomarkers”). Because cancers involve complex changes to cells and tissues, there are typically many potential biomarkers available, some more informative than others. Examples of CRC biomarkers known to be present in feces included blood proteins, mutated DNA, long fragments of DNA from dying cells, methylated DNA (DNA modified by addition of a methyl group), and RNA. It was broadly recognized that increasing the number of biomarkers used in such a test could improve its sensitivity and/or specificity.⁷ By the Priority Date, a variety of protein and nucleic acid biomarkers detectable in stool were known to be useful for the diagnosis of CRC.

⁷ e.g., G.P. Young, “Fecal Immunochemical Tests (FIT) vs. Office-Based Guaiac Fecal Occult Blood Test (FOBT),” *Practical Gastroenterology* 28(6): 46-56 (2004) (“Young”); Lenhard; Itzkowitz; 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) (“Kutzner”); 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) (“Rennert”); 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) (“Karl”).

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1. Sensitivity and Specificity

22. Two typical industry measures of diagnostic assay performance are “sensitivity” and “specificity.” Sensitivity refers to the frequency at which a diagnostic test correctly provides positive results in subjects with disease (the true positive rate). Thus, a test with high sensitivity will produce few false-negative results, leaving few patients untreated. Specificity refers to the frequency at which the test correctly identifies a negative result in subjects without disease (the true negative rate). A test with high specificity will produce few false-positive results, so that patients are rarely subjected to unnecessary further testing or procedures.

23. Diagnostic tests are typically neither perfectly sensitive nor perfectly specific. Although a good test is often correct, due to imperfect sensitivity, at some frequency a test will identify a patient who has cancer as being healthy (a “false negative”). Likewise, due to imperfect specificity, at some frequency a test will identify a patient without cancer as having cancer (a “false positive”). The frequency of these events varies between tests.

24. Having a high sensitivity is particularly important in fecal CRC tests, where the consequence of false-negative results is that CRC patients do not receive needed cancer treatment, leading to a worse prognosis and potentially death. There are several possible sources of false-negative results, two of which are insufficient types and numbers of biomarkers, and secondly, insufficient quantity or integrity of analytes. As discussed below, sample quality (the quantity and integrity of analytes) can be negatively impacted by not preserving samples sufficiently during collection and transport to laboratories for processing and analysis.

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2. Fecal Occult Blood Tests (FOBT)

25. Many early diagnostic tests for CRC were based on the detection of small amounts of blood in a patient's stool. Blood proteins, such as hemoglobin, are often present in the stool of individuals with CRC because CRC results in polyps and lesions that may bleed into the fecal stream. The fecal blood used to diagnose CRC is referred to as "occult" because it is typically not visible to the naked eye. Fecal occult blood testing ("FOBT") was perhaps the first established non-invasive stool test to screen subjects for CRC, and has been common practice since at least the 1970's. FOBT remains a central feature of many diagnostic protocols for CRC, owing at least in part to its ease and historical foundations.⁸ Nevertheless, it was also well known that FOBT alone was an imperfect test for CRC. For example, some colonic lesions do not bleed detectably into stool, or bleed intermittently, leading to false-negative results, while there are also other non-cancerous conditions that can cause blood in stool, such as ulcerative colitis, which can lead to false-positive results.⁹

26. The earliest FOBTs developed were based on a well-established chemical reaction between heme (a molecule that is part of hemoglobin) and guaiac (a compound from *Guaiacum* trees). These tests are referred to as "gFOBTs". When heme reacts with guaiac it causes a visible change in its color. This was the basis for the Hemoccult® slide

⁸ JB Simon, "Occult Blood Screening for Colorectal Carcinoma: A Critical Review," *Gastroenterology*, 88:820-837 (1985) ("Simon"), p. 822

⁹ Victoria White and Richard Miller, "Colorectal Cancer: Prevention and Early Diagnosis," *Medicine*, 35(6) 297-301 (2007) ("White"), p. 298; Suzanne Mahon, "Prevention and Screening of Gastrointestinal Cancers," *Seminars in Oncology Nursing*, 25(1): 15-31 (2009), ("Mahon"), p. 22; K.S. Tagore et al. "Review Article: The Evolution to Stool DNA Testing for Colorectal Cancer," *Aliment Pharmacol. Ther.*, 19: 1225-1233 (2004) ("Tagore"), p. 1226.

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test (Smith-Kline Diagnostics) that was first commercialized in the 1970's.¹⁰ Such gFOBT, however, had poor sensitivity.¹¹ Moreover, gFOBT could be fooled by a variety of confounding sources, resulting in low specificity.¹² For example, guaiac reacts with common dietary elements, such as blood proteins from eating red meat, so patients had to restrict dietary intake in advance of testing for gFOBT to work well.¹³ Moreover, due to the stability of the heme molecule, non-diagnostic heme could also reach stool from other parts of the gastrointestinal tract, *e.g.*, from the stomach, which can result in additional false positive results for CRC.¹⁴

27. A new form of FOBTs that detected fecal blood using antibodies was developed in the 1980s. These newer tests are referred to as immunochemical fecal occult blood tests (iFOBT, sometimes alternatively referred to as fecal immunochemical tests, or FIT).¹⁵ In iFOBTs, the antibodies used are specific for human hemoglobin, eliminating the need for dietary restrictions.¹⁶ Because the hemoglobin detected by iFOBTs is rapidly digested in stomach and small intestine, iFOBTs are more selective for occult bleeding of colorectal origin than gFOBTs.¹⁷ iFOBTs are generally more sensitive than their guaiac

¹⁰ Simon, pp. 822-823; Donald Ostrow, "Tests for Fecal Occult Blood, in *Clinical Methods: The History, Physical, and Laboratory Examinations*." Boston: Butterworths; Chapter 98 (1990) ("Ostrow"), p. 489.

¹¹ *Id.*

¹² *Id.*

¹³ Ostrow, pp. 489-490; Charles Kahi et al., "Screening, Surveillance, and Primary Prevention for Colorectal Cancer: A Review of the Recent Literature," *Gastroenterology*, 135: 380-399 (2008) ("Kahi"), p. 385.

¹⁴ *Id.*

¹⁵ Simon, pp. 822-823; Ostrow, p. 489.

¹⁶ *Id.*

¹⁷ *Id.*

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predecessors.¹⁸ As an additional advantage, iFOBTs could be automated and produce quantitative results, allowing physicians to select an optimal threshold hemoglobin level, above which they arrange for their patient to undergo a colonoscopy.¹⁹

3. DNA Biomarkers

28. As mentioned above, blood is far from the only indicator of CRC found in stool. Others can include, for example, mutated DNA and DNA that is chemically modified with a methyl group (*i.e.*, methylated DNA). Accumulation of certain nucleic acid changes is central to the development of CRC disease.²⁰ These types of DNA biomarkers are found in stool samples because cancer cells and cellular debris are exfoliated into the fecal stream of patients with CRC.²¹

29. Fecal DNA biomarkers have been used in CRC diagnostic assays since the 1990s. Early studies found that fecal DNA from CRC patients often contained mutations in genes associated with cancer (“oncogenes”), including, for example, genes known as *APC*, *K-RAS* and *p53*.²² Because these cancer-associated mutations are more likely to be present in exfoliated CRC cells than in normal cells, they can serve as biomarkers for CRC and be detected in fecal DNA to identify patients with CRC.

¹⁸ GP Young et al., “New Stool Screening Tests for Colorectal Cancer,” *Digestion*, 76:26-33 (2007) (“Young 2007”); p. 29; Kahi, p. 385.

¹⁹ Young 2007, p. 30; Vilkin, pp. 2519-2520.

²⁰ White, p. 297.

²¹ Young 2007, p. 27.

²² Susumu Eguchi et al., “Mutations of the P53 Gene in Stool of Patients with Resectable Colorectal Cancer,” *Cancer*, 77:1707-1710 (1996) (“Eguchi”); D. Sidransky, “Identification of Ras Oncogene Mutations in the Stool of Patients with Curable Colorectal Tumors,” *Science*, 256:102-105 (1992) (“Sidransky”); 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) (“Villa”).

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30. The DNA from CRC cells can also be distinguished based on the pattern of methyl groups present on particular nucleotides in certain genes. When DNA is modified by methyl groups (“methylation”), the pattern or amount of methylation can be indicative of different cellular states. DNA methylation can be particularly important in regions of DNA that regulate gene expression, including gene promoters.²³

Hypermethylation (DNA regions containing many methylated cytosines) is often associated with decreased expression or silencing of certain genes. In cancer patients, hypermethylation often occurs on genes that would otherwise help suppress cancer (tumor suppressor genes). By contrast, hypomethylation (DNA regions containing few methylated cytosines) is often associated with increased expression.²⁴ In cancer patients, hypomethylation is often associated with oncogenes (to activate expression of genes that enhance cancer). Diagnostic analysis of methylation in stool samples for detection of CRC dates back to at least 2004.²⁵

4. RNA Biomarkers

31. RNA is another type of nucleic acid that is produced by cells when genes are expressed. The type and amount of RNA expressed by a cell presents a contemporaneous picture of the state of that cell. Accordingly, changes in the types and

²³ 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). (“Chen”), p. 1124.

²⁴ *Id.*

²⁵ Hannes Müller et al., “Methylation Changes in Faecal DNA: A Marker for Colorectal Cancer Screening?” *Lancet*, 63:1283-1285 (2004). (“Müller”).

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amounts of RNA can be used to distinguish cancer cells from healthy cells in real time, and the type and amount of RNA in a fecal sample can be a biomarker of CRC.²⁶

32. Use of RNA as a biomarker is challenging because RNA is much less stable than DNA. RNA is expressed from genes as a relatively unstable single strand, whereas double-stranded DNA is stabilized and protected by the interactions between the strands. Additionally, RNA-degrading enzymes (RNases) are significantly more prevalent than DNA-degrading enzymes (DNases). The inherent instability of RNA, which is more prone to degradation compared to DNA, makes its preservation and extraction difficult, especially from samples like stool that are rich with other components, including degrading enzymes, DNA, and bacteria. For at least these reasons, processes for stabilizing and extracting DNA from fecal samples are typically insufficient for the stabilization and extraction of RNA.

B. Biomarker Panels

33. By the Priority Date, it was recognized that fecal CRC detection assays that combined multiple biomarkers had important advantages over assays that detected biomarkers individually. Indeed, the heterogeneity of the disease necessitates the use of multiple markers in combination to improve assay sensitivity.²⁷ This was true whether

²⁶ Shigeru Kanaoka et al., “Potential Usefulness of Detecting Cyclooxygenase 2 Messenger RNA in Feces for Colorectal Cancer Screening,” *Gastroenterology*, 127:422-427 (2004). (“Kanaoka”).

²⁷ 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) (“Ahlquist 2000”), pp. 1219-1220; Lenhard, White, 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) (“Levin”); Kutzner.

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the test combined different types of DNA markers, or a combined DNA markers and occult blood.

34. Thus, by the Priority Date, it was recognized that fecal CRC diagnostics could be improved by combining fecal occult blood testing with additional nucleic acid or protein markers. It was widely recognized that FOBT screening alone, while cost-effective, had relatively low sensitivity.²⁸ Studies had shown that even careful use of FOBT only decreases CRC mortality by 15-33%, demonstrating further opportunity for improvement.²⁹ FOBT also detects CRC only when it has developed sufficiently to cause occult blood in stool, whereas other approaches based on DNA biomarkers were thought to permit earlier detection.³⁰ In practice, these factors translate to undiagnosed cancers from false negative results and unproductive follow-up screening from false positive results, typically by colonoscopy.³¹ The fact that the consequence of a false positive test is a low risk, routine procedure like a colonoscopy, as balanced against the risk of patient death associated with false negative diagnoses, favors the development of CRC screening tests with higher sensitivity (*i.e.*, fewer false negatives), even if some tradeoff against specificity (*i.e.*, more false positives) is required.

35. It was therefore well understood by the Priority Date that the sensitivity of diagnostic assays could be improved by combining fecal DNA tests with FOBT. This

²⁸ Kutzner, p. 40; Rennert, Abstract; 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) ("Leung"), p. 1070.

²⁹ Lenhard, p. 142.

³⁰ Lenhard, p. 147.

³¹ Rennert, p. 259; Leung, p. 1070.

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general principle was taught in a number of publications. For example, a paper on K-ras point mutations in fecal DNA noted that such assays “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.**”³² Another report, using methylation of fecal DNA as a biomarker for CRC, stated “[t]he **combination of HIC1 methylation analysis with FOBT** allowed for the **detection of two thirds of CRCs**” and “**all localized cancers.**”³³ Kutzner et al. combined FOBT with DNA biomarkers, concluding 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**”³⁴ 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 [another acronym for iFOBT] at the time of testing would **improve sensitivity [of DNA-based assays] without adversely affecting specificity.**”³⁵

36. Before the Priority Date, a number of laboratories had developed diagnostics that combined FOBT with other types of tests. For example, Rennert et al. proposed a combined test that included analysis of a representative DNA marker (a K-ras mutation) in stool DNA with FOBT to improve predictive value and separate true

³² 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) (“Nishikawa”), p. 112 (emphasis added).

³³ Lenhard, pp. 143, 147 (emphasis added).

³⁴ Kutzner, p. 34, Abstract (emphasis added).

³⁵ Levin, p. 1578 (emphasis added).

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positives from false positives.³⁶ Kutzner et al. found that the sensitivity of combining FOBT with analysis of several DNA markers “resulted in an overall sensitivity, which could not be achieved by any of the methods alone and which is in the range of invasive diagnostic methods.”³⁷ Karl et al. performed an analysis of six immunoassays including iFOBT and immunoassays measuring five other proteins, to identify an optimal subset.³⁸ Lenhard et al. tested samples for both methylation of DNA biomarkers and fecal occult blood.³⁹

37. It was thus widely understood that one mechanism for increasing sensitivity and/or specificity of CRC screening would be to combine use of multiple biomarkers, including both fecal DNA and FOBT.⁴⁰ Use of multiple biomarkers directly increased sensitivity where any positive result was considered a positive diagnosis, and increased specificity where multiple positive results were required for a positive diagnosis. Under either approach, increasing the number of biomarkers used in such a diagnostic test resulted in an improved assay.

C. Home Collection of Fecal Samples

38. Although CRC biomarkers are often analyzed by complex molecular diagnostic assays, patients can collect stool samples at home and ship them to a

³⁶ Rennert, Abstract.

³⁷ Kutzner, Abstract.

³⁸ Karl.

³⁹ Lenhard, p. 145, Abstract.

⁴⁰ Nishikawa, p. 112; Lenhard, pp. 143, 147; Kutzner, p. 34, Abstract; Levin, p. 1578; Rennert, p. 258; White, p. 301; International Patent Application Publication Number WO97/25925 (“Taylor”), 15:3 – 17:17.

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laboratory for analysis.⁴¹ Home collection is convenient, supports patient compliance, and reduces use of hospital resources. Long before Priority Date, patients were collecting fecal samples at home and then shipping them unfrozen to a diagnostic laboratory for iFOBT or DNA-based CRC testing.⁴² As a result, fecal assays typically utilize stool samples that are collected by patients at home using specially designed kits and then shipped to a laboratory for testing.⁴³

1. Collecting Stool Samples

39. Many CRC tests require stool sample collection by the patients themselves, and, as a consequence, a variety of collection means had been devised by the Priority Date. In some tests, a patient recovers stool from the toilet bowl or other receptacle (ideally kept clear of the toilet water) using a wooden applicator and smears a small portion onto a test paper.⁴⁴ Other tests provided a spatula, brush, or probe to transfer stool into a collection vessel with a buffer.⁴⁵ Some kits included a stool collection vessel that mounts onto the toilet bowl to collect a patient's stool, after which

⁴¹ Vilkin, p. 2519; Itzkowitz, pp. 112, 115; Tagore, p. 1227; 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) ("Imperiale"), p. 2705; Mahon, p. 22; 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) ("Olson"), p. 183.

⁴² *Id.*

⁴³ *Id.*

⁴⁴ Young 2007, p. 29; Ostrow, p. 489; Young 2004, p. 49.

⁴⁵ Young 2007, p. 29; Young 2004, pp. 49, 53-54.

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stabilizing buffer is added to the vessel.⁴⁶ All of these systems were designed for use by patients at home. Samples are then shipped to a laboratory facility for testing.⁴⁷

40. Kits designed for home collection of stool have been available for many decades, and typically included a collection basin into which a patient can directly defecate, where the basin could be sealed and/or portions of the sample could be transferred to smaller receptacles, optionally including a stabilizing buffer.

2. Use of Buffers to Preserve Biomarkers in Fecal Samples

41. By the Priority Date, preservation of biomarkers in stool samples during transport from a home to a laboratory was recognized as an important concern that could be addressed through the use of appropriate stabilizing buffers. At room temperature, bacterial enzymes found in stool can degrade human DNA (and RNA is even less stable). This is a particularly important problem because, in stool, bacterial cells outnumber human cells by orders of magnitude. Similarly, protein biomarkers, such as hemoglobin, can be degraded by bacteria or enzymes contained in feces, resulting in loss of detectable protein in the absence of preventative measures. Freezing is a common preservation technique, but is not well suited to at-home collection. Home users typically do not have access to standardized, laboratory-quality freezing equipment, nor a convenient means to ship frozen samples to testing facilities.

42. As a result of the above concerns, many assays used optimized stabilizing buffers to maintain sample integrity between a patient's home and a receiving laboratory,

⁴⁶ Itzkowitz, p. 112.

⁴⁷ Ostrow, p. 489; Itzkowitz, p. 112; Shuber.

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without freezing.⁴⁸ For example, certain buffers prevent degradation of DNA, and are therefore used when DNA is used as a biomarker.⁴⁹ Other buffers stabilize proteins and are therefore used when hemoglobin is used as the biomarker.⁵⁰

43. By the Priority Date, numerous published studies had emphasized the importance of using appropriate buffers to preserve DNA in stool samples being used in CRC diagnostic assays. For example, in a publication that I co-authored, entitled “DNA Stabilization Is Critical for Maximizing Performance of Fecal DNA-Based Colorectal Cancer Tests,” my co-authors and I describe the stabilization of DNA from stool using a specially formulated buffer, and also directly demonstrate the improvement in performance of a DNA-based CRC assay when such a DNA stabilization buffer is used.⁵¹ In this study, 11 stool samples from patients with CRC were stored at room temperature (for 36 and 48 hours), with and without the DNA stabilization buffer. When the sample was stored without DNA stabilization buffer, 9 of the 11 samples were so degraded after 36 hours at room temperature that they tested negative. By contrast, when the stool samples were stored in DNA stabilization buffer, all 11 correctly tested positive. Additional experiments demonstrated that when stool samples were stored without DNA stabilization buffer 65% to 98% of the recoverable DNA in the sample was lost.

⁴⁸ Olson, Abstract; Shuber, 10:10-15; Vilkin, pp. 2520-2521; U.S. Patent No. 5,952,178 (“Lapidus ’178”), 3:10-14; Itzkowitz, pp. 111-112.

⁴⁹ Olson, p. 183; Shuber, 10:10-15; Itzkowitz, pp. 111-112.

⁵⁰ Vilkin, pp. 2520-2521; Karl, p. 1127; 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) (“Hirata”), p. 1573.

⁵¹ Olson.

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44. Different buffers that stabilize proteins are important for fecal assays in which hemoglobin is detected.⁵² In one study, the authors noted that “[b]ecause patients in a screening situation are likely to collect stool samples at home, the sampling procedure and analyte stability are crucial,” especially for hemoglobin.⁵³ The solution to this concern was that “[n]ovel sampling devices, that are prefilled with extraction buffer and can be mailed to the laboratory at ambient temperature.”⁵⁴ Vilkin, for example, reported use of a “fecal test sampling device is shaped like a small test tube with the fecal probe inserted into it,” where the “[t]he tip [of the probe] is then put in a closed amount of Hb [hemoglobin] stabilizing buffer.”⁵⁵

45. Thus, by the Priority Date, the use of appropriate buffers to stabilize stool proteins and nucleic acids without freezing was routine.

3. Partitioning Samples into Multiple Vessels for Stabilization during Shipment

46. By the Priority Date, it had long been recognized that, where samples were needed for two or more different tests, the patient could separate the fecal sample into two separated vessels or compartments prior to shipment to a laboratory.

47. Indeed, as illustrated in Figure 1, below, the need to partition a fecal sample and separately preserve each portion in different stabilizing solutions was reported decades before the Priority date. According to the illustrated schematic, which is adapted from a 1949 publication and appeared in a 1985 laboratory manual, a stool

⁵² Hirata, p. 1573.

⁵³ Karl, p. 1127.

⁵⁴ *Id.*

⁵⁵ Vilkin, p. 2520.

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sample is first collected by direct defecation into a receptacle (panel 2).⁵⁶ The sample is then separated into two portions, each of which is preserved in a separate stabilizing buffer for shipment to a diagnostics laboratory (panels 3 and 4). Thus, by the Priority Date, it had been routine for decades for a patient to separate a fecal sample into different sealable containers, each containing a different stabilizing buffer, in order to preserve different biomarkers during shipment to a diagnostic laboratory.

⁵⁶ 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) ("Melvin"), p. 12.

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Figure 1

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.



48. The need for at-home separation of a fecal sample into different vessels so different buffers can be used to preserve the distinct biomarkers of interest is also the basis

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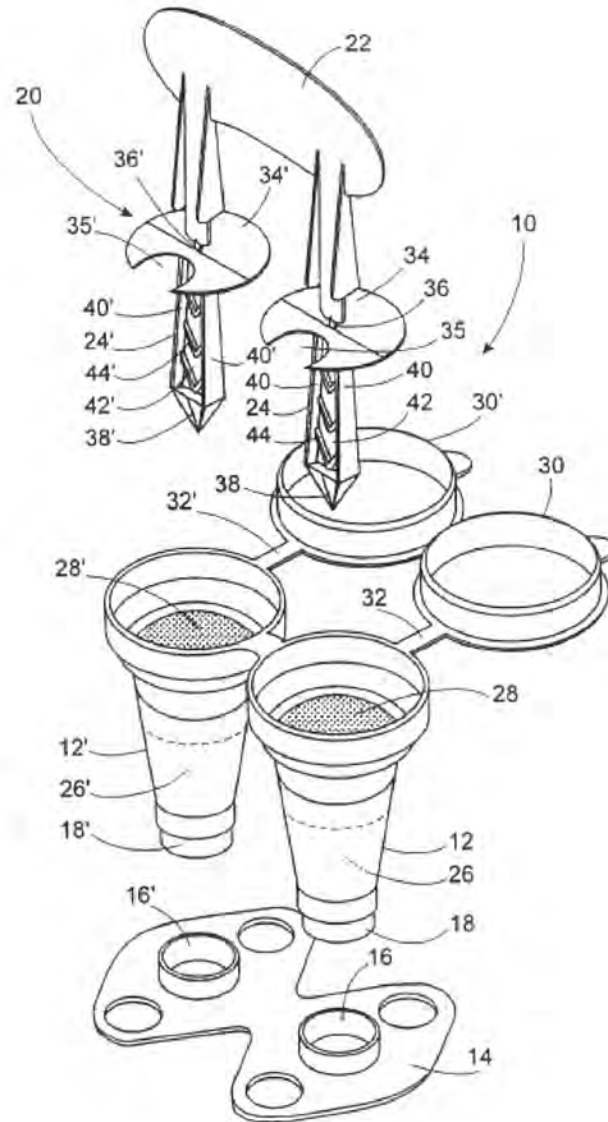
of the fecal sampling device illustrated below in Figure 2. This device, which is disclosed and claimed in a 1997 patent application, is designed to separately collect two portions of a sample into separate buffers. The patent application states that the device is useful for collection and transportation of stool with a preservation medium, which can include “at least two containers, each holding a different preservation medium” when “a variety of different entities have to be assayed in the pasty material.”⁵⁷ As explained in the application, “in the case of a pasty material which is to be sampled for the purpose of two or more different laboratory assay, such as stool, it would be preferable to provide a system for collection and preservation of pasty material which comprises two or more separate containers, each one holding a different transport or suspension medium.”⁵⁸ Thus, Figure 2, and the application from which it is derived, provide another example of at-home separation of a fecal sample into portions so that separate biomarkers are separately preserved in different buffers for shipment to a diagnostic laboratory.

⁵⁷ International Patent Application Publication Number WO97/25925 (“Inbar”), 1:1-22, 4:13-22.

⁵⁸ *Id.* 3:3-8.

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Figure 2



49. The prior art includes further examples in which patients separated fecal samples at home to facilitate testing of different biomarkers. For example, in one paper in which an FOBT was combined with DNA testing, patients could remove a portion of the sample for FOBT testing, and then ship both the removed portion and the remaining

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portion to the diagnostic laboratory for testing.⁵⁹ Additional examples of patients separating fecal samples at home to facilitate testing of different biomarkers include Karl, in which iFOBT was combined with other protein biomarkers, and which explains that “[e]ach participant provided two different portions of approximately 1 g of feces from one bowel movement using a stool collection tube.”⁶⁰

50. Thus, 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.

D. Fecal Sample Processing is Different for Different Biomarkers

1. Different Stabilization Buffers are Required for DNA and RNA

51. Stool is a challenging sample type to work with. Human stool samples consist primarily of food waste and the anaerobic bacteria that act upon food during the digestion process. At any given moment, the bacterial cells in the gut of a healthy adult outnumber the number of human cells in that person’s body. The cells that line a person’s intestine (gastrointestinal epithelial cells) are also continuously shed and refreshed, with a full replacement occurring every 4-7 days. In healthy adults, an estimated 10^{10} epithelial

⁵⁹ 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) (“Ahlquist 2008”), pp. 442-443.

⁶⁰ Karl, p. 1123.

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cells are shed from the gastrointestinal tract per day. Yet, even with this continuous shedding, human cells only make up about 1% of the dry weight of stool.⁶¹

52. Stool presents a harsh environment for cells, as well as for cell-free DNA, RNA, and proteins. This is primarily due to the activity of bacteria and enzymes that are present in stool the purpose of digesting food and other biological materials. The abundant degrading enzymes in the gut, many specific to DNA (DNases), RNA (RNases), or proteins (proteases), destabilize sample integrity. Stabilization of biomolecules in fecal samples is significantly more challenging than in most other biological sources. Extensive scientific effort has therefore been required to develop buffer solutions capable of stabilizing biomolecules in stool samples.

53. Optimal conditions to stabilize a sample depend on the type of biomarker to be recovered (*e.g.*, cells, proteins, DNA, or RNA). The stability of each type of biomarker is governed by its own unique chemical composition, structure, and susceptibility to enzymatic degradation. Therefore, different types of biomarkers typically require different measures to curtail degradation and to enable recovery of ample quantities for downstream analysis. While freezing (*e.g.*, at -80 °C) is a standard method that effectively stabilizes most biomolecules, the equipment and shipping requirements to maintain such a low temperature is incompatible with the goals of convenient, at-home sample collection. As a result, specialized stabilization conditions often need to be developed and clinically validated to prove their effectiveness for

⁶¹ Vincent, C., Mehrotra, S., Loo, V. G., Dewar, K., & Manges, A. R. "Excretion of Host DNA in Feces Is Associated with Risk of *Clostridium difficile* Infection," *Journal of Immunology Research*, 1–7, (2015) ("Vincent").

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preserving a given biomarker from a given sample type under applicable conditions (*e.g.*, for DNA or protein, from stool, for shipment to a laboratory via a traditional courier).

54. While employed at Exact in the early 2000s, I helped develop and test the DNA stabilization buffer described in Olson *et al.*, a publication on which I am a coauthor and that is cited in the Asserted Patents.⁶² As reported in, for example, patent application number WO 2005/113769 and U.S. patent number 6,551,777, both filed by Exact, developing the composition of this DNA stabilization buffer required substantial scientific research performed by my colleagues at Exact. The objective of the Olson *et al.* study was to demonstrate that the buffer we developed effectively stabilized DNA in stool samples. The optimized buffer we developed was never intended to stabilize RNA, and I would not expect it to do so effectively given RNA's increased susceptibility to degradation compared to DNA.

55. While DNA and RNA are both nucleic acids, they differ significantly in their stability and susceptibility to degradation and require different buffer formulations to achieve sufficient stabilization. RNA is a fragile biomolecule, exhibiting reduced stability compared to DNA primarily due to its single-stranded structure and susceptibility to hydrolytic cleavage. Additionally, RNA nucleases are abundant in biological samples, including fecal matter, and can rapidly degrade RNA if not properly inhibited. Furthermore, the complex and diverse microbiome environment in fecal samples may contribute to a high level of RNase activity, making RNA stabilization in such samples particularly challenging. Therefore, it is generally recognized that additional precautions must be taken for isolating RNA and running RNA-based testing

⁶² Olson; '781 patent, 36:37-38.

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protocols compared to DNA-based testing. Accordingly, RNA stabilization buffers need to be specifically formulated to address the unique challenges posed by RNA's fragility and susceptibility to degradation by RNases, and thus differ in composition from DNA stabilizing buffers.

2. Different Extraction Methods are Required for DNA and RNA

56. As discussed above, RNA is a fragile biomolecule that is significantly less stable than and structurally distinct from DNA. Therefore, additional precautions must be taken and different techniques used for isolating RNA and performing RNA-based testing protocols compared to DNA-based testing. Methods developed to optimize recovery, stabilization and handling of DNA will typically not translate to RNA. Indeed, one of the purposes of many DNA extraction methods is to separate the DNA in a sample from other contaminating biomolecules, including RNA. Thus, DNA extraction methods are often specifically designed to exclude RNA from the resulting extract. Likewise, elimination of contaminating DNA is often an object of RNA extraction methods.

57. The DNA extraction process disclosed in the Asserted Patents generally follows the one my colleagues and I had described in Olsen *et al.* In this process, extracting DNA from stool samples begins by spinning the samples in a centrifuge, which helps separate solid particles from the liquid portion of the stool, with the latter containing the majority of the sample's cell-free DNA. The liquid portion is then treated with an RNA nuclease enzyme (RNase A), *for the specific purpose of degrading any RNA remaining in the sample*. The DNA is then purified from the rest of the material using chemicals that clumps DNA together, allowing it to be separated. The separated DNA is passed through a filter that is designed to trap the DNA while allowing other unwanted materials to pass through. Following extensive washing to remove any

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remaining impurities, the purified DNA is released, and can then be utilized for further tested (*e.g.*, for DNA methylation).

58. Due to both the molecular properties of RNA and the diversity of RNA types present in biological samples, RNA extraction can be challenging, particularly in nuclease-rich environments such as fecal matter. Additionally, the various forms of RNA—such as messenger RNA (mRNA), microRNA (miRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA)—each exhibit different levels of stability and abundance. For instance, mRNA, the form of RNA typically detected in diagnostic assays, is particularly fragile and prone to degradation, while miRNA, being much smaller, requires specialized purification techniques due to its size. In contrast, rRNA displays higher stability, but still requires extraction protocols tailored to its unique characteristics.

59. This complexity highlights the need for specialized approaches pertaining to RNA extraction methods. The distinct characteristics of each RNA type require different purification methods, that account for their molecular stability, size, and abundance, rather than the use of a single extraction protocol. Furthermore, the high concentration of RNases in fecal matter, many of which originate from the huge abundance of bacteria, further hinders the extraction process, thus necessitating the utilization of RNase inhibitors to prevent enzymatic degradation. Successful RNA extraction protocols, particularly from complex samples like stool, require specialized buffers that both inactivate RNases and preserve RNA integrity throughout the process. These buffers are crucial for ensuring that RNA remains intact, particularly for sensitive

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diagnostic applications where even minimal RNA degradation can compromise the accuracy of the outcomes.

60. Given the specialized and delicate nature of RNA extraction, the techniques used for extracting DNA are generally incompatible with RNA. Proper extraction and purification procedures are essential for reliable nucleic acid detection, as contaminants and bacterial nucleic acids present in stool may interfere with downstream detection assays.

61. More recently, Geneoscopy developed a different approach to improve stability and recovery of fecal RNA for clinical testing, in which a buffer that preserves the integrity of intact human cells in stool is added to the stool, which is then shipped to a laboratory wherein the human cells are first isolated from other parts of the stool, including the bacteria, and RNA is purified from the isolated human cells. This approach provides at least two advantages over the approach of directly isolating cell-free fecal RNA previously used. First, the RNA is protected within intact cells from the harsh stool environment. Second, by specifically isolating human cells from the mass of bacterial cells in stool, the challenges associated with human RNA representing only a minor fraction of the total RNA in stool is minimized.

E. Cologuard

62. Cologuard is a non-invasive colorectal cancer (CRC) screening test developed by Exact Sciences. The test is designed to detect CRC, pre-cancerous lesions, and advanced adenomas by analyzing DNA and blood protein biomarkers in a stool sample.

63. A patient collects a stool sample and separates it into two parts: one for DNA analysis and the other for an immunochemical test to detect the blood protein

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hemoglobin. The portion of the sample for DNA analysis is combined with a buffer that stabilizes DNA, while the portion that is for blood protein analysis is combined with a buffer that preserves proteins. The sample portions are transported to a laboratory where molecular techniques are used to analyze one portion of the sample for a specific combination of DNA mutation and DNA methylation biomarkers, while the other portion is subjected to an iFOBT test for hemoglobin. A software program processes these results through an algorithm, providing a predictive score that helps clinicians predict whether the patient may have CRC.

64. In the portion of the sample on which the DNA test is performed, Cologuard utilizes buffers and processes that lyse both human and bacterial cells in the stool sample, thus allowing the release of genomic DNA from both. However, detecting human DNA in a stool sample is challenging due to the presence of bacterial DNA, which comprises the majority of the genetic material. To address this limitation, the Cologuard test uses magnetic beads to capture and purify the human DNA fragments on which the DNA biomarkers are found. These purified fragments are then subjected to further tests to determine whether they contain certain mutated or methylated genes.

65. In summary, the highly specific technical protocols utilized by Cologuard are meticulously optimized to stabilize, isolate, identify, and analyze DNA mutations and DNA methylation. They are not appropriate or workable for RNA.

F. ColoSense

66. ColoSense, is a novel non-invasive test developed by Geneoscopy for detecting colorectal cancer (CRC) and precancerous lesions. Unlike Cologuard's traditional DNA-based methods, ColoSense detects a panel of RNA biomarkers, specifically messenger RNA (mRNA), to detect cancer. Use of RNA as a biomarker to

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detect CRC offers potential advantages in terms of early detection of advanced adenomas and CRC, particularly in younger patient populations, who are frequently underrepresented in traditional CRC screening.

67. During a key step of the ColoSense assay, human cells containing the RNA to be tested are purified away from contaminating bacterial cells using differential centrifugation. Thus, unlike with the Cologuard assay where cells are lysed, the ColoSense assay requires the human cells in the at-home collected stool sample to remain intact during transport to the diagnostic laboratory. To achieve this, ColoSense combines the stool sample a highly optimized stool stabilization solution specifically designed to preserve the integrity of cells, which also protects the RNA that they contain.

68. Following differential centrifugation at the diagnostic laboratory, the purified human cells are lysed under contaminant-free conditions to extract RNA. This step ensures the isolation of high-quality, intact RNA for further analysis. The purified human RNA is then further processed and tested using molecular biology techniques for detecting and quantifying certain RNA biomarkers associated with CRC.

69. The RNA biomarker panel utilized in ColoSense has been selected by Geneoscopy scientists based on extensive research that links gene expression to the presence of CRC. Specifically, ColoSense evaluates eight (8) different human mRNAs including *ACY1*, *AREG*, *CDH1*, *EGLN2*, *GAPDH*, *KRAS*, *SMAD4*, and *TNFRSF10B*. Quantification of each of these markers is used in conjunction with an iFOBT to determine the likelihood of a patient developing CRC, advanced adenomas, or serrated precancerous lesions. This curated RNA biomarker panel provides insights into the intricate biological processes contributing to CRC, and it provides information that is

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distinct from the information provided by DNA mutations or methylation markers as used in Cologuard.

VI. Legal Standards

A. Obviousness

70. I have been informed that a patent claim is invalid if the claimed invention would have been obvious to the POSA at the time the alleged invention was made. Whether a claimed invention would have been obvious depends on (1) the scope and content of the prior art; (2) differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) objective indicia of non-obviousness. Objective indicia of non-obviousness (which I understand are also known as secondary considerations) include: copying, long-felt but unsolved need, failure of others, commercial success, unexpected results or properties achieved by the claimed invention, and skepticism of skilled artisans before the invention.

71. In particular, I have been advised that, for an invention to be regarded as “obvious,” the POSA must have had a reason or been motivated to modify the prior art or to combine one or more prior art references in a manner that would yield the claimed invention. I understand, however, that the prior art does not need to contain an explicit reason or motivation to modify the prior art, but that a motivation or reason may be found explicitly or implicitly in market forces, design incentives, the interrelated teachings of multiple patents and publications, any need or problem known in the field of endeavor at the time of the invention, and the background knowledge, creativity, and common sense of the POSA.

72. I have been informed that exemplary rationales that may support obviousness include: (a) combining prior art elements according to known methods to

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yield predictable results; (b) simple substitution of one known element for another to obtain predictable results; (c) use of known technique to improve similar devices (methods, or products) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (e) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success or “obvious to try”; (f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and (g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

73. I have also been informed that, for a claim to be obvious, the POSA must have had a reasonable expectation of success with respect to the claimed invention. I understand that a reasonable expectation of success does not require certainty of success, and that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.

74. I understand that the use of hindsight in an obviousness analysis is impermissible. In other words, I understand that it is improper to start from the challenged patent as blueprint to work backwards to the claimed invention. As such, I have not used hindsight in my analysis. I further understand that it is *not* hindsight to rely on knowledge that was within the level of ordinary skill, nor must there be an express motivation to modify or combine the prior art.

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75. Finally, I have been informed that, while objective indicia or secondary considerations can support non-obviousness, they are only relevant if there is a nexus between the merits of the claimed invention and the evidence of objective indicia. I understand that, in order to show nexus, a patentee must show that the evidence of secondary considerations results both from what is claimed and what is novel in the claim. I also understand that nexus requires a showing that any product asserted to be the source of secondary considerations both embodies and is co-extensive with the claims challenged as obvious.

B. Written Description

76. I understand that a patent must contain a written description of the product or method claimed in the patent. The issue of written description is decided on a claim-by-claim basis, not as to the entire patent or groups of claims. To satisfy the written description requirement, the patent specification must describe each and every limitation of a patent claim, in sufficient detail to disclose the claimed invention, although the exact words found in the claim need not be used. If the patent specification does not include an adequate written description of the full scope of the claim, then the claim is invalid.

77. When determining whether the specification discloses the invention, the claim must be viewed as a whole. The written description requirement is satisfied if the specification clearly allows a person of ordinary skill in the field of the invention to recognize that the inventors invented the full scope of what is claimed as of the effective filing date of the claimed invention.

78. I understand that the patent specification demonstrates possession by describing the claim invention with all of its limitations using such descriptive means as words, structures, figures, and diagrams, that fully set forth the claimed invention.

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Factors to consider in evaluating whether the specification has provided an adequate written description include: 1. the nature and scope of the patent claims; 2. the complexity, predictability, and maturity of the technology at issue; 3. the existing knowledge in the relevant field; and 4. the scope and content of the prior art.

79. I also understand that written description of a broad genus requires description of both the outer limits of the genus and also a description of either a representative number of members of the genus or structural features common to members of the genus. I am informed that this description must sufficiently disclose enough so that a person of ordinary skill in the art can visualize or recognize members of the genus.

C. Enablement

80. I understand that a patent must disclose sufficient information to enable or teach persons of ordinary skill in the field of the invention, as of the effective filing date of the claimed invention, to make and use the full scope of the claimed invention without undue experimentation. If a patent claim is not enabled, it is invalid.

81. Factors to consider in determining whether persons of ordinary skill in the field of the invention would require undue experimentation to make and use the full scope of the claimed invention include the quantity of experimentation necessary and whether that experimentation involves only known or commonly used techniques.

82. Other factors relevant to enablement include: 1. the amount of direction or guidance disclosed in the patent; 2. the presence or absence of working examples in the patent; 3. the nature of the invention; 4. the state of the prior art; 5. the relative skill of those in the art; 6. the predictability or unpredictability of the art; and 7. the breadth of the claims.

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VII. The Asserted Patents

A. The Asserted Patents

83. I understand that the Asserted Patents share a common specification, that both are titled “Fecal Sample Processing and Analysis Comprising Detection of Blood,” and that their only named inventor is Joost Louwagie. I understand that Joost Louwagie was an OncoMethylome employee.⁶³

84. I understand that the Asserted Patents are part of a family of applications that claims priority to a provisional application filed on February 3, 2009, by the Belgian company OncoMethylome (the “OncoMethylome Patent Family”). I understand that in April 2017, the OncoMethylome Patent Family was assigned to Exact.⁶⁴

85. I understand that Exact filed the application that gave rise to the ’781 patent on September 28, 2022. I understand that the only rejection issued by the patent office during its prosecution was for obviousness-type double patenting over a co-pending family member, which Exact overcame by filing a terminal disclaimer. I understand that the ’781 patent issued on April 25, 2023.

86. I understand that Exact filed the application that gave rise to the ’746 patent on March 7, 2023. I understand that the only rejections issued by the patent office during its prosecution were for obviousness-type double patenting over members of the same patent family, including the ’781 patent, which Exact overcame by filing terminal disclaimers. I understand that the ’746 patent issued on April 30, 2024.

⁶³ Transmittal Notice for U.S. Provisional Patent Application US61/149,581; LinkedIn Page of Joost Louwagie, <https://www.linkedin.com/in/joost-louwagie/>.

⁶⁴ Recorded Assignment of US Patent No. 11,634,781 dated April 25, 2017.

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87. The common specification of the Asserted Patents is directed to methods of separately detecting both blood proteins and epigenetically-modified DNA in a fecal sample for diagnosis of CRC. Indeed, the common specification states that “[t]he invention is based upon a combination of tests for detecting proteins and epigenetic modification markers respectively in the same fecal sample.”⁶⁵

88. The common specification also acknowledges that fecal blood protein and fecal DNA tests were known in the art,⁶⁶ though it asserts that “[t]o date, immunochemical tests and DNA tests for CRC detection have been evaluated and compared on a separate basis only.”⁶⁷ I disagree. As discussed in section V(B), by the Priority Date, the advantages associated with combining fecal DNA tests and FOBT in a CRC assay were well known in the art.

89. The common specification also relies upon known buffers to separately stabilize DNA or blood proteins in portions of fecal samples. With respect to “a buffer which prevents denaturation or degradation of blood proteins,” the application states that “[s]uitable buffers for protein preservation are known in the art and commercially available.”⁶⁸ With respect to “buffers for maintaining DNA integrity,” the application merely notes that “a suitable stabilizing buffer as known to those in the art, may be added.”⁶⁹

⁶⁵ '781 patent, 4:3-16, 6:40-67.

⁶⁶ *Id.*, 1:56-64; 3:5-22; 3:41-45.

⁶⁷ *Id.*, 1:56-64, 3:5-22, 3:41-45.

⁶⁸ *Id.*, 18:1-21.

⁶⁹ *Id.*, 11:48-54, 18: 26-28.

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B. Summary of the Claimed Subject Matter

90. I understand that in this preliminary injunction proceeding Exact has asserted claim 1 of the '781 patent and claim 3 of the '746 patent.

91. Claim 1 of the '781 patent is an independent claim that recites a method of processing a freshly collected fecal sample without freezing in which a subject first collects a stool sample at home by defecating directly into a sealable collection vessel. A portion of the stool is then removed to a separate sealable container where it is combined with a buffer that prevents denaturation or degradation of blood proteins. The sealable container is then sealed shut.⁷⁰ The remaining portion is combined with a stabilizing buffer and the second sealable container is sealed.⁷¹

92. Claim 3 of the '746 patent is a dependent claim that depends from independent claim 1. Like claim 1 of the '781 patent, claim 1 of the '746 patent is also directed to a method of processing a freshly collected fecal sample without freezing. The sample is collected by a subject at home, and then, in a sealable vessel, a first portion of the stool is combined with a stabilizing buffer. The sealable vessel is then sealed. In a sealable container, a second portion of the fecal sample is combined a solution that prevents denaturation or degradation of blood proteins found in a fecal sample. The sealable container is then sealed.

93. In claim 3 of the '746 patent, a sealed container containing the first portion of the fecal sample and a sealed vessel containing the second portion of the fecal sample are first obtained by the method of claim 1 described above. Nucleic acid is extracted

⁷⁰ *Id.*, Claim 1, Claim 14.

⁷¹ *Id.*, Claim 1.

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from the first portion and then tested for an amount of a human nucleic acid. Then, the second portion of the fecal sample is tested for an amount of a blood protein.

94. In declarations I previously submitted in IPR proceedings No. IPR2024-00459 and IPR2024-01330, I analyzed the claims of the '781 patent and the '746 patent, respectively, and concluded that they were obvious (and, in some cases, anticipated).⁷² I understand that a panel of administrative patent judges at the United States Patent Trials and Appeals Board (PTAB) instituted IPR2024-00459, finding that there was "a reasonable likelihood... that the challenged claims [of the '781 patent] would have been unpatentable as obvious."⁷³ While the PTAB has the institution decision is still pending in IPR2024-01330, the claims of the '746 patent are nearly identical to (and broader than) those of the '781 patent. For example, the main difference between claim 3 of the '746 patent and claim 3 of the '781 patent is that the claims of the '746 patent do not require "defecation directly into a sealable collection vessel," but claims of the '781 patent do. Accordingly, the claims of the '746 patent is broader than the corresponding claims of the '781 patent, and the PTAB's reasons for finding it likely that the claim of the '781 patent are obvious apply equally to the claims of the '746 patent.

VIII. SUMMARY OF SELECTED PRIOR ART REFERENCES

95. In my opinion, Lenhard, Itzkowitz, and Vilkin, which are described in detail below, render both claim 1 of the '781 patent and claim 3 of the '746 patent obvious. It is also my opinion that another combination of references, Shuber and Vilkin also render the Asserted Claims obvious. Below, I briefly summarize the teachings of

⁷² Whitney Declarations Submitted in IPR2024-00459 and IPR2024-01330

⁷³ IPR-2024-00459 Institution Decision.

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Lenhard, Itzkowitz, Vilkin, and Shuber as they would have been understood by a POSA as of the Priority Date.

A. Lenhard

96. Lenhard is a journal article published in the February, 2005 issue of the journal *Clinical Gastroenterology and Hepatology*.⁷⁴ Lenard was therefore publicly available more than a year before the Priority Date.

97. Lenhard describes a diagnostic CRC in which a patient's stool sample was separated into two portions and then a gFOBT (to detect blood proteins) was performed on one portion and a DNA methylation assay was performed on the other.⁷⁵

98. The FOBT used in Lenhard was a commercially available guaiac fecal occult blood test (gFOBT).⁷⁶ In this test, a portion of the fecal sample is applied to an FOBT test card coated with guaiac immediately after receipt at the laboratory.⁷⁷ In such tests, the presence of heme (and therefore blood) in the fecal sample is indicated by a color change on the test card.

99. For the DNA methylation assay, DNA was extracted from the remaining portion of the sample and tested for DNA methylation. In particular, Lenhard tested the methylation status of the promoter of the hypermethylated in cancer 1 (HIC1) gene,

⁷⁴ Lenhard, p. 143.

⁷⁵ *Id.*, pp. 143, 147.

⁷⁶ *Id.*, pp. 143, 145.

⁷⁷ *Id.*

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which was a known biomarker for CRC.⁷⁸ A process called methylation-specific PCR (in Lenhard's manuscript, "MSP") was performed to detect the DNA methylation.⁷⁹

100. Lenhard's results demonstrated that the combined application of both the DNA methylation assay and the FOBT detected CRC with greater sensitivity than either assay alone.⁸⁰ Indeed, Lenhard found that "[t]he **combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.**"⁸¹ Specifically, Lenhard determined that while HIC1 methylation alone detected 42% of CRCs and FOBT alone detected 35% of CRCs, the combination of the two tests was able to detect 65% of CRCs.⁸² Lenhard also noted that "the combined test detected all localized cancers."⁸³

B. Vilkin

101. Vilkin is a journal article published in the November, 2005 issue of the journal *The American Journal of Gastroenterology*.⁸⁴ Vilkin was therefore publicly available more than a year before the Priority Date. Vilkin describes the use and assesses the performance of an automated, quantitative immunochemical FOBT (iFOBT) assay.

102. In the iFOBT of Vilkin, an 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 (Hb) stabilizing buffer:

⁷⁸ *Id.*

⁷⁹ *Id.*, pp. 142-144.

⁸⁰ *Id.*, pp. 143, 147.

⁸¹ *Id.*, pp. 143, 147 (emphasis added).

⁸² *Id.*, Table 4 and p. 147.

⁸³ *Id.*, p. 147.

⁸⁴ Vilkin.

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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 scraper, 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.**⁸⁵

103. The at-home patient then ships the stabilized sample to the diagnostic laboratory without freezing.⁸⁶ When stored in the stabilizing buffer at 4°C, all fecal samples “maintained their elevated fecal Hb levels for 21 or more days.”⁸⁷

104. Once the removed portion of the sample was received in the testing laboratory, it was analyzed on an automated desktop instrument (the OC-Sensor instrument, depicted in the right panel of figure 1, reproduced below), which performs the automated immunochemical detection of human Hb.⁸⁸

⁸⁵ *Id.* p. 2520 (emphasis added).

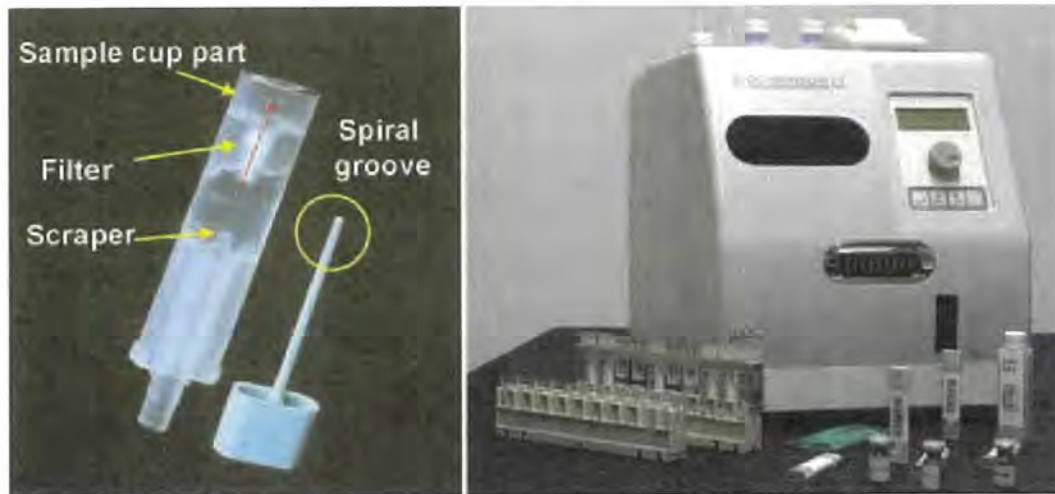
⁸⁶ *Id.*

⁸⁷ *Id.*, p. 2521.

⁸⁸ *Id.*, pp. 2520-2521.

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Vilkin Figure 1. Left: Fecal test sampling device/ Right: Desktop instrument.



105. Vilkin concludes that they “found this desktop, automated-developed and quantified Hb version of the immunochemical occult blood test to provide a highly sensitive teste for detecting significant colorectal neoplasia with an acceptable specificity and consequent high negative predictive value.”⁸⁹ Another important conclusion of the article is that “[t]he introduction of the instrument-developed, quantitative, fecal occult blood testing allows the physician to choose the optimal fecal Hb threshold level that triggers a follow-up colonoscopy.”⁹⁰ Applying this methodology to a population of high-risk and symptomatic patients, Vilkin found that “all cases of cancer and most advanced adenomas would be detected and a negative test would provide a very high degree of certainty that there was no clinically significant colorectal neoplasia.”⁹¹

⁸⁹ *Id.*, p. 2524.

⁹⁰ *Id.*

⁹¹ *Id.*

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106. Vilkin also sets forth numerous advantages of its iFOBT assay over guaiac-based FOBT (gFOBT).⁹² 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.”⁹³ As has also been noted above, gFOBT are sensitive to dietary peroxidases from meat and vegetables, meaning that gFOBT come with dietary restrictions with important compliance ramifications.⁹⁴ 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.”⁹⁵

C. Itzkowitz

107. Itzkowitz is a journal article published in the January, 2007 issue of the journal *Clinical Gastroenterology and Hepatology*.⁹⁶ Itzkowitz names several Exact employees as co-authors, including the senior author Mr. Anthony Shuber.⁹⁷ Itzkowitz was therefore publicly available more than a year before the Priority Date.

108. Itzkowitz describes a DNA-based CRC diagnostic assay developed by Exact.⁹⁸ The assay disclosed in Itzkowitz is an improved, “version 2” of their earlier

⁹² *Id.*, Abstract.

⁹³ *Id.*, p. 2519.

⁹⁴ *Id.*, p. 2524, Abstract.

⁹⁵ *Id.*, p. 2519.

⁹⁶ Itzkowitz, p. 117.

⁹⁷ *Id.*, p. 111.

⁹⁸ *Id.*, pp. 111-112.

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“version 1” DNA-based CRC assay.⁹⁹ This second version differs from the prior version, in part, because it “uses improved DNA stabilization/isolation techniques and a new promoter methylation marker.”¹⁰⁰

109. In Itzkowitz, “each subject provided a single stool sample” using “a special stool collection kit that is mounted on the toilet bowl.”¹⁰¹ 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.”¹⁰² Adding the DNA stabilizing buffer to the stool “was shown to prevent DNA degradation for several days” which improved the sensitivity of both the assay.¹⁰³ The patients shipped the stabilized stool samples to the clinical laboratory at room temperature, where they were assayed for the presence of tumor-derived DNA.¹⁰⁴

110. Itzkowitz articulates advantages of fecal tests where the sample is collected at home, noting the importance of “a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction has the potential to significantly increase participation.”¹⁰⁵ Although home tests require mailing, there are also attendant advantages because “geographic access becomes less of a barrier, there is no loss of time from work, and no formal health care

⁹⁹ *Id.*, Abstract.

¹⁰⁰ *Id.*, Abstract.

¹⁰¹ *Id.*, p. 112.

¹⁰² *Id.*, p. 112.

¹⁰³ *Id.*, pp. 111, 116.

¹⁰⁴ *Id.*, p. 112.

¹⁰⁵ *Id.*, p. 115.

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visit.”¹⁰⁶ 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.”¹⁰⁷ They also concluded that the disclosed method of stabilizing DNA during specimen transport contributed to increasing assay sensitivity from 52% to 72.5%.¹⁰⁸

D. Shuber

111. Shuber is an international patent application on which I am a named inventor. Shuber was filed by Exact in 2005 and published later that year. Shuber was therefore publicly available more than a year before the Priority Date.

112. Shuber is premised on the well-known principle that cancer can shed distinctive cellular debris and DNA into bodily samples such as stool.¹⁰⁹ However, DNA in stool and other samples degrades, limiting efficacy of DNA assays.¹¹⁰ Shuber addresses this problem by describing a buffer that stabilizes DNA in a fecal sample.¹¹¹ Shuber reports that the use of such buffers provides marked advantages, such that samples “do not require refrigeration or freezing.”¹¹² Moreover, “a stabilization solution may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center.”¹¹³

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*, pp. 116-117.

¹⁰⁸ *Id.*, p.116.

¹⁰⁹ Shuber, 1:16-29.

¹¹⁰ *Id.*, 1:30-32.

¹¹¹ *Id.*, 6:2-20, 7:10-21.

¹¹² *Id.*, 7:10-21.

¹¹³ *Id.*, 10:10-15.

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113. The DNA stabilizing buffer disclosed in Shuber is useful in many different DNA biomarker assays. As Shuber explains, a sample stabilized by buffer “can be characterized in a nucleic acid integrity analysis, multiple mutation assay, or methylation study.”¹¹⁴ Shuber states that “aspects of the invention may be particularly useful for detecting indicia of adenoma and/or early stage cancer” where “many cancers (*e.g.*, carcinomas such as colorectal carcinomas) are thought to develop from adenomas.”¹¹⁵ Shuber also considers combining multiple assays to improve the test’s sensitivity for detection of CRC, noting that “the invention may be useful 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.)”¹¹⁶

114. Shuber also discusses stool collection. 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 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.”¹¹⁷ A POSA would understand that when a sample is a stool sample, being “directly deposited into a container” refers to direct defecation into that container, which is a standard method of collecting a fecal

¹¹⁴ *Id.*, 8:27-31, 12:8-14, 13:21-14:16.

¹¹⁵ *Id.*, 28:18-27, 13:5-6.

¹¹⁶ *Id.*, 28:18-27.

¹¹⁷ *Id.*, 29:8-13.

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sample. The “container with sample and stabilization solution may be sealed for storage/shipping.”¹¹⁸

IX. THE ASSERTED CLAIMS ARE OBVIOUS

A. Lenhard, Itzkowitz and Vilkin render the Asserted Claims obvious

115. It is my opinion that Lenhard, in view of Itzkowitz and Vilkin, renders obvious the method of processing a freshly collected fecal sample recited in claim 1 of the '781 patent and claim 3 of the '746 patent. Specifically, it is my opinion that it would have been obvious for a POSA to improve the fecal screening method of Lenhard by replacing its gFOBT with the iFOBT of Vilkin and by incorporating the fecal collection and DNA stabilization process of Itzkowitz to arrive at the methods of the Asserted Claims.

116. As discussed above in section VIII(A), Lenhard discloses a method for performing a noninvasive CRC detection assay in which both DNA methylation and blood proteins are detected in a fecal sample. In the assay disclosed in Lenhard, a portion of a patient's fecal sample is removed and tested for blood proteins using gFOBT, and then the remainder of the sample is tested for tumor-derived DNA using DNA methylation as a biomarker.¹¹⁹

117. A POSA would understand from the disclosure of Lenhard that combining a DNA methylation test with FOBT resulted in a diagnostic process that is more sensitive than when either test was performed alone. For example, Lenhard states that “[t]he combination of HIC1 methylation analysis with FOBT allowed for the detection of two

¹¹⁸ *Id.*, 29:18-19.

¹¹⁹ Lenhard, pp. 142, 144-145.

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thirds of CRCs.”¹²⁰ In Table 4 Lenhard shows that whereas the DNA methylation test alone detected 42% of all cancers and the FOBT alone detected 35% of all cancers, the combination of the two tests detected 65% of all cancers.¹²¹ Detecting both tumor-derived DNA and fecal blood resulted in “increased detection rates for CRCs” and, in fact “detected all localized cancers.”¹²²

118. Lenhard’s finding that diagnostic sensitivity can be improved by combining a fecal DNA test with FOBT is consistent with what was known in the art as of the Priority Date. As I explain above, by the Priority Date, it was widely understood that assay sensitivity is improved through the detection of multiple biomarkers. This is particularly true in cases like fecal DNA and FOBT, where the false-negatives missed by the two tests would not be expected to completely overlap. Specifically, false negatives missed in by the fecal DNA test because their carcinoma did not contain a methylated HIC1 promoter might still test positive for fecal blood, and vice-versa. In other words, combining a fecal DNA test with a FOBT is simply the obvious application of the well-established strategy of combining different biomarkers to improve diagnostic assay sensitivity.

119. Lenhard discloses a method of processing a fecal sample that includes collecting a fecal sample from a subject, removing a portion of sample for blood protein testing and then testing the remaining portion of the sample for cancer-specific DNA. The samples in Lenhard were collected in a hospital setting and received by the diagnostic lab

¹²⁰ *Id.*, p. 143.

¹²¹ *Id.*, p. 146.

¹²² *Id.*, p. 147.

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within ten hours,¹²³ and Lenhard does not disclose use a buffer to prevent degradation of blood proteins in the removed portion or a stabilizing buffer that retains DNA integrity was used in the remaining portion. However, use of such buffers was routine in the art by the Priority Date, such as described in Itzkowitz.

1. A POSA would be motivated to use the iFOBT of Vilkin in place of the gFOBT of Lenhard

120. A POSA would have found it obvious to replace the gFOBT used in Lenhard with the automated iFOBT disclosed in Vilkin, in which a removed portion of a stool sample is stabilized in a buffer that prevents degradation of a blood protein (hemoglobin, or Hb) so it can be sent to a diagnostic laboratory for automated analysis.¹²⁴

121. A POSA would be motivated to modify Lenhard's assay to include Vilkin's iFOBT because the advantages of automated iFOBT, like the one disclosed in Vilkin, were well known in the art by the Priority Date. In fact, Vilkin itself expressly teaches numerous advantages of using iFOBT instead of 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.¹²⁵ Thus, a POSA would recognize Vilkin's iFOBT as a superior alternative to the gFOBT used in Lenhard.

122. Even beyond the express teachings of Vilkin, the advantages of iFOBT over gFOBT were well recognized in the art by the Priority Date. For example, Young, a 2007 review article, explains that iFOBT technology "simplifies the testing process,

¹²³ *Id.*, p. 143.

¹²⁴ Vilkin, pp. 2519-2520.

¹²⁵ *Id.*, pp. 2519, 2524.

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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.”¹²⁶ It also explains that iFOBT “provide for an improved sensitivity/specificity ratio; in other words, they can achieve better sensitivity without an unacceptable deterioration in specificity.”¹²⁷ Young concludes that “[o]bviously, [iFOBT assays] 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.”¹²⁸

123. Guittet, another 2007 paper, directly compares iFOBT with gFOBT, and notes that “[e]vidence in favor of the substitution of G-FOBT by I-FOBT is increasing, the gain being more important for high risk adenomas than for cancers.”¹²⁹ Guittet also notes that “[t]he automated reading technology allows choice of the positivity rate associated with an ideal balance between sensitivity and specificity.”¹³⁰ Guittet concludes:

Evidence in favour of the use of the I-FOBT over the G-FOBT is increasing. 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

¹²⁶ Young 2007, p. 29.

¹²⁷ *Id.*

¹²⁸ *Id.*, p. 30.

¹²⁹ Lydia Guittet et al., “Comparison of A Guaiac Based And An Immunochemical Faecal Occult Blood Test In Screening For Colorectal Cancer In A General Average Risk Population,” *Gut*, 56:210-214 (2007) (“Guittet”), Abstract.

¹³⁰ *Id.*

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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.**¹³¹

124. Thus, based on the express teachings of Vilkin and the general knowledge in the art, a POSA would have been motivated to modify the diagnostic assay disclosed in Lenhard by replacing the gFOBT with the superior automated iFOBT of Vilkin, including its use of a stabilization buffer to permit at-home collection and shipment of the sample to a diagnostic laboratory.

2. A POSA would have been motivated to use the sample collection methodology of Itzkowitz in Lenhard's process

125. A POSA 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 prior to its shipment to a diagnostic laboratory, as was done in Itzkowitz.¹³²

126. Lenhard does not explain how its samples were collected beyond stating that "[s]tool samples were collected before cathartic preparation for scheduled surgery or colonoscopy."¹³³ 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.¹³⁴

127. By the priority date, fecal collection by direct defecation into a sealable container was a standard and well-accepted method of fecal sample collection for decades. Advantageously, such a method allows for the collection and shipment of a

¹³¹ *Id.*, p. 214.

¹³² Itzkowitz, p. 112.

¹³³ Lenhard, p. 143.

¹³⁴ Itzkowitz, p. 112.

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large portion of the stool sample for testing at a diagnostic laboratory. Using the original container to hold at least a portion of the fecal sample has the added advantage of reducing the amount of fecal manipulation by the patient.

128. Indeed, by the Priority Date, direct defecation into a sealable container had been a standard method for collecting stool samples for decades. 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.”¹³⁵ 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.”¹³⁶

129. A POSA would therefore be motivated to have a patient collect the fecal sample analyzed in Lenhard by directly defecating into a sealable container at least because it was a routine, convenient and well-established method for at-home fecal sample collection.

3. A POSA would have been motivated to use the DNA stabilizing buffer of Itzkowitz in Lenhard’s process

130. Once the sample was collected, a POSA would have been motivated by Itzkowitz’s teachings to add a stabilization buffer to the sample so it can be shipped to a diagnostic laboratory without freezing.¹³⁷

¹³⁵ Melvin, p. 2.

¹³⁶ U.S. Patent No. 5,741,650 (“Lapidis ’650”), 7:45-49, Figure 2.

¹³⁷ Itzkowitz, p. 112.

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131. As I explain above in section V(C)2, by the Priority Date, use of stabilizing buffer to reduce DNA degradation during shipment of stool samples was routine. For example, Itzkowitz states that addition of the DNA stabilizing buffer to the stool “was shown to prevent DNA degradation for several days” which improved assay sensitivity.¹³⁸ 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.”¹³⁹

132. Consistent with Itzkowitz’s teachings, by the Priority Date the advantages of using a stabilization buffer that preserves DNA integrity of stool samples were well recognized in the art. In particular, Olson, a 2005 paper cited by Itzkowitz on which I am a co-author, 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.”¹⁴⁰ 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.”¹⁴¹ Olson concludes that “addition of stabilization buffer to samples upon collection should provide a robust means of storing (and transporting) samples at room temperature.”¹⁴²

¹³⁸ *Id.*, pp. 111, 116.

¹³⁹ *Id.*, pp. 116-117.

¹⁴⁰ Olson, p. 186.

¹⁴¹ *Id.*, p. 190.

¹⁴² *Id.*

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133. A POSA would therefore 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 shipped to the diagnostic laboratory at room temperature.

134. In summary, as of the Priority Date, a POSA would have been motivated to modify the non-invasive CRC diagnostic method of Lenhard by replacing the gFOBT with the automated iFOBT of Vilkin and using the stool collection and stabilization methods of Itzkowitz. 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). The patient would then send both sealed containers to a diagnostic laboratory for analysis of DNA methylation and FOBT, which Lenhard teaches provides improved assay sensitivity compared to either test alone.

135. A POSA would recognize that separation of the sample by the patient at home is necessary to ensure that the relevant biomarker in each portion (hemoglobin in one, DNA in the other) was stabilized with an appropriate buffer prior to shipment, as taught by Vilkin and Itzkowitz.¹⁴³ A POSA would also recognize that it is more convenient for the patient to use the Vilkin sampling device before the fecal sample is immersed in the DNA stabilizing buffer of Itzkowitz.

¹⁴³ Vilkin, p. 2520; Itzkowitz, p. 112.

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136. It is also my opinion that one of skill in the art would have a reasonable expectation that the resulting assay would be successful at least because it amounts to no more than the routine performance, in combination, of two well-established and prior art tests that have already been shown to work on fecal samples.

137. As set forth below, the above-described assay rendered obvious by Lenhard in view of Itzkowitz and Vilkin meets all limitations claim 1 of the '781 patent and claim 3 of the '746 patent.

4. Claim 1 of the '781 patent

138. Claim 1 of the '781 patent is directed to the routine separation of a fecal sample into two portions in order to permit two standard diagnostic tests—one detecting blood proteins and the other detecting nucleic acids—to be performed on the sample. Each portion is preserved in a well-established prior art stabilizing buffer. Nothing in this claim is inventive. The method of claim 1 amounts to no more than the routine use of standard methods to prepare a fecal sample for performance of well-established complementary diagnostic assays, and therefore was obvious.

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

139. I understand that in patent law the preamble of a claim may or may not be limiting. To the extent the preamble of claim 1 is limiting, it is rendered obvious by Lenhard in view of Vilkin and Itzkowitz.

140. Specifically, when the diagnostic assay of Lenhard is improved by the obvious incorporation of the sample collection stabilization method of Itzkowitz and the iFOBT of Vilkin, as described above, the resulting assay produces two sample portions,

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each in their own stabilization buffer, that are shipped to a diagnostic laboratory without freezing.¹⁴⁴

141. Accordingly, both Vilkin and Itzkowitz teach processing fecal samples without freezing, which would also be a feature of the fecal sample processing method rendered obvious by Lenhard in view of Vilkin and Itzkowitz.

- 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;”**

142. Collecting a fecal sample from a subject is disclosed by each of Lenhard, Vilkin and Itzkowitz, and also rendered obvious by the three references. Indeed, collecting a fecal sample from a human subject is a prerequisite for performing the diagnostic assays disclosed in all three references. The method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz would therefore also include such a step.¹⁴⁵

143. As explained above, Itzkowitz describes sample collection by a patient 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” to which DNA-stabilizing buffer was added following defecation.¹⁴⁶ As the sample was subsequently “shipped at room temperature,” to the diagnostic laboratory, a POSA would

¹⁴⁴ Vilkin, p. 2520; Itzkowitz, p. 112.

¹⁴⁵ Lenhard, p. 143; Vilkin, p. 2520; Itzkowitz, p. 112.

¹⁴⁶ Itzkowitz, p. 112.

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understand that the sample was collected at home and that the container into which the stool sample and DNA-stabilizing buffer was added must have been sealable.¹⁴⁷

144. By the Priority Date, it was recognized that sample collection is preferably completed by patients at home. Indeed, Itzkowitz notes importance of “a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction has the potential to significantly increase participation.”¹⁴⁸ Although home tests require mailing, there are also attendant advantages because “geographic access becomes less of a barrier, there is no loss of time from work, and no formal health care visit.”¹⁴⁹

145. Indeed, by the Priority Date, direct defecation into a sealable container at home had been a standard method for collecting stool samples for decades. A laboratory manual from 1985 recommends collecting fecal samples in a sealable container and that “[f]eces should be passed directly into the container.”¹⁵⁰ Similarly, 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.”¹⁵¹ By the Priority Date, Exact offered a commercial fecal DNA test that used direct defecation into a sealable container at home as the method by which the stool sample was collected.

¹⁴⁷ Itzkowitz, p. 112.

¹⁴⁸ *Id.*, p. 115.

¹⁴⁹ *Id.*

¹⁵⁰ Melvin, p. 2.

¹⁵¹ Lapidis '650, 7:45-49, Figure 2.

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146. 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 stool collection method that would be used in the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz.¹⁵²

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;”**

147. As I explain above in section VIII(A), Lenhard describes an assay in which a portion of a patient’s stool sample removed and tested for the presence of blood proteins using gFOBT and then the remainder of the sample is tested for the presence of tumor-derived DNA.¹⁵³ Lenhard therefore discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample, but does not expressly state that the removed portion was removed to a separate sealable container.

148. However, as I also discuss above, it would have been obvious to replace the gFOBT described in Lenhard with the automated iFOBT of Vilkin at least because of the numerous advantages to iFOBT over gFOBT taught in Vilkin and known in the art.¹⁵⁴

149. In the iFOBT described in Vilkin, a portion of the fecal sample is removed using a “fecal test device” that is shaped like a small test tube that has a probe with a serrated tip attached to the inner portion of the device’s cap (illustrated below).¹⁵⁵ The probe is “poked into the stool and then pushed back into the tube, past a scraper and

¹⁵² Itzkowitz, p. 112.

¹⁵³ Lenhard, p. 143-145.

¹⁵⁴ Vilkin, p. 2519.

¹⁵⁵ *Id.*, p. 2520.

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through a membrane into the sample cup.”¹⁵⁶ 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.¹⁵⁷



150. Accordingly, when the gFOBT of Lenhard is replaced with the automated iFOBT of Vilkin the resulting assay includes 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.

- 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”**

151. As I explain above, it would have been obvious to replace the gFOBT described in Lenhard with the automated iFOBT of Vilkin at least because of the

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*, p. 2520.

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recognized advantages of iFOBT.¹⁵⁸ 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.”¹⁵⁹ This results in sealing of the fecal test sampling device with the tip “put in a closed amount of Hb stabilizing buffer.”¹⁶⁰

152. Accordingly, when the gFOBT of Lenhard is replaced with the automated 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.

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

153. The above-described method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz also includes combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the collection vessel.

154. As I explain above, a POSA would have been motivated to use the DNA stabilizing buffer described in Itzkowitz to preserve the DNA in 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 is shipped a diagnostic laboratory for analysis.¹⁶¹ Itzkowitz states that addition of the DNA stabilizing buffer to the stool “was shown to

¹⁵⁸ *Id.*, p. 2519.

¹⁵⁹ *Id.*, p. 2520.

¹⁶⁰ *Id.*

¹⁶¹ Itzkowitz, p. 112.

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prevent DNA degradation for several days” which improved the sensitivity of both the DNA marker panel used and the DNA integrity assay (DIA) for detecting CRC.¹⁶² The DNA stabilizing buffer used in Itzkowitz was known to maintain DNA stability in the sample at room temperature for several days, thereby facilitate at-home sample collection by greatly simplifying transport of the sample.¹⁶³ 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.”¹⁶⁴ As Itzkowitz teaches that inclusion of a DNA stabilizing buffer resulted in an improved “second-generation fecal DNA test,” it would have been obvious to use this known approach to similarly improve the DNA test used in Lenhard in the same way.¹⁶⁵

155. 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 sample is contained and emanation of odors is prevented.¹⁶⁶

156. Accordingly, when the DNA stabilizing buffer used in Itzkowitz is incorporated into the assay of Lenhard it results in 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.

157. In summary, when the automated iFOBT and sample stabilization of Vilkin and the fecal collection and DNA stabilization process of Itzkowitz are

¹⁶² *Id.*, pp. 111, 116.

¹⁶³ Olson, p. 190.

¹⁶⁴ Itzkowitz, pp. 116-117.

¹⁶⁵ *Id.*, pp. 111-112.

¹⁶⁶ Lapidis '650, 7:45-49.

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incorporated into the diagnostic method of Lenhard it results in a method in which each of the steps of claim 1 is performed. The method of claim 1 would therefore be obvious to a person of skill in the art.

5. Claim 3 of the '746 Patent

158. Claim 3 of the '746 patent is a dependent claim directed to the performance of standard and routine assays on the portions of a fecal sample obtained by the method of the '746 patent's claim 1. Accordingly, in the below analysis, I first address why claim 1 of the '746 patent is rendered obvious by Lenhard, Vilkin, and Itzkowitz, and then address why these references also render obvious the performance the well-known assays set forth in claim 3 on the fecal portions produced by the process of claim 1.

a. Claim 1 of the '746 patent

159. Claim 1 of the '746 patent closely mirrors, and is, in fact, broader than, claim 1 of the '781 patent. I understand that during prosecution of the application that gave rise to the '746 patent the examiner held the claims of the '746 patent to be patentably indistinct from those of the '781 patent. The method set forth in claim 1 of the '746 patent is therefore rendered obvious by Lenhard, Vilkin and Itzkowitz for effectively the same reasons set forth above with respect to claim 1 of the '781 patent. Like claim 1 of the '781 patent, the method claim 1 of the '746 patent is also directed to the routine separation of a fecal sample into two portions, each preserved in a well-established prior art stabilizing buffer. Nothing in this claim is inventive. The method of claim 1 amounts to no more than the routine use of standard methods to prepare a fecal sample for performance of well-established complementary diagnostic assays, and therefore was obvious.

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- i. **“A method of processing a freshly-collected fecal sample without freezing, the method comprising:”**

160. To the extent the preamble of claim 1 is limiting, it is rendered obvious by Lenhard in view of Vilkin and Itzkowitz. When the diagnostic assay of Lenhard is improved by the obvious incorporation of the sample collection stabilization method of Itzkowitz and the iFOBT of Vilkin, as described above, the resulting assay produces two samples: a “first portion” in a DNA stabilizing buffer¹⁶⁷ and a “second portion” in a blood protein stabilizing buffer, both of which are processed without freezing.¹⁶⁸ Accordingly, as both Vilkin and Itzkowitz teach processing fecal samples without freezing, this would also be a feature of the fecal sample processing method rendered obvious by Lenhard in view of Vilkin and Itzkowitz.

- ii. **“a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;”**

161. Collecting a fecal sample from a subject is disclosed by each of Lenhard, Vilkin and Itzkowitz, and also rendered obvious by the three references. Indeed, collecting a fecal sample from a human subject is a prerequisite for performing the diagnostic assays disclosed in all three references. The method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz would therefore also include such a step.¹⁶⁹

¹⁶⁷ Itzkowitz, p. 112.

¹⁶⁸ Vilkin, p. 2520.

¹⁶⁹ Lenhard, p. 143; Vilkin, p. 2520; Itzkowitz, p. 112.

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162. By the Priority Date, it was recognized that sample collection is preferably completed by patients at home. Indeed, Itzkowitz notes importance of “a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction has the potential to significantly increase participation.”¹⁷⁰ Although home tests require mailing, there are also attendant advantages because “geographic access becomes less of a barrier, there is no loss of time from work, and no formal health care visit.”¹⁷¹

163. Accordingly, by the Priority Date, a POSA would have recognized the at-home collection methods disclosed in Vilkin and Itzkowitz as a routine and convenient stool collection method that would be used in the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz.¹⁷²

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

164. Lenhard describes an assay in which a first portion of a patient’s stool sample is tested for the presence of tumor-derived DNA and a second portion is tested for the presence of blood proteins using gFOBT.¹⁷³ Lenhard therefore discloses removing a portion of the fecal sample to produce a first portion and a second portion of the fecal sample, but does not expressly state that one of the portions of the fecal sample is combined with a stabilizing buffer in a sealable container.

¹⁷⁰ *Id.*, p. 115.

¹⁷¹ *Id.*

¹⁷² Itzkowitz, p. 112.

¹⁷³ Lenhard, p. 143-145.

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165. However as I explain above, a POSA would have been motivated to use the DNA stabilizing buffer described in Itzkowitz to preserve the DNA in the first portion of the fecal sample in a sealable vessel to preserve the integrity of the DNA in that portion of the sample when it is shipped a diagnostic laboratory for analysis.¹⁷⁴ 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 the assay.¹⁷⁵ 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.”¹⁷⁶ As Itzkowitz teaches that inclusion of a DNA stabilizing buffer resulted in an improved “second-generation fecal DNA test,” it would have been obvious to use this known approach to similarly improve the DNA test used in Lenhard in the same way.¹⁷⁷

166. A POSA would also understand that the collection vessel containing the first portion of the fecal sample and the DNA stabilizing buffer would be sealed prior to shipping so that the sample is contained and emanation of odors is prevented.¹⁷⁸

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

¹⁷⁴ Itzkowitz, p. 112.

¹⁷⁵ *Id.*, pp. 111, 116.

¹⁷⁶ Itzkowitz, pp. 116-117.

¹⁷⁷ *Id.*, pp. 111-112.

¹⁷⁸ Lapidis '650, 7:45-49.

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

168. Lenhard does not expressly state that the second portion of the sample, on which the gFOBT was performed, was combined in a sealable container with a solution that prevents denaturation or degradation of blood proteins. However, as I explain above, it would have been obvious to replace the gFOBT described in Lenhard with the automated iFOBT of Vilkin, which requires a second portion of the fecal sample being combined with a solution that prevents denaturation or degradation of blood proteins in a sealable container.¹⁷⁹ In particular, when the iFOBT described in Vilkin is performed, 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 fecal test sampling device’s cap (illustrated below).¹⁸⁰ 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.”¹⁸¹ This results in sealing of the fecal test sampling device with the tip “put in a closed amount of Hb stabilizing buffer.”¹⁸²

¹⁷⁹ Vilkin, p. 2519.

¹⁸⁰ *Id.*, p.2520.

¹⁸¹ *Id.*, p. 2520.

¹⁸² *Id.*

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169. Thus, when the gFOBT of Lenhard is replaced with the iFOBT of Vilkin, the resulting assay includes combining a second portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

170. Thus, when the automated iFOBT and sample stabilization 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 1 is performed. The method of claim 1 would therefore be obvious to a person of skill in the art.

b. Claim 3 of the '746 patent

171. Claim 3 is directed to the performance of the same prior art assays that are performed in Lenhard, Vilkin and Itzkowitz on the portions of a fecal sample collected in claim 1. The method therefore amounts to no more than the routine use of standard diagnostic assays fecal samples that had been prepared using standard methodology for exactly that purpose, and therefore it is obvious.

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i. “A method of processing a fecal sample, the method comprising:”

172. To the extent the preamble of claim 3 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.¹⁸³

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

173. As discussed above, the method of processing a fecal sample rendered obvious by Lenhard in view of Vilkin and Itzkowitz includes the receipt of the sealed containers containing the first and second portions of the fecal sample by technicians at medical diagnostics laboratory, where the portions of the sample are then analyzed.

174. The DNA methylation assays disclosed in Lenhard and Itzkowitz and the automated iFOBT disclosed in Vilkin are each complicated molecular biology assays requiring specialized equipment and expertise. At-home performance of such assays is therefore not practical (and probably not even possible). At the same time, most patients prefer the convenience and privacy afforded by at-home collection of fecal samples. As such, a person of skill in the art would recognize that the portions of fecal samples in their respective buffers that were collected at home according to the methods of Itzkowitz and Vilkin would be delivered to a medical diagnostics laboratory for analysis.

¹⁸³ Lenhard; Vilkin; Itzkowitz.

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175. 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.

iii. “b) extracting nucleic acid from the first portion of the fecal sample;”

176. Performance of fecal DNA analysis typically requires extraction of the DNA from other components in the fecal sample prior to DNA analysis. Consistently, performance of the DNA methylation assay described in Lenhard includes isolation of DNA from the first portion of the stool sample (“DNA was isolated using the QiaAmp DNA Stool Mini-Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions.”).¹⁸⁴ Similarly, Itzkowitz extolls the advantages of an “enhanced DNA extraction” process on fecal DNA tests.¹⁸⁵

177. Extracting nucleic acid from the first portion of the fecal sample is therefore 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.

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

178. Performance of the DNA methylation assay described in Lenhard includes testing the first portion of the fecal sample for an amount of methylated DNA (“[w]e show that HIC1 promoter methylation can be detected frequently and with high specificity in stool samples from patients with CRCs.”).¹⁸⁶ Likewise, the second-

¹⁸⁴ Lenhard, p. 143.

¹⁸⁵ Itzkowitz, p. 112.

¹⁸⁶ Lenhard, p. 144.

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generation stool DNA test described in Itzkowitz tests the fecal sample for the presence of long DNA using a DNA integrity assay (DIA) and an amount of methylated vimentin DNA using a methylation assay.¹⁸⁷ Accordingly, testing the nucleic acid 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.

v. **“d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample”**

179. As explained above, it would have been obvious to replace the gFOBT described in Lenhard with the automated iFOBT of Vilkin at least because of the numerous known advantages of using the iFOBT 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.¹⁸⁸ Such advantages were well recognized in the art by the Priority Date.

180. The Vilkin iFOBT is a quantitative test of the level of the human blood protein, hemoglobin (Hb), in a portion of a stool sample.¹⁸⁹ The quantitative nature of Vilkin's assay is reflected in Table 1, which provides the hemoglobin levels of fecal samples from individuals having different CRC diagnoses (copied below).

¹⁸⁷ Itzkowitz, p. 112.

¹⁸⁸ *Id.*, pp. 2519, 2524.

¹⁸⁹ *Id.*, pp. 2519, 2522.

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Table 1. Fecal Occult Blood Levels Detected According to Colonoscopy and Pathology Findings

Diagnosis	No.	Fecal Hb (ng/mL) (Mean $\pm$ SD)	Significance*
Normal [†]	381	29.1 $\pm$ 103.8	
Adenomas			
All	113	231.9 $\pm$ 567.5	NS
Non-AAP	85	58.0 $\pm$ 156.5	NS
AAP	28	759.8 $\pm$ 935.7	$P < 0.01$
Cancer	6	1154.3 $\pm$ 793.0	$p < 0.01$
CRC + AAP	34	829.4 $\pm$ 913.8	$p < 0.01$

AAP = advanced adenomatous polyps; CRC = colorectal cancer.

* As compared to the normal group.

[†] Includes 64 patients with only hyperplastic polyps.

181. Thus, when the gFOBT of Lenhard is replaced with the automated iFOBT of Vilkin the resulting assay therefore includes testing of a second portion of the sample for an amount of blood protein in that portion.

182. In view of the above, when the automated 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 are performed, rendering the claim obvious.

B. Shuber and Vilkin render obvious the Asserted Claims

183. Shuber and Vilkin likewise render obvious a method of processing a freshly collected fecal sample according to claims 1 of the '781 Patent and claim 3 of the '746 patent. The Asserted 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 the portions. It would have been obvious for a person of ordinary skill to

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combine the fecal DNA assay set forth in Shuber with the iFOBT of Vilkin to arrive at the methods of the Asserted Claims.

184. As I explain above, Vilkin discloses a quantitative iFOBT in which a portion of the fecal sample is removed using a “fecal test device” that is shaped like a small test tube that has a probe with a serrated tip attached to the inner portion of the device’s cap.¹⁹⁰ 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.”¹⁹¹ 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.¹⁹² The sealed container is transported to a diagnostic laboratory without freezing, where a benchtop instrument is used to automatically quantitate the level of hemoglobin in the sample.¹⁹³

185. 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.”¹⁹⁴ 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.”¹⁹⁵ The “container with sample and stabilization solution may be sealed for

¹⁹⁰ Vilkin, p. 2520.

¹⁹¹ *Id.*

¹⁹² *Id.*

¹⁹³ *Id.*, pp. 2520-2521.

¹⁹⁴ Shuber, 29:8-19.

¹⁹⁵ *Id.*, 7:19-21.

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storage/shipping.”¹⁹⁶ Shuber emphasizes that “[m]ethods of the invention do not require refrigeration or freezing.”¹⁹⁷

186. One of skill in the art would have further been motivated to combine a DNA-based stool test, such as the one disclosed in Shuber, with a blood protein-based stool test, such as the one disclosed in Vilkin, to generate a CRC diagnostic test with improved sensitivity.

187. By the priority date, the advantages of combining such stool DNA and blood protein assays were well understood in the art. 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** and other methods for detecting genetic abnormalities.”¹⁹⁸

188. That combining fecal DNA assays with FOBT increases assay 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**.”¹⁹⁹ 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.²⁰⁰ Lenhard also noted that “the combined test detected all localized cancers.”²⁰¹

¹⁹⁶ *Id.*, 29:8-19.

¹⁹⁷ *Id.*, 7:12-15.

¹⁹⁸ Nishikawa, p. 112 (emphasis added).

¹⁹⁹ Lenhard, p. 143.

²⁰⁰ *Id.* p. 147, Table 4.

²⁰¹ *Id.* p. 147.

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189. Further evidencing the recognized value of combining DNA assays with fecal blood assays, 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** and which is in the range of invasive diagnostic methods [*i.e.*, colonoscopy].”²⁰²

190. 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 [another acronym for iFOBT] at the time of testing would **improve sensitivity [of DNA-based assays] without adversely affecting specificity.**”²⁰³

191. Accordingly, one of skill in the art would have been motivated to combine a fecal DNA test, such as those disclosed in Shuber, with a fecal blood test, like the one disclosed in Vilkin to improve the sensitivity of CRC diagnosis. 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). A POSA would recognize that separation

²⁰² Kutzner, p. 34, Abstract.

²⁰³ Levin, p. 1578 (emphasis added).

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of the sample by the patient at home is necessary to ensure 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.²⁰⁴ A POSA would also recognize that it is more convenient for the patient to use the Vilkin sampling device before the fecal sample is immersed in buffer.

192. One of skill in the art would have a reasonable expectation of combining such assays because doing so requires no more than the use of routine methods to perform a pair of well-established assays on portions of a fecal sample.

193. 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 claim 1 of the '781 patent and claim 3 of the '746 patent.

1. Claim 1 of the '781 patent

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

194. To the extent the preamble of claim 1 is limiting, it is rendered obvious by Shuber and Vilkin. Both Vilkin and Shuber teach the processing of freshly-collected fecal samples without freezing.²⁰⁵ Accordingly, the obvious combination of the two assays would also involve processing a fresh fecal sample without freezing.²⁰⁶

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;"

²⁰⁴ Vilkin, p. 2520; Shuber, 29:8-19.

²⁰⁵ Vilkin, p. 2520, Shuber, 7:12-15.

²⁰⁶ Shuber; Vilkin.

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195. 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 at home by direct defecation into a container, 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.”²⁰⁷ Shuber notes that such stabilizing solution “may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center.”²⁰⁸ Vilkin also emphasizes that the iFOBT assay allows for at-home sample collection.²⁰⁹

196. Indeed, by the Priority Date, direct defecation of into a sealable container by a patient at home had been a standard method for collecting stool samples for decades. A laboratory manual from 1985 recommends collecting fecal samples in a sealable container and that “[f]eces should be passed directly into the container.”²¹⁰ Similarly, 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.”²¹¹

197. Accordingly, by the Priority Date, a person of ordinary skill would have recognized collecting a stool sample at home by direct defecation into a sealable collection vessel, as described in Shuber, as a routine method for collection of a stool

²⁰⁷ Shuber, 29:8-19.

²⁰⁸ *Id.*, 10:12-14.

²⁰⁹ Vilkin, p. 2524.

²¹⁰ Melvin, p. 2.

²¹¹ Lapidis '650, 7:45-49, Figure 2.

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sample. It would therefore have been obvious to use such a collection method when performing that assays of Shuber and Vilkin on a stool sample.

- 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;”**

198. When the Vilkin assay is performed on the stool sample, a portion of the fecal sample is obtained using a “fecal test device” that is shaped like a small test tube that has a probe with a serrated tip attached to the inner portion of the device’s cap.²¹² 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.”²¹³ 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, creating a removed portion and a remaining portion of the fecal sample.²¹⁴

199. 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.

- 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”**

²¹² Vilkin, p. 2520.

²¹³ *Id.*

²¹⁴ *Id.*

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200. When the Vilkin assay is used, 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.”²¹⁵ This results in sealing of the fecal test sampling device with the tip “put in a closed amount of Hb stabilizing buffer.”²¹⁶ The Hb stabilizing buffer facilitates the convenient shipment of the at-home collected sample to a diagnostic laboratory for analysis.

201. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample result 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 the sealing of the sealable container.

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

202. As discussed above, 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.”²¹⁷ 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.”²¹⁸ The “container with sample and stabilization solution may be sealed for storage/shipping.”²¹⁹

²¹⁵ *Id.*, p. 2520.

²¹⁶ *Id.*

²¹⁷ Shuber, 7:19-21.

²¹⁸ *Id.*, 29:8-19.

²¹⁹ *Id.*, 29:8-19.

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203. Thus, 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 are performed, rendering the claim obvious.

2. Claim 3 of the '746 patent

204. As discussed above, claim 3 of the '746 patent is a dependent claim directed to the performance of standard and routine assays on the portions of a fecal sample obtained by the method of the '746 patent's claim 1. Accordingly, in the below analysis, I first address why claim 1 of the '746 patent is rendered obvious by Shuber and Vilkin, and then address why these references also render obvious the performance the well-known assays set forth in claim 3 on the fecal portions produced by the process of claim 1.

a. Claim 1 of the '746 patent

205. As discussed above, claim 1 of the '746 patent is similar to but broader in scope than claim 1 of the '781 patent. The method set forth in claim 1 of the '746 patent is therefore rendered obvious by Shuber and Vilkin for effectively the same reasons set forth above with respect to claim 1 of the '781 patent.

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

206. Both Vilkin and Shuber teach the processing of freshly-collected fecal samples without freezing.²²⁰ Accordingly, the obvious combination of the two assays would also involve processing a fresh fecal sample without freezing.²²¹

²²⁰ Vilkin, p. 2520, Shuber, 7:12-15.

²²¹ Shuber, Vilkin.

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- ii. **“a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;”**

207. Both Shuber and Vilkin disclose the collection of a fecal sample by a human subject at home.²²² The at-home collection methods disclosed in Shuber and Vilkin therefore would be used in the method they render obvious.

- iii. **“b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and”**

208. As discussed above, 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.”²²³ 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.”²²⁴ The “container with sample and stabilization solution may be sealed for storage/shipping.”²²⁵

209. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample result in a first portion of the fecal sample being combined with a stabilizing buffer in a sealable vessel and the sealable vessel being sealed.

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

²²² Vilkin, p. 2520; Shuber, 2:27-32, 6:9-20, 14:25-30, 29:8-19.

²²³ Shuber, 7:19-21.

²²⁴ *Id.*, 29:8-19.

²²⁵ *Id.*, 29:8-19.

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210. When the Vilkin assay is used, a probe 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.²²⁶ 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.”²²⁷ This results in sealing of the fecal test sampling device with the tip “put in a closed amount of Hb stabilizing buffer.”²²⁸ The Hb stabilizing buffer facilitates the convenient shipment of the at-home collected sample to a diagnostic laboratory for analysis.

211. Thus, 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 are performed, rendering the claim obvious.

b. Claim 3 of the '746 patent

212. Claim 3 is directed to the performance of the same prior art assays that are performed in Shuber and Vilkin on the portions of a fecal sample collected in claim 1. The method therefore amounts to no more than the routine use of standard diagnostic assays fecal samples that had been prepared using standard methodology for exactly that purpose, and is therefore obvious.

i. “A method of processing a fecal sample, the method comprising:”

²²⁶ *Id.*, p. 2520.

²²⁷ *Id.*

²²⁸ *Id.*

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213. To the extent the preamble of claim 3 is limiting, it is rendered obvious by Shuber and Vilkin, as both references directed to methods of processing fecal samples.²²⁹

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

214. Both Shuber and Vilkin disclose delivery of the collected fecal samples to a medical diagnostics laboratory for testing.²³⁰ Accordingly, when the fecal DNA test of Shuber and the iFOBT of Vilkin are both performed on a stool sample, sealed containers containing the portions of the fecal sample in their respective buffers will be obtained by technicians at a medical diagnostics laboratory.

- c. **“b) extracting nucleic acid from the first portion of the fecal sample;”**

215. Performance of fecal DNA analysis typically requires extraction of the DNA from a portion of the fecal sample prior to DNA analysis. Consistently, the fecal DNA assays described in Shuber includes purification of DNA from the first portion of the stool sample.²³¹ Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample results in the extracting nucleic acid from the first portion of the fecal sample.

²²⁹ Shuber; Vilkin.

²³⁰ Shuber, 10:12-14; Vilkin, p. 2520.

²³¹ Shuber, 15:18-16:17.

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

216. 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.”²³² Each of these assays includes the testing of a nucleic acid extracted from feces for an amount of a human nucleic acid.

217. Thus, performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample result in the extracted nucleic acid being tested for an amount of a human nucleic acid.

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

218. The Vilkin iFOBT is a quantitative test of the level of human hemoglobin (Hb) in a portion of a stool sample.²³³ For example, Table 1 of Vilkin provides the Hb levels detected in fecal samples obtained from patients with or without colorectal adenomas or cancer.²³⁴ Performing the fecal DNA test of Shuber and the iFOBT of Vilkin on a stool sample therefore results in the testing of the second portion of the sample for an amount of blood protein in that portion.

²³² *Id.*, 7:19-21.

²³³ Vilkin, p. 2519.

²³⁴ *Id.*, p. 2522.

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219. Thus, 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 are performed, rendering the claim obvious.

X. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

220. I have reviewed Dr. Patterson's "preliminary opinions" concerning secondary considerations of non-obviousness (sometimes called "objective indicia of non-obviousness") included in the declaration he submitted in this proceeding.²³⁵ I disagree with Dr. Patterson's opinion that Exact Sciences' Cologuard Products "provide evidence of objective indicia of nonobviousness of the Asserted claims, including satisfying long-felt but unmet needs, commercial success, praises by the industry, and copying by others."²³⁶ In particular, I disagree with Dr. Patterson's contention that there is a nexus between the supposed success of Cologuard upon which Dr. Patterson relies and the methods of the Asserted Claims.

221. I understand that to accord substantial weight to secondary considerations, the evidence of secondary considerations must have a "nexus" to the claims. I understand that the patentee bears the burden of showing a nexus exists, and that presuming nexus is only appropriate when the patentee shows that the asserted secondary consideration is tied to a specific product and that product embodies the claimed features *and is coextensive with them*. On the other hand, when the product that is the basis of the secondary consideration is not coextensive with the patented invention—for example, if

²³⁵ Declaration of Bruce K. Patterson, M.D., in Support of Plaintiff Exact Sciences Corporation's Motion for a Preliminary Injunction, ¶¶321-344.

²³⁶ *Id.*, ¶321.

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the patented invention is only a component of a product, the patentee is not entitled to a presumption of nexus.

222. I note that, while Dr. Patterson repeatedly asserts that Cologuard embodies Asserted Claims, he never addresses whether Cologuard is coextensive with them. This is because the purported invention of the challenged method claims is, at best, a minor component of the Cologuard product. It is further my opinion that, to the extent any of the challenged claims possess novel features, those features have little or nothing to do with Cologuard's purported success.

223. Cologuard is a product for home CRC screening that is marketed by Exact.²³⁷ Cologuard is a combination of many components and processes, including, but not limited to, a multi-component at-home collection kit, numerous reagents and methods required to assess a diverse collection of specified biomarkers during sample testing, and a proprietary algorithm that translates biomarker data into a screening outcome during data analysis.²³⁸

224. The complex, multi-component nature of Cologuard is demonstrated by the FDA-approved Cologuard Physician Brochure, which explains that "Cologuard uses a multi-target approach" in which "[t]here different categories of biomarkers are targeted

²³⁷ Cologuard Patient Guide, p. 1.

²³⁸ Cologuard Patient Guide, p. 8; Imperiale, et al., "Multitarget Stool DNA Testing for Colorectal-Cancer Screening," *The New England Journal of Medicine*, 370(14):1287-1297 (2014) ("Imperiale 2014"), Abstract; Exact Sciences 2023 Form 10-K; Cologuard Physician Brochure; Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use.

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and provide an additive association with CRC and pre-malignant colorectal neoplasia.”²³⁹

The Physician Brochure describes these three categories of biomarkers as follows:²⁴⁰

The first category of biomarkers involves epigenetic DNA changes characterized by aberrant gene promoter region methylation. The specific methylated gene targets include N-Myc Downstream-Regulated Gene 4 (NDRG4) and the Bone Morphogenetic Protein 3 (BMP3). NDRG4 and BMP3 have been shown to be hypermethylated in colorectal cancer. The Cologuard procedure incorporates bisulfite conversion of nonmethylated cytosine residues to uracil in the DNA sequence to enable sensitive detection of hypermethylated NDRG4 and BMP3.

The second category targets specific DNA point mutations in the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, which encodes a small GTPase that is activated transiently as a response to extracellular stimuli or signals. KRAS mutations have been detected in up to 35% of colorectal cancers and the 7 mutations in Exon 2 detected by Cologuard account for 98% of KRAS mutations.¹⁶ KRAS mutations, along with NDRG4 and BMP3 methylation markers, have been shown to be detected in the stool of subjects with colorectal neoplasia, including subjects with colorectal cancer and pre-malignant lesions.

The third category of biomarker is non-DNA based and detects hemoglobin, which can be associated with colonic bleeding. Results from the methylation, mutation, and hemoglobin assays are combined in the laboratory analysis to determine a positive or negative reportable result or no result.

225. The Physician Guide summarizes the numerous, complex assays run during the Cologuard process as follows:²⁴¹

The patient stool samples are processed at the laboratory to isolate the DNA for testing. Amplification and detection of methylated target DNA (NDRG4, BMP3), KRAS point mutations, and ACTB (a reference gene for quantitative estimation of the total amount of human DNA in each sample) is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTS™) technology. Multi-plexed QuARTS reactions are processed using a real-time cyclor with each marker (NDRG4, BMP3, KRAS, and ACTB) monitored separately through independent fluorescent detection channels. The hemoglobin stool sample is prepared

²³⁹ Cologuard Physician Guide, p. 4.

²⁴⁰ *Id.* Internal citations omitted.

²⁴¹ *Id.*

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and analyzed in a quantitative Enzyme-Linked Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.

Run control samples for both the QuARTS assays and hemoglobin assay are tested along with patient samples to show that the process has been performed appropriately. Results from the methylation, mutation, and hemoglobin assays are combined during analysis to determine a positive result, negative result, or no result.

226. The complex, multi-component nature of Cologuard is further demonstrated by *85-page long* Cologuard Instructions for Use approved by FDA.²⁴² Within these lengthy instructions, the specimen collection process is summarized in a single sentence, simply stating that “[s]pecimens for use with Cologuard must be collected with the Cologuard Collection Kit (Exact Sciences, 100026), including a stool sample for DNA testing (Container) and a stool sample for Hemoglobin testing (Tube).”²⁴³ In contrast, the Laboratory Instructions include approximately five pages devoted to reagents and instrumentation used in Cologuard,²⁴⁴ about 23 pages devoted to performance of the laboratory assays used in Cologuard,²⁴⁵ and about seven pages directed to data analysis and interpretation.²⁴⁶ The remainder of the Laboratory Instructions is devoted to procedural notes and precautions, quality control, a troubleshooting guide, and assay performance characteristics.²⁴⁷

227. Exact’s advertisements also demonstrate the critical importance of components of Cologuard not claimed in the Asserted Patents. For example, Exact

²⁴² Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use.

²⁴³ *Id.* p. 15.

²⁴⁴ *Id.*, pp. 9-14.

²⁴⁵ *Id.*, pp. 15-39.

²⁴⁶ *Id.*, pp. 39-46.

²⁴⁷ *Id.*, pp. 47-83.

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advertises on its website that it uses specific proprietary platforms for each of the marker assays.²⁴⁸ Regarding DNA stability, Exact Sciences states that developing “an enhanced DNA stabilizing buffer was a *critical* step in the process of creating a reliable at-home screening kit” (emphasis added).²⁴⁹ Exact emphasizes the importance of the DNA Cologuard DNA isolation process, stating that their “scientists needed to first solve the essential problem of effectively isolating DNA from stool before achieving the goal of developing a noninvasive colon cancer screening test.”²⁵⁰ Exact also credits its DNA biomarker detection platform, stating that it “developed our proprietary QuARTS technology (Quantitative Allele-specific Real-time Target and Signal Amplification) which efficiently amplifies and quantifies two separate methylated DNA markers (NDRG4 and BMP3) along with seven distinct KRAS gene point mutations.”²⁵¹ Regarding hemoglobin stability and detection, Exact Sciences states that it “improved upon the technology for the ELISA-based detection of a protein biomarker (hemoglobin) through an additive in the stabilization buffer.”²⁵² Regarding its algorithm, Exact’s website states that “[t]his algorithm is the vital workhorse that translates our invisible biology into actionable information.”²⁵³

²⁴⁸ Exact Science’s webpage regarding the Cologuard test as obtained from <https://www.exactsciences.com/our-tests/cologuard> on August 15, 2024.

²⁴⁹ *Id.*

²⁵⁰ *Id.*

²⁵¹ *Id.*

²⁵² *Id.*

²⁵³ *Id.*

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228. Cologuard identifies on its website 54 patents unrelated to the '746 patent that cover components of Cologuard and its use.²⁵⁴ An additional eight patents were identified on Exact's webpage as covering Cologuard in 2014, but I understand are now expired.²⁵⁵ The claims of these patents are directed to numerous distinct components of Cologuard, including those set forth below:

- **Patents related to general use of stool in CRC screening:** *e.g.*, U.S. Pat. Nos. 5,741,650, 5,952,178, 6,303,304, 6,586,177.
- **Patents related to containers for collecting and storing stool samples:** *e.g.*, U.S. Pat. Nos. 9,211,112, 9,750,482, 10,265,054, 10,486,158, 10,702,250, 10,894,256.
- **Patents related to DNA stabilizing buffer:** *e.g.*, U.S. Pat. Nos. 6,551,777, 8,722,330.
- **Patents related to DNA isolation methods:** *e.g.*, U.S. Pat. Nos. 6,268,136, 6,406,857, 8,993,341, 8,999,176, 9,000,146, 9,057,098, 9,163,278, 9,169,511, 9,657,330, 9,631,228, 9,845,491, 9,856,515, 10,047,390, 10,822,639.
- **Patents related to DNA markers:** *e.g.*, U.S. Pat. Nos. 8,673,555, 8,969,046, 9,121,070, 9,127,318, 9,163,278, 9,169,511, 9,399,800, 9,783,856, 9,803,249, 9,845,491, 10,435,753.
- **Patents related to methods of preparing DNA for methylation analysis:** *e.g.*, U.S. Pat. Nos. 9,315,853, 10,144,953, 10,704,083.

²⁵⁴ Printout of Exact Sciences' "Patents and Trademarks" page from their website, as visited on August 9, 2024.

²⁵⁵ Printout of Exact Sciences' "Patents and Trademarks" page from their website as of December 6, 2014. Downloaded from Wayback Machine on August 9, 2024.

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- **Patents related to methods of testing for methylated DNA:** *e.g.*, U.S. Pat. Nos. 8,916,344, 9,637,792, 10,519,510, 10,590,489, 10,808,286.
- **Patents related to methods of detecting DNA mutations:** *e.g.*, U.S. Pat. Nos. 8,361,720, 8,715,937, 9,024,006, 9,121,071, 9,212,392, 9,290,797, 9,376,721, 10,000,817, 10,106,844, 10,590,489.
- **Patents related to control molecules used with DNA assays:** *e.g.*, U.S. Pat. Nos. 9,212,392, 10,106,844, 10,138,524, 10,253,358, 10,889,867.

229. In my opinion, there is no nexus between the supposed advantages of Cologuard identified by Dr. Patterson and the Asserted Claims. I am not aware of any secondary considerations related to Cologuard that can be attributed to the invention of the challenged claims, as opposed to the other Cologuard components listed above. Consistently, as reported by Exact, “[s]ensitivity is the most important characteristic for screening tests,” which it stated was “*attributed to the DNA marker and algorithm components of the test*.”²⁵⁶

230. During prosecution of an unrelated patent (U.S. Pat. No. 9,163,278, “the ‘278 patent”), Exact attributed Cologuard’s success, not to the method of the Asserted Claims, but rather to “a particular combination of markers and methods for extracting the marker DNA from stool.”²⁵⁷ Exact noted that Cologuard “comprises the system components recited in the instant claims as amended: stool homogenization buffer, PVPP inhibitor adsorbant, spin filter and guanidine thiocyanate, and magnetic target-specific

²⁵⁶ Imperiale 2014, pp. 1288, 1295, emphasis added.

²⁵⁷ Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of ‘278 patent, p. 9.

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capture particles for capturing NDRG4, BMP3 and KRAS target human DNAs.”²⁵⁸ Exact then argued that was these components of Cologuard that addressed the “long-felt need for a way to screen for colorectal cancers based on DNA screening” and “succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.”²⁵⁹

231. The ’278 patent asserts a priority date of May 12, 2011, more than two years *after* the February 3, 2009 priority date asserted by the Asserted Patents.²⁶⁰ Thus, when Exact argued during prosecution of the ’278 patent that the particular combination of markers and methods for extracting the marker DNA from stool claimed by that patent solved the “long-felt need for screen for a way to screen for colorectal cancers based on DNA screening,” it was *admitting that this problem had not been solved by the method claimed in the Asserted Patents*.

232. In his Declaration, Dr. Patterson premises his argument for nexus on his assertion that “[t]he convenience of at-home sample collection and the high sensitivity for CRC detection are two of the most important and distinguishing features of the Cologuard Products—both features are directly related to, and result from, the novel stool-sampling methods claimed in the ’781 and ’746 Patents.” I disagree.

233. *First*, “convenient at-home sample collection” is not a novel feature of the Asserted Patents. As discussed above in section V(C), fecal samples used in diagnostic assays had been conveniently collected at home for decades before the 2009 priority date

²⁵⁸ *Id.*, pp. 6-7.

²⁵⁹ *Id.*, p. 9.

²⁶⁰ U.S. Patent No. 9,163,278; ’746 patent.

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of the Asserted Patents. Indeed, prior art references that form the basis of the grounds for obviousness I set forth above, including Itzkowitz, Vilkin, and Shuber, all describe methods for convenient at-home sample collection. At-home sample collection is simply not a distinguishing feature of the Asserted Claims or the Cologuard product.

234. *Second*, the “high sensitivity for CRC detection” of Exact’s Cologuard product is not attributable to the Asserted claims of OncoMethylome’s patent family, but rather to the specific panel of DNA markers. Indeed, Exact has acknowledged that the improved sensitivity of Cologuard over standard FIT tests was “*attributed to the DNA marker and algorithm components of the test*,” since the test performance of the hemoglobin immunoassay component of the DNA test was nearly identical to that of FIT.”²⁶¹

235. Notably, Exact only developed the specific panel of DNA markers used in Cologuard that allows for its sensitivity *after* the 2009 priority date of the Asserted Claims. Indeed, during prosecution of the ’278 patent, which has a later priority date of 2011, Exact attributed Cologuard’s success to the “particular combination of markers and methods for extracting the marker DNA from stool” claimed in the ’278 patent.²⁶² Cologuard’s sensitivity therefore cannot be a product of the Asserted Claims, which were purportedly invented by OncoMethylome by the 2009 Priority Date, because such sensitivity only became possible years later when Exact developed Cologuard’s DNA marker panel.

²⁶¹ Imperiale 2014, pp. 1288, 1295, emphasis added.

²⁶² Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of ’278 patent, p. 9.

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236. Based on my experience as an executive working in the field of molecular diagnostics, it is my opinion that the commercial success of the Cologuard product can be attributed in large part to Exact's extensive marketing and advertising investments as well as the exclusivity afforded to Exact by the dozens of other, earlier-issued blocking patents covering Cologuard, including those listed above.

237. Indeed, the important role of Exact's marketing efforts to Cologuard's commercial success is confirmed by a recent article published in Forbes.²⁶³ In this article, Exact's CEO Kevin Conroy explains that, shortly after Cologuard's launch, Exact ran direct-to-consumer (DTC) marketing tests in five cities. As explained by Mr. Conroy, "We ran targeted TV commercials in these five markets and compared them to the five control markets. These markets grew cumulatively 10% per week over the five control markets. After 9 weeks, we were up 100% compared to the control markets."²⁶⁴ Notably, in the above DTC marketing test, the exact same Cologuard product was being sold in both the test market and the control market. The 100% improvement in commercial success observed over nine weeks in the test markets can therefore only be attributable to the advertising Exact placed in those markets, and is certainly not attributable to the Asserted Claims.

238. Cologuard's purported success therefore has little or no nexus with the methods of the Asserted Claims, and the secondary considerations identified by Dr. Patterson therefore should be given little or no weight.

²⁶³ Feiger, Chase, "How This CEO Consumerized Cancer Into a \$13B Enterprise" Forbes, April 8, 2024.

²⁶⁴ *Id.*, p. 6.

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XI. THE CLAIMS OF THE '781 PATENT LACK WRITTEN DESCRIPTION AND ENABLEMENT

A. Written Description

239. I understand that a patent must contain a written description of the method claimed in the patent. I understand that the written description requirement is met only if a POSA would conclude from the specification of the patent that the inventors invented the full scope of what is claimed as of the effective filing date of the claimed invention. In other words, the specification of the patent must demonstrate that the inventors were in possession of the full scope of the claimed invention.

240. The common specification of the Asserted Patents does not convey possession of the full scope of the invention of the Asserted Claims. For example, as described in detail below, the common specification does not describe:

- Combining a portion of a fecal sample with a “stabilizing buffer” other than one for stabilizing DNA or blood proteins in a fecal sample. In particular, the Asserted Patents do not convey possession of a method of processing a fecal sample that includes use of a buffer that stabilizes fecal material generally, or fecal RNA in particular;
- “Extracting nucleic acid” other than DNA from a portion of a fecal sample. The Asserted Patents do not convey that the inventors were in possession of a method of processing a fecal sample that includes extraction from a fecal sample of nucleic acids generally, or RNA in particular;
- Testing “nucleic acid extracted from a portion of a fecal sample” for “an amount of a human nucleic acid” other than testing extracted DNA for an amount of epigenetically modified DNA. The Asserted Patents do not convey that the

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inventors were in possession of a method of testing any nucleic acid extracted from a fecal sample for an amount of human any human nucleic acid, or, in particular, for testing extracted RNA for an amount of human RNA; or

- testing a portion of a fecal sample “for an amount of a blood protein” other than hemoglobin. There are tens of thousands of different proteins in blood, and the Asserted Patents only describe a test for a one of them: hemoglobin.

241. The common specification of the Asserted Patents therefore conveys only possession of a narrow subset of the broadly claimed genus of fecal processing methods covered by the Asserted Claims. It is therefore my opinion that the Asserted Patents do not provide written description for the full scope of claim 1 of the '781 patent or claim 3 of the '746 patent.

1. The common specification does not describe combining a portion of a fecal sample with a “stabilizing buffer”

242. In both the '781 patent and the '746 patent, claim 1 requires a portion of a fecal sample to be combined with a “stabilizing buffer.” Similarly, claim 3 of the '746 patent requires the step of obtaining “a sealed vessel containing a first portion of a fecal sample and a stabilizing buffer.” The common specification of the Asserted Patents does not have written description for a combining a fecal sample with a generic “stabilizing buffer.” It is therefore my opinion that the common specification does not provide written description for the full scope of claim 1 of the '746 patent or claim 3 of the '746 patent.

243. As discussed above, the common specification of the Asserted Patents discloses combining a portion of a fecal sample with either (1) a buffer that prevents

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denaturation or degradation of blood proteins,²⁶⁵ or (2) a buffer that maintains DNA integrity.²⁶⁶ There is no discussion in the Asserted Patents of buffers for stabilizing any other fecal components, including fecal RNA.

244. In the *only* disclosure in the Asserted Patents of a method of processing a fecal sample by partitioning it, as required by the Asserted Claims, the Asserted Patents explicitly state that a removed portion of the fecal sample is added “to *a buffer which prevents denaturation or degradation of blood proteins* found in the sample” and that “suitable *buffers for maintaining DNA integrity* may be added to the remaining portion of the sample.”²⁶⁷ Nothing in the Asserted Patents suggests combining a portion of a fecal sample with a buffer that stabilizes anything other than DNA or blood proteins. There is no disclosure of partitioning a fecal sample and then combining a portion of it with a generic “stabilizing buffer” or a buffer that stabilizes RNA.

245. As discussed above in section V(D), buffers that stabilize one type of biomolecule do not necessarily stabilize a different one. For example, because buffers that stabilize DNA may not also stabilize blood proteins, the Asserted Patents require a different buffer to be used to stabilize the portion of the fecal sample in which blood proteins is detected from the one used to stabilize the portion in which DNA methylation is detected.²⁶⁸ Similarly, buffers that stabilize DNA, such as the one I helped develop at

²⁶⁵ ‘781 patent, Abstract, 1:3-36, 4:17-22, 18:3-6, 18:19-21, 25:5-8.

²⁶⁶ *Id.*, 11:48-52; 18:26-28; 36:28-40 (specifying that the buffer used was the DNA stabilizing buffer described Olson, which I co-authored).

²⁶⁷ *Id.*, 17:65-18:28, emphasis added.

²⁶⁸ *Id.*, 17:65-18:31.

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Exact that is described in Olson et al. and referenced in the Asserted Patents,²⁶⁹ would not be expected to effectively stabilize RNA. Indeed, as I explain above in section V(D), RNA is notoriously unstable and far more difficult to stabilize than proteins or DNA. The disclosure in the Asserted Patents of a buffer that specifically “prevents denaturation or degradation of blood proteins” and a buffer that is specifically “for maintaining DNA integrity” therefore does not convey possession of the genus of “stabilizing buffers” in general, and especially does not convey possession of buffers that stabilize RNA.

246. It is therefore my opinion that a POSA reading the specification of the Asserted Patents, which only describes buffers for stabilizing blood proteins and DNA, would not conclude that the inventor was in possession of the full scope of the claimed invention, in which a portion of a fecal sample can be combined with *any* “stabilizing buffer.”

2. The common specification does not describe “extracting nucleic acid from the first portion of the fecal sample”

247. Claim 3 of the '746 patent recites a step of “extracting nucleic acid from a first portion of the fecal sample.” However, the Asserted Patents only disclose extracting *DNA* from a fecal sample, not extracting nucleic acids generally. For this reason as well, it is therefore my opinion that the common specification does not provide written description for the full scope of claim 3 of the '746 patent.

248. The only nucleic acid that the Asserted Patents describe being extracted from a fecal sample is DNA. For example, the specification states:

The methods of the invention may be carried out on purified or unpurified DNA-containing samples. However, in specific embodiments, DNA is isolated/extracted/purified from the sample. Any suitable DNA isolation

²⁶⁹ *Id.*, 36:36-39.

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technique may be utilised... In some embodiments, purification involves *alcohol precipitation of DNA*. Preferred alcohols include ethanol and isopropanol. Suitable purification techniques also include salt-based precipitation methods. Thus, in specific embodiments *the DNA purification technique* comprises use of a high concentration of salt to precipitate contaminants... The method may further include steps of removal of contaminants which have been precipitated, *followed by recovery of DNA through alcohol precipitation*.²⁷⁰

249. Extraction of DNA is emphasized throughout the specification, which further states that in alternative embodiments the “*the DNA purification technique* is based upon the use of organic solvents...”²⁷¹ It notes that “*extracted DNA is recovered* through alcohol precipitation.”²⁷² It emphasizes that “[r]eliable results may be achieved *by isolating, extracting, or purifying DNA* from less than 5 g of faecal sample.”²⁷³ The specification notes that “[t]he faecal ample may be present in an appropriate homogenizing buffer *to facilitate DNA isolation, extraction and purification*.”²⁷⁴ The specification also identifies commercially available kits that “may be employed in order to *extract the DNA* and remove potential inhibitors from the faecal sample.”²⁷⁵ Indeed, only DNA is extracted from fecal samples in both of the specification’s examples.²⁷⁶

250. In contrast to these repeated and pervasive disclosures of DNA extraction, there is no description in the common specification of any method that includes

²⁷⁰ *Id.*, 10:49-67 (emphasis added).

²⁷¹ *Id.*, 11:1-3 (emphasis added).

²⁷² *Id.*, 11:9-11 (emphasis added).

²⁷³ *Id.*, 11:64-66.

²⁷⁴ *Id.*, 11:67-12:3 (emphasis added).

²⁷⁵ *Id.*, 12:4-16 (emphasis added).

²⁷⁶ *Id.*, 28:38-30:2, 36:41-50. *See, also, Id.*, 11:25-36, 19:15-18, 25:8-15, 25:34-29, 26:51-56, and 27:33-39 for additional descriptions of DNA extraction in the common specification of the Asserted Patents.

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extracting nucleic acids generally from a fecal sample, or describes extracting RNA in particular. It is therefore my opinion that a POSA reading the specification of the Asserted Patents, which only describes extracting from a fecal sample *DNA specifically*, would not conclude that the inventor was in possession of the full scope of the claimed invention, which recites a step of extracting from a fecal sample *nucleic acids generally*, including extraction of RNA.

3. The common specification does not describe “testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid”

251. Claim 3 of the '746 patent requires a step of “testing nucleic acid extracted from a first portion of the fecal sample for an amount of a human nucleic acid.” However, the Asserted Patents only convey possession of testing DNA extracted from a fecal sample for an epigenetic modification, such as DNA methylation, and do not convey possession of testing any type of extracted nucleic acids for an amount of human nucleic acids generally. It is therefore my opinion that the common specification does not provide written description for the full scope of claim 3 of the '746 patent for this reason as well.

252. *First*, as discussed above, the Asserted Patents do not disclose extraction of any nucleic acid other than DNA from a fecal sample. As such, there is no disclosure of any extracted nucleic acid other than DNA being tested for anything, and, indeed, the patents repeatedly emphasize that assays are being run specifically on “extracted DNA.”²⁷⁷ There is no disclosure in the Asserted Patents of performing any tests on extracted nucleic acid generally, or extracted RNA in particular.

²⁷⁷ *Id.*, 11:25-27, 11:55-12:16, Example 1, Example 2.

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253. *Second*, the asserted patents are clear that they are directed to methods for *detecting epigenetic modifications in DNA*, not to testing “for an amount of a human nucleic acid” generally. For example, the “Summary of the Invention” section of the Asserted Patents states that “[t]he invention provides a method of detecting a predisposition to, or the incidence of, colorectal cancer in a faecal sample comprising... *detecting an epigenetic modification in the DNA* contained within the faecal sample.”²⁷⁸ The detailed description explains that “[t]he invention is based upon a combination of tests for detecting proteins *and epigenetic modification* markers respectively in the same faecal sample.”²⁷⁹ Notably, epigenetic modifications occur on DNA but not RNA. Indeed, the Asserted Patents define “epigenetic modification” to “include *any alternation to the DNA*, generally resulting in diminished gene expression, which is mediated by mechanisms other than alterations in the primary nucleotide sequence of the gene.”²⁸⁰ A POSA would therefore understand the invention disclosed in the Asserted Patents to require detection of epigenetic modifications in DNA. A generic test for “an amount of a human nucleic acid” as claimed is not contemplated.

254. Indeed, the only disclosure in the Asserted Patents of a method of processing a sample by partitioning it, as required by the Asserted Claims, the common specification states that a removed portion of the fecal sample is used to test “for the presence of blood in the faecal sample,” while the remaining portion is used to test for “*epigenetic modification in the DNA* contained within the faecal sample.”²⁸¹ The

²⁷⁸ *Id.*, 4:3-12.

²⁷⁹ *Id.*, 6:49-54.

²⁸⁰ *Id.*, 12:35-39.

²⁸¹ *Id.*, 17:65-18:28, emphasis added.

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Asserted Patents do not disclose testing a portion of a partitioned fecal sample for “an amount of a human nucleic acid,” as required by claim 3 of the ’746 patent.

255. Consistently, the Examples of the Asserted Patents are specifically directed to the detection of epigenetic modifications in DNA.²⁸² Example 1 discloses a multicenter screening trial conducted by OncoMethylome starting in 2006 in which “subjects aged 50 or above are screened with colonoscopy, FOBt and real-time MSP [methylation specific PCR] using DNA from stool and blood.”²⁸³ Example 2 similarly describes FIT and DNA methylation testing on frozen stool samples collected between 2003 and 2008.²⁸⁴ Neither example includes the stabilization, extraction, or testing of any other nucleic acid, including RNA.

256. The only mention of RNA expression in the Asserted Patents is in a passage that begins by stating that “[s]ince hypermethylation of a gene may result in diminished gene expression *it may be possible*, in certain embodiments, to carry out the methods of the invention by determining gene *expression of the DNA in the faecal sample* rather than investigating the methylation status of the DNA directly.”²⁸⁵ However, like the rest of the common specification, this passage also does not convey that the inventor was in possession of a method of testing nucleic acid extracted from a portion of a fecal sample for an amount of a human nucleic acid.

257. First, this statement that it “may be possible” to assess the methylation status of fecal DNA by determining gene expression of DNA in the fecal sample does not

²⁸² *Id.*, 28:9-37:7.

²⁸³ *Id.*, 28:14-17.

²⁸⁴ *Id.*, 36:21-26.

²⁸⁵ *Id.*, 13:4-8.

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convey to a POSA that the inventors were in possession of such a method. Indeed, by using the phrase “it may be possible” the inventor acknowledges that *he does not know* whether it is even possible to perform such an analysis. A POSA would not understand an inventor to be in possession of a method that he does not know is possible to perform.

258. Second, the aforementioned passage, like the rest of the common specification, relates to the possible detection of an *epigenetic modification in the fecal DNA (in this case DNA methylation)* and not to a general test “for an amount of a human nucleic acid” as claimed. Specifically the passage states that “[s]ince hypermethylation of a gene may result in diminished gene expression it may be possible, in certain embodiments, to carry out the methods of the invention *by determining gene expression of the DNA in the faecal sample rather than investigating the methylation status of the DNA directly*.”²⁸⁶ Thus, the common specification, at best, includes a discussion of the possibility of *detecting DNA methylation in a fecal sample by looking at the expression of fecal DNA*, and not of testing a fecal sample “for an amount of human nucleic acid” generally.

259. It is therefore my opinion that a POSA reading the specification of the Asserted Patents, which only describes detecting an epigenetic modification in DNA extracted from a fecal sample, would not conclude that the inventor was in possession of the full scope of the claimed invention, which generically recites a step of testing nucleic acid extracted from a portion of a fecal sample for an amount of any human nucleic acid.

²⁸⁶ *Id.*, 13:4-8.

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4. The common specification does not describe “testing the second portion of the fecal sample for an amount of a blood protein”

260. Claim 3 of the '746 patent recites the step of “testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample” but does not specify which blood proteins are being tested for. The term “blood protein” encompasses an enormous genus of different molecules. Specifically, blood contains over 20,000 different proteins, each with having its own structure and present at widely varying concentrations, ranging from <1 ng/L (troponin) to 50 g/L (serum albumin).²⁸⁷ In contrast, the common specification discloses only the detection of a single blood protein—hemoglobin.

261. The reagents and methods provided in the specification for detecting hemoglobin are not representative of the reagents and methods that would be used to detect the over 20,000 other blood proteins. Each different blood protein has its own different structure, and the methods disclosed in the common specification for detecting hemoglobin would not work to detect other blood proteins. Indeed, the specification specifies that the antibodies used to detect hemoglobin are specific to hemoglobin and don't bind to unrelated proteins, stating:

The term “antibody” or “antibodies” herein refers to an antibody or antibodies, or derivative thereof that retains specific binding activity. **By specific binding activity is meant the ability to specifically bind to hemoglobin. Thus, such a reagent does not bind, or does not bind to a significant degree, to unrelated proteins found in the faecal sample.**²⁸⁸

²⁸⁷ Song *et al.*, “Point-of-care technologies for molecular diagnostics using a drop of blood,” *Trends Biotechnol.* 32:3 132-139 (2014) (“Song”).

²⁸⁸ '781 patent, 7:30-36

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262. The common specification therefore does not support the full scope of the claimed genus of testing for “blood proteins” and therefore does not provide written description for claim 3 of the ’746 patent.

B. Enablement

1. The Asserted Patents do not enable the testing of any extracted nucleic acid for an amount of any human nucleic acid

263. The common specification of the Asserted Patents does not enable a POSA to practice the full scope of claim 3 of the ’746 patent.

264. Claim 3 broadly recites the extraction of any type of nucleic acid from a fecal sample and then testing it for any human nucleic acid. This claim therefore encompasses, for example, (a) the testing of extracted DNA for an amount of any mutated or unmutated human gene; (b) the testing of extracted DNA for an amount of any mutated or unmutated non-coding DNA sequence; (c) the testing of extracted DNA for an amount of any epigenetically modified human DNA sequence, including DNA methylation of coding or non-coding DNA sequences; (d) the testing of extracted RNA for an amount of any messenger RNA (mRNA) expressed by any mutated or unmutated human gene; (e) the testing of extracted RNA for an amount of any human microRNA (miRNA); (f) the testing of extracted RNA for an amount of any human transfer RNA (tRNA); (g) the testing of extracted RNA for an amount of any human ribosomal RNA. Claim 3 therefore encompasses the testing of many different types of nucleic acid structures that collectively encompass many thousands of unique sequences.

265. I understand that factors relevant to enablement include: 1. the breadth of the claims; 2. the amount of direction or guidance disclosed in the patent; 3. the presence or absence of working examples in the patent; 4. the nature of the invention; 5. the state

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of the prior art; 6. the relative skill of those in the art; 7. the predictability or unpredictability of the art; and. In my opinion, collective consideration of these factors strongly supports that claim 3 is not enabled.

266. As discussed above, the claim 3 is extremely broad, and encompasses extraction of any type of nucleic acid from a fecal sample and then testing it for any human nucleic acid.

267. In contrast to the broad scope of claim 3, the amount of direction or guidance disclosed in the common specification of the Asserted Patents is minimal. In particular, the Asserted Patents provides methods for stabilizing and extracting fecal DNA and then testing it for methylation for thirteen specific genes: *PHACTR*, *FOXE1*, *NDRG4*, *GATA4*, *OSMR*, *SYNE1*, *SFRP2*, *SOX17*, *LAMA1*, *MMP2*, *CDOI*, and *TFPI2*.²⁸⁹ There is no disclosure in the common specification of RNA biomarkers or sequences, or of any method for stabilizing, extracting or detecting any form of RNA.

268. The lack of working examples in which any nucleic acid other than the DNA methylation of the thirteen genes listed above also supports the conclusion that claim 3 is not enabled. In particular, there are no examples in which RNA of any kind are extracted or tested for.

269. Similarly, the nature of the invention, the state of the prior art, and the predictability of the art further support the conclusion that claim 3 is not enabled. The claimed method encompasses extraction of any type of nucleic acid from a fecal sample and then testing it for any human nucleic acid. However, only a relatively small number of nucleic acid biomarkers had been successfully isolated and tested for in the prior art,

²⁸⁹ *Id.*, 8:61-10:5, Table 1, Example 1, Example 2.

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and the methods and reagents required to test for an amount of a human nucleic acid vary depending on the type and sequence of the human nucleic acid to be detected. Combined with the fact that molecular biology is an inherently unpredictable field, it would have required undue experimentation to practice the full scope of the broadly claimed invention.

270. The only factor that slightly leans towards enablement would be the relatively high level of skill possessed by a POSA with respect to the Asserted Patents. However, given the extreme breadth of claim 3 and the lack of guidance and working examples in the specification, in my opinion even a highly skilled scientist would require undue experimentation to practice the full scope of claim 3.

271. Accordingly, the limited disclosure the common specification would not enable a POSA to practice the full scope of claim 3 of the '746 patent without undue experimentation.

2. A POSA would not enable the full scope of “testing the second portion of the fecal sample for an amount of a blood protein”

272. As discussed above, claim 3 of the '746 patent encompasses testing the second portion of the fecal sample for an amount of any blood protein, but the common specification only discloses methods for the detection of a single blood protein—hemoglobin.

273. There are over 20,000 different proteins in blood, each having its own structure.²⁹⁰ The reagents and methods provided in the specification are specific for detecting hemoglobin, and they would not work to detect any other blood protein. Indeed,

²⁹⁰ Song.

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the specification specifies that the antibodies it uses to detect hemoglobin are specific to hemoglobin and do not bind to unrelated proteins, stating:

The term “antibody” or “antibodies” herein refers to an antibody or antibodies, or derivative thereof that retains specific binding activity. **By specific binding activity is meant the ability to specifically bind to hemoglobin. Thus, such a reagent does not bind, or does not bind to a significant degree, to unrelated proteins found in the faecal sample.**²⁹¹

274. To practice the full scope of claim 3 a POSA would at least have to develop antibody reagents specific for each of the more than 20,000 blood proteins encompassed by the claim. As such, the common specification does not enable a POSA to practice the full scope of claim 3 of the '746 patent without undue experimentation. It is therefore my opinion that for this additional reason, claim 3 of the '746 patent is not enabled and therefore is invalid.

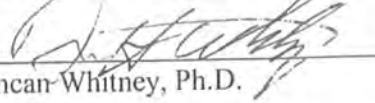
²⁹¹ '781 patent, 7:30-36

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I hereby declare under penalty of perjury that that the foregoing is true and correct.

Dated: September 26, 2024

Respectfully submitted,


Duncan Whitney, Ph.D.