

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

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

**DECLARATION OF VADIM BACKMAN, Ph.D.
IN SUPPORT OF PATENT OWNER'S RESPONSE TO PETITION FOR
INTER PARTES REVIEW OF U.S. PATENT 11,970,746**

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I. QUALIFICATIONS

1. I am currently employed as the Sachs Family Professor of Biomedical Engineering and Medicine, Professor of Biochemistry and Molecular Genetics at the Feinberg School of Medicine, Associate Director and Leader of the Cancer and Physical Sciences Program at the Robert H. Lurie Comprehensive Cancer Center, Director of the Center for Physical Genomics and Engineering, and Director of the Cellular Cancer Biology Imaging Center at Northwestern University.

2. I completed a Doctor of Philosophy (Ph.D.) in Medical Engineering and Medical Physics from the Massachusetts Institute of Technology and Harvard University in 2001. My Ph.D. thesis was on minimally invasive early diagnosis and detection of gastrointestinal (colorectal and esophageal) cancers.

3. I joined Northwestern University as an Assistant Professor in 2001. Since 2006, I have served as a full professor. My research is at the convergence of biological, physical sciences, and medicine and focuses on elucidating the function of the human genome and its dysregulation in disease, enabled by the development of new analytical, nanoimaging, and computational genomics technologies that lead to novel methods for regulation of global patterns of gene expression and their clinical translation for disease diagnostics. My research spans

from basic science to new technology development to large-scale multicenter clinical trials. My research has been recognized by numerous awards including being selected as one of the top 100 innovators in the world by the MIT Technology Review Magazine and the Cozzarelli Prize from the National Academy of Sciences. I have served on the editorial boards of seven journals including, most recently, Science Advances. I have also served on more than eighty NIH, NSF, and other grant review panels. I have authored more than 250 peer-reviewed publications.

4. Prior to 2009, I received federal NIH and NSF grants in the amount of \$15,799,078 related to the development of biomarkers and early detection of colorectal cancer (“CRC”). Altogether, I have received 74 NIH, NSF, and other major foundations research grants, most of which focused on cancer research and technology.

5. Starting from my joining Northwestern University as a faculty in 2001, the major thrust of my work has been on CRC screening and understanding its pathophysiology through the development of novel biomarkers. I direct one of the largest National Cancer Institute-funded cancer biomarker development research programs in the country. As an Associated Director of the Robert H. Lurie Comprehensive Cancer Center at Northwestern University, I review the

progress in emerging technologies in cancer screening for clinical translation. As the Director of the Center for Physical Genomics, I lead an interdisciplinary team of faculty leading to new cancer screening methods.

6. Since 2008, I have served as the Program Leader for Cancer and Physical Sciences at the Robert H. Lurie Comprehensive Cancer Center. In this role, I oversee the clinical translation of new cancer technologies, including those for CRC screening.

7. Since 2007, I have been a member of the Steering Committee for the NCI Early Detection Research Network, an NIH body tasked with spearheading, evaluating, and reviewing the discovery, validation, and clinical translation of cancer biomarkers for screening and early detection, focusing on CRC detection and including fecal occult blood tests (“FOBT”) and fecal DNA methylation and mutation analyses.

8. I have directed research on CRC biomarkers since 2001. One of my areas of research expertise is fecal biomarkers for CRC screening, in particular dysregulation of microRNAs in early colon carcinogenesis and their implications for CRC screening. Another closely relevant area of research is the alterations in chromatin architecture in mucus layer fecal colonocytes and their implications for CRC pathophysiology and screening. These projects were launched in 2006 and

were supported by funding from NCI. My laboratory was the first to develop new optical technologies for the assessment of mucosal microvascular alterations in CRC, leading to the discovery of the increased microvascular blood supply in colon carcinogenesis with the initial publication in 2005.

9. Since 2003, my laboratory has been active in the development of new technologies and conducting mechanistic and clinical studies aimed at understanding chromatin, mucosal, microvascular, methylation, and metabolic mechanisms in the field of carcinogenesis, a biological phenomenon underlying several CRC screening techniques and, in particular, colonoscopy.

10. Additional details concerning my background and qualifications are set forth in my curricular vitae, a copy of which is included as Exhibit 2002. My CV includes the publications that I have authored in the last 28 years.

II. SCOPE OF WORK

11. I was asked by counsel for Exact Sciences Corporation (“Exact Sciences”) to review the Petition for *Inter Partes* Review of U.S. Patent 11,970,746 and exhibits thereto, including the ’746 patent itself, the Declaration of Duncan Whitney, Ph.D., and the references cited in the Petition. I have also reviewed the file history of the ’746 patent, the Board’s February 14, 2024 Institution Decision, the transcript of the May 16, 2025 deposition of Dr. Duncan

Whitney, and the materials cited in this declaration. I have also reviewed materials from and submitted declarations in connection with the Petition for *Inter Partes* Review of U.S. Patent 11,634,781 (IPR2024-00459), including the Board's Institution Decision, the transcript of the October 10, 2024 deposition of Dr. Duncan Whitney, and the transcript of the January 9, 2025 deposition of Dr. Duncan Whitney.

12. I am being compensated at my usual consulting rate of \$650 per hour. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

13. I was asked to provide my opinion as to whether the claims of the '746 patent would have been obvious to a person of ordinary skill in the art ("POSA") as of February 3, 2009 (the "Priority Date").

14. In connection with that request, I was also asked to provide my opinion concerning the level of skill of a POSA in the relevant field as of the Priority Date.

15. The statements in this Declaration are based upon my own knowledge and opinion. This Declaration represents only the opinions I have formed to date. I may consider additional documents as they become available. I

reserve the right to revise, supplement, or amend my opinions based on new information and on my continuing analysis.

III. SUMMARY OF OPINION

16. The challenged claims of the '746 patent are not rendered obvious by the Lenhard, Itzkowitz, and Vilkin combination. A POSA at the time would not have been motivated to combine FOBT, particularly the immunochemical FOBT (“iFOBT,” also referred to as “FIT”) of Vilkin with nucleic acid-based testing, particularly not in a method involving collecting and separating fecal sample at home. In fact, Lenhard itself would have discouraged any such combination. A POSA also would not have had a reasonable expectation that combining the iFOBT of Vilkin with nucleic acid-based testing would improve diagnostic performance. Further, even if there had been a motivation to combine the two types of tests for home collection at the time – which there was not – there is no motivation in the art to select the specific elements of the claims from the different references and combine them to arrive at the claimed invention.

17. The challenged claims of the '746 patent are also not rendered obvious by the Shuber and Vilkin combination. As already noted, a person of ordinary skill in the art at the time would not have been motivated to combine the iFOBT of Vilkin with nucleic acid-based testing, and particularly not in a method

involving collecting and separating fecal sample at home. In fact, the references on which Geneoscopy relies would have discouraged any such combination. A POSA also would not have had a reasonable expectation that combining iFOBT, particularly the iFOBT of Vilkin, with nucleic acid-based testing would improve performance. There was also no motivation in the art to select the specific elements of the claims from the different references and combine them to arrive at the claimed invention.

18. For the same reasons that the challenged claims are not rendered obvious by the Shuber and Vilkin combination; they are also not rendered obvious by the Inbar, Shuber, and Vilkin combination.

19. A POSA would not have been motivated to develop a test requiring at-home separation of fecal samples. Even if a POSA had been motivated to develop an at-home collection method for purposes of testing for both nucleic acid and blood protein in stool, the cited references provide no motivation for at-home separation of the sample by the subject. A POSA would have understood that one buffer could have been used to preserve both nucleic acid and blood protein.

20. A POSA would not have been motivated to combine the frozen-sample COX-2 RNA detection of Kanaoka with any of the combinations of Grounds I, III, and VI to arrive at the claimed method of processing freshly-

collected fecal sample without freezing where the sample is collected at home by the human subject. Further, contrary to Petitioner's assertion, the Nechvatal reference does not support a reasonable expectation of successfully combining the COX-2 RNA detection of Kanaoka in an at-home collection process without freezing.

21. Other factors including the commercial success of Exact Sciences' Cologuard® test, the long-felt need that was met by the Cologuard test, the number of failed attempts to develop effective CRC screening tests prior to the Cologuard test, praise for the Cologuard test, and Geneoscopy's copying of the patented technology all further support my opinion that the claims of the '746 patent would not have been obvious to a POSA as of the Priority Date.

22. A POSA 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. Such a person could have been an individual or a member of a team of scientists addressing fecal sample processing and analysis.

IV. LEGAL UNDERSTANDING

23. I am not a lawyer and will not provide any legal opinions. Although I am not a lawyer, I have been advised that certain legal standards are to be applied

by technical experts in forming opinions regarding the meaning and validity of patent claims.

24. I understand that to obtain a patent, a claimed invention must have, as of the priority date, been nonobvious in view of prior art in the field. I understand that an invention is obvious when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a POSA.

25. I understand that to prove that prior art, or a combination of prior art, renders a patent claim obvious, it is necessary to: (1) identify the particular references that singly, or in combination, make the patent claim obvious; (2) specifically identify which elements of the patent claim appear in each of the asserted references; and (3) explain how the prior art references could have been combined to create the inventions claimed in the asserted claim.

26. I understand that a patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.

27. I also understand that a reference may be said to teach away when a POSA, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that

was taken by the applicant. Even if a reference is not found to teach away, I understand its statements regarding preferences are relevant to a finding regarding whether a POSA would be motivated to combine that reference with another reference.

28. I further understand that one of the factual inquiries when determining the obviousness of a patent claim is to consider objective evidence related to the issue of obviousness, sometimes called “secondary considerations of non-obviousness” or “objective indicia of non-obviousness.” I understand that such evidence can often be probative of the issues of obviousness.

29. I understand that examples of objective evidence include (1) commercial success, (2) long-felt but unsolved need, (3) failure of others, (4) industry praise, (5) copying, and (6) skepticism.

30. I understand that there must be a nexus between the patented invention and the evidence of secondary considerations. I further understand that there is a presumption of such a nexus if the claims of the patent are coextensive with a product or products that are the subject of the secondary considerations evidence. I understand that a product is coextensive with the claims when the product is essentially the claimed invention. In other words, to the extent that the product includes unclaimed features, those features are insignificant. I also

understand that if the product is not coextensive with the claims, such that there is no presumption of nexus, nexus can still be shown by establishing that the secondary considerations are the direct result of the unique characteristics of the claimed invention.

V. TECHNOLOGY BACKGROUND

31. CRC remains the second leading cause of cancer deaths in the United States. While colon cancer is eminently curable when diagnosed early, the typical symptoms are generally harbingers of advanced, incurable disease, whereas patients harboring localized malignancies are usually asymptomatic. Asymptomatic population screening is of paramount importance in reducing CRC deaths. Efforts have focused on exploiting biological events in colon carcinogenesis in order to develop modalities that could facilitate more of the population to undergo accurate CRC screening.

32. The adenoma-carcinoma sequence is a well-established paradigm for neoplastic transformation in the colon. *See, e.g., Daniel C. Chung, The Genetic Basis of Colorectal Cancer: Insights Into Critical Pathways of Tumorigenesis*, 119 *Gastroenterology* 854, 854-865 (2000) (Ex. 2010); *see also* Ex. 1004 at 1 (“The majority of CRCs follow the adenoma-carcinoma sequence, requiring a time period of usually more than 10 years.”). The earliest recognizable

morphological lesion is the aberrant crypt foci (ACF). A small fraction of ACF progresses to adenomatous polyps. A fraction of adenomas develops into invasive cancer. Overall, about 10% of adenomas progress into invasive cancer with the rate of progression depending on their size and morphology. Although the vast majority of patients who harbor ACF or diminutive adenomas will never develop carcinomas, advanced adenomas portend a much higher risk of CRC with the annual progression rate close to 2-6%. *See, e.g., Hermann Brenner et al., Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies*, 56(11) *Gut* 1585, 1585-1589 (2007) (Ex. 2011). Screening that detects not only CRC, but also advanced adenomas, provides the potential to prevent CRC and CRC-related deaths. *See, e.g., Sidney J. Winawer and Ann G. Zauber, The Advanced Adenomas as the Primary Target of Screening*, 12(1) *Gastrointestinal Endosc. Clin. N. Am.* 1, 1-9 (2002) (Ex. 2009); *see also* Ex. 1004 at 1 (“Detection of early disease and precancerous adenomatous lesions leads to a decrease in CRC-related mortality.”); Ex. 1012 at 1 (“The diagnosis and the therapy of early-stage tumours have the potential to decrease morbidity and mortality of colorectal cancer patients.”); Ex. 1013 at 4 (“It is the strong opinion of this expert panel that *colon cancer prevention* should be the primary goal of CRC screening.”).

33. As pointed out in the Young article submitted with Geneoscopy's petition, "[a]s the goal of screening for colorectal cancer is to reduce population mortality from and/or morbidity due to colorectal cancer, potential screening tests require a rigorous evaluation that goes beyond what is required for diagnostic tests being used in situations where disease prevalence is high." Ex. 1020 at 1. As that article correctly notes, CRC screening tests are "applied to healthy people where the risk of disease is relatively low." *Id.* A significant difficulty in uptake for such screening tests is for patients to screen as a routine procedure when they are not experiencing any signs of disease. As the Young article summarized, new tests were needed because "there is much room to improve participation rates of those being invited to screen, to improve sensitivity for cancer, to improve sensitivity for adenomas, and to achieve the improved sensitivity without unacceptable deterioration in specificity." *Id.* at 3. Low sensitivity results in disease not being detected, while low specificity results in an unacceptable number of false positives which then lead to unnecessary colonoscopies.

34. By 2009, there were a number of endoscopic, radiological or fecal-based screening modalities available. However, barriers to widespread screening included cost, resource constraints, and patient reluctance. Discomfort from tests in particular meant that the screening rates for CRC were dramatically lower than

for other common malignancies such as breast and prostate cancer. *See, e.g.,* David L. Zack et al., *Colorectal Cancer Screening Compliance by Medicine Residents: Perceived and Actual*, 96(10) Am. J. Gastroenterology 3004, 3004-3008 (2001) (Ex. 2012). The poor screening rate is juxtaposed by the documented effectiveness of CRC screening; a variety of interventions have been proven to prevent CRC occurrence through interdiction of preneoplastic lesions. Thus, there are dire consequences (preventable fatalities) to the inadequate rate of CRC screening.

35. Colonoscopy has been the gold standard of CRC screening since before 2009. The goal of colonoscopy is to identify and remove premalignant adenomatous polyps with the advanced adenoma being the primary target. Identification and removal of adenomatous polyps during colonoscopy effectively prevents CRC in the absolute majority of cases. For this reason, the role of colonoscopy is more than CRC screening but rather CRC screening, risk-stratification, and prevention.

36. Besides screening and prevention benefits, colonoscopy has risk-stratification benefits. In CRC, synchronous and metachronous lesions are frequently found. Accordingly, even after the removal of adenomas during an index colonoscopy, patients are at risk of recurrent (metachronous) lesions and

require follow up. The timing of follow-up depends on the colonoscopy findings.

Patients with no adenomas and no other major risk factors are typically recommended to repeat colonoscopy 10 years after the index colonoscopy.

Patients with small adenomas are typically recommended to repeat colonoscopy in 5 years, and those with advanced or multiple adenomas are recommended to have colonoscopy within 3 years. Patients with major predisposition to CRC, such as those with inflammatory bowel disease (IBD), typically receive colonoscopy once a year or even more frequently.

37. Despite its benefits, colonoscopy has significant drawbacks.

Although the overall risk of complications is low, they are significant given the large number of patients who are recommended to undergo colonoscopy. For example, there is approximately 0.1% risk of perforation requiring surgery. *See, e.g.,* Ex. 1042 at 5; *see also* Ex. 1034 at 12-13.

38. There are also a number of practical barriers related to patient reluctance and cost. For the patient perspective, many patients are reticent to undergo colonoscopy because of discomfort. The colonic purge can cause considerable distress and is often cited as the major reason patients do not undergo colonoscopy. The reluctance to undergo colonoscopy is higher among women, minorities, patients residing in rural areas, and underserved patient populations.

39. There is also a significant financial cost and there are limitations to access. Colonoscopies must be performed at a hospital or other medical facility, requiring the patient to travel and potentially to also take time off from work. *See, e.g.,* Ex. 1034 at 12-13. The societal cost of screening the entire at-risk population with colonoscopy is significant and has been estimated to be in the tens of billions of dollars per year. *See, e.g.,* Amnon Sonnenberg and Fabiola Delcò, *Cost-effectiveness of a Single Colonoscopy in Screening for Colorectal Cancer*, 162(2) Arch Intern Med. 163, 163-168 (2002) (Ex. 2013). And there is also a lack of trained endoscopists. *See, e.g.,* Ex. 1021 at 1; *see also* Ex. 1034 at 13.

40. For all of these reasons, considerably less than half of the eligible population received regular colonoscopic screening before 2009. *See, e.g.,* Ex. 1042 at 2; Ex. 1043 at 1. The prevalence has improved since then, to approximately 59% in 2021, but work remains to be done to capture the entire eligible population. *See, e.g.,* United States Department of Health and Human Services, “Increase the proportion of adults who get screened for colorectal cancer — C-07,” <https://health.gov/healthypeople/objectives-and-data/browse-objectives/cancer/increase-proportion-adults-who-get-screened-colorectal-cancer-c-07> (Ex. 2018). This is juxtaposed by the fact that over 90% of screening colonoscopies are negative for significant neoplasia (advanced adenomas or

carcinomas) making it inefficient to perform colonoscopy on the entire average-risk population.

41. There are two critical aspects of screening tests: diagnostic accuracy (e.g., sensitivity and specificity) for a clinically significant endpoint (e.g., advanced adenomas, early cancer) and uptake (utilization). The number of prevented cases (e.g., cancers), life years saved, etc. are a function of both diagnostic accuracy and uptake. Uptake depends on cost and complexity for both the patient and the provider. A POSA working in the field as of the Priority Date would have sought to balance sensitivity and specificity in a test that could be made widely available, and that would be acceptable to users.

42. The references cited by Petitioner support my opinion concerning the importance of both diagnostic accuracy (as measured by sensitivity and specificity) and uptake (which is informed by factors such as acceptability to patients, simplicity, cost, and ease of implementation). For example, the 2006 Hoepffner reference states that “[A]n ideal screening test must be non-invasive, acceptable to patients, simple, have high sensitivity and specificity, inexpensive, cost-effective, easy to implement across a large population and should be effective in reducing morbidity and mortality from CRC in the screened population.” Ex. 1023 at 146. The 2007 Young reference states that “The most immediate

measurable events when screening will be participation rate, test positivity rate, adenoma detection, downstaging of the detected cancers and, at a later stage, prolonged survival after treatment. Presymptomatic detection of localized cancer will result in a reduction in morbidity and/or mortality. If screening detects preinvasive lesions, namely dysplasia, it will reduce cancer incidence.” Ex. 1020 at 28.

43. Before the introduction of the Cologuard test, CRC screening techniques had varying performance characteristics, costs, and patient acceptability but none was able to provide the much-needed population screening with sufficient diagnostic accuracy, particularly for advanced adenomas. Fecal occult blood test (FOBT) was the most widely used non-invasive test with about 20% prevalence and has been shown to lead to a modest decrease in mortality from CRC. However, the sensitivity and predictive value of FOBT were suboptimal with approximately 10% sensitivity for advanced adenomas. *See, e.g.*, Ex. 1042 at 7-8. In order to improve upon these modest performance characteristics, fecal DNA analysis had been explored, primarily in the experimental setting. However, DNA analysis at the time offered only marginal increase in sensitivity for advanced neoplasia, including advanced adenomas and CRC, to 18.2% offset by increased cost per test. *See id.* Other approaches were

considered and studied, including sigmoidoscopy, virtual colonoscopy (also known computed tomographic colonography or “CTC”), and Imaging Capsule. *See, e.g.,* Peter B. Cotton et al., *Computed Tomographic Colonography (Virtual Colonoscopy): A Multicenter Comparison With Standard Colonoscopy for Detection of Colorectal Neoplasia*, 291(14) JAMA 1713, 1713-1719 (2004) (Ex. 2014); Nathalie Schoofs et al., *PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study*, 38(10) Endoscopy 971, 971-977 (2006) (Ex. 2015).

44. Each of these approaches had limitations, and by 2009, colonoscopy was still the “gold standard” of CRC screening with most other implemented and experimental alternatives not being able to provide sufficient clinical value and patient benefits.

45. This situation remained until the introduction of the Cologuard test by Exact Sciences, which through the combination of fecal DNA analysis and identification of blood proteins in the stool offered excellent sensitivity and specificity for early-stage CRCs and robust sensitivity and excellent specificity for advanced adenomas. For example, Imperiale *et al* reported in an article published in the New England Journal of Medicine in 2014 that the Cologuard test achieved 92.3% sensitivity and 86.6% specificity for CRC. *See Multitarget Stool DNA*

Testing for Colorectal-Cancer Screening, 370(14) N. Eng. J. Med., 1287, 1287-1297 (2014) (“Imperiale 2014”) (Ex. 1077). Imperiale 2014 also reported that the Cologuard test achieved 42.4% sensitivity for detecting advanced precancerous lesions. *Id.* Imperiale 2014 further reported that Cologuard’s rate of detection was 69.2% for polyps with high-grade dysplasia and 42.4% for serrated sessile polyps measuring 1 cm or more. *Id.* In comparison with fecal immunochemical testing (“FIT” or “iFOBT”), Imperiale reported that “As measured by the area under the ROC curve (AUC), the discrimination between colorectal cancer and the combination of nonadvanced neoplasia and lesser findings was significantly higher with DNA testing than with FIT (0.94 vs. 0.89, $P = 0.04$) (Fig. 3A); the AUC values for discrimination between advanced colorectal neoplasia (colorectal cancer plus advanced precancerous lesions) and all other findings were 0.73 and 0.67, respectively ($P < 0.001$) (Fig. 3B).” Ex. 1077 at 8. In other words, the Cologuard test was statistically significantly superior to FIT for both CRC and advanced colorectal neoplasia when compared as a POSA would, by considering the AUC. The Cologuard test had strong uptake by patients and patient accessibility due to its non-invasive nature and lack of complications, thus addressing all major limitations of the other attempts at CRC screening.

VI. OVERVIEW OF THE '746 PATENT

46. As explained in the detailed description of the invention, the invention of the '746 patent "is based upon successful attempts to improve the detection of colorectal cancer. In particular, the invention aims to improve the positive and negative predictive value and also the sensitivity and specificity of detection of colorectal cancer through non-invasive means." Ex. 1001 at 6:50-55. The patent also explains that "[t]he methods of the invention may permit effective detection of colorectal cancer without the requirement for relatively expensive, highly invasive and painful procedures such as digital rectal examination, colonoscopy and sigmoidoscopy to be performed. The invention is based upon a combination of tests for detecting proteins and epigenetic modification markers respectively in the same faecal sample, shown for the first time herein to provide a particularly useful overall test." *Id.* at 6:55-63.

47. The Background of the Invention in the '746 patent is consistent with my experience and the discussion above concerning CRC and CRC screening. Ex. 1001 at 1:41-3:67.

48. Claim 3 of the '746 patent describes a method of processing a freshly-collected fecal sample without freezing, the method comprising (a) home collection of a fecal sample from a human subject; (b) combining a first portion of

the fecal sample with a stabilizing buffer in a sealable vessel, and sealing the vessel; (c) combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins in the fecal sample in a separate sealable container, and sealing the container; (d) obtaining the described first and second portions in the respective containers; (e) extracting nucleic acid from the first portion of the fecal sample; (f) testing the extracted nucleic acid for an amount of human nucleic acid; and (g) testing the second portion of the fecal sample for an amount of blood protein. Ex. 1001 at 45:56-67, 46:56-47:16.

VII. LEVEL OF ORDINARY SKILL IN THE ART

49. I understand that a person of ordinary skill in the relevant art at the time of the invention (also referred to herein as “POSA”) is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity, not an automaton.

50. I have been asked to consider the level of ordinary skill in the field that someone would have had at the time the claimed invention was made. In deciding the level of ordinary skill, I considered the following:

- the education level of the inventor;
- the levels of education and experience of persons working in the field;
- the types of problems encountered in the field;

- prior art solutions to the problems;
- the speed at which innovations are made, and
- the sophistication of the technology.

51. I have reviewed the declaration of Dr. Whitney, including his opinion concerning a POSA. Specifically, Dr. Whitney opines that “a POSA relevant to the ’746 Patent would have a Ph.D. in chemistry, biochemistry, biology, or a related field and at least five years of experience designing and performing diagnostic assays on fecal samples.” Ex. 1002 at ¶ 12. Dr. Whitney does not tie this opinion to the factors that may be considered in determining the level of ordinary skill. *Id.* at ¶¶ 11, 12.

52. I have also reviewed the level of ordinary skill in the field that Geneoscopy included in its request for reexamination U.S. Patent No. 11,634,781, the parent to the ’746 patent, which Geneoscopy attributed to Mr. Anthony Shuber, who submitted a declaration in that proceeding. Ex. 2042 at 6-7. There, Geneoscopy asserted that a person of ordinary skill in the relevant field of the invention of the ’781 patent:

would have had at least a Bachelor of Science degree in Biology (or a similar major) and several years of experience in the processing of biological samples, such as fecal samples from a human. Such a person would have been well-acquainted with methods of collecting fecal samples, preserving proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, and

subsequently evaluating the fecal samples for proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, as of February 3, 2009.

Id. at 7.

53. I note that there is a substantial difference between the two levels proposed by Geneoscopy. I disagree with both of them. To begin, the education level of a Bachelor of Science degree in Mr. Shuber's proposal is less than is typical for individuals of ordinary skill in this field. On the other hand, while I agree with Dr. Whitney that a person of ordinary skill would have a doctoral degree, Dr. Whitney adds an extraordinary requirement of at least five years of experience with the narrow focus of designing and performing diagnostic assays on fecal samples.

54. Based on my knowledge of the field, and knowledge of individuals working in the field at the time, it is my opinion that the appropriate level of ordinary skill is somewhere between Mr. Shuber's opinion and Dr. Whitney's opinion. Specifically, a POSA 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. Further, such a person could have been an individual or a member of a team of scientists addressing fecal sample processing and analysis.

55. I understand that in its Institution Decision as well as in the Institution Decision concerning IPR2024-00459, the Patent Trial and Appeal Board (“Board”) adopted a definition of a POSA consistent with my opinion concerning the level of skill of a POSA for purposes of the Institution Decision; Paper 10 at 8; Ex. 1033 at 8.

56. Whichever of the three levels of skill is used, I satisfy at least the level of skill of a POSA. As of February 2009, I satisfied both Mr. Shuber’s level of ordinary skill as well as my own opinion concerning a person of ordinary skill. As of February 2009, I satisfied Dr. Whitney’s proposed level of ordinary skill with respect to education level, and I also had more than 3 years of experience designing and performing diagnostic assays on fecal samples by that time.

57. No matter which of the three different levels of skill is applied, it does not change my opinion that the claims of the ’746 patent would not have been obvious to a POSA as of the Priority Date.

VIII. OVERVIEW OF THE ART CITED IN THE GROUNDS

A. Lenhard (Ex. 1004)

58. Lenhard is an article from 2005 that focuses on comparison of a single epigenetic marker with guaiac FOBT (“gFOBT”) for purposes of distinguishing between patients with CRCs and those without. *See* Ex. 1004 at 1 (Background & Aims) (“We explored the potential of a single epigenetic marker

in comparison with fecal occult blood testing (FOBT)...”). Lenhard provides few details about sample collection, stating that samples “were collected before cathartic preparation for scheduled surgery or colonoscopy,” and referring to “defecation at the laboratory.” *Id.* at 2.

59. Lenhard does not describe either at home collection or processing freshly-collected samples. Lenhard states that samples “were received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80°C .” Ex. 1004 at 2. The samples “were subjected to FOBT (Beckman Coulter, Fullerton, CA) immediately upon receipt and before freezing.” *Id.* at 4. The frozen samples “were thawed on ice and DNA was isolated” using a commercially available kit according to manufacturer’s instructions. *Id.* at 2.

60. In its comparison of the specific HIC1 methylation marker with a gFOBT test, Lenhard notes the combined results of the two individual tests. Ex. 1004 at 2, 6. Lenhard states that “the combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.” *Id.* at 2, 6.

61. The Beckman Coulter FOBT test used in Lenhard is a gFOBT. GFOBT involves application of a sample to test cards. The sample for such tests would be left to dry, then a drop of peroxide catalyst would be added to the test card. *See* Ex. 1004 at 4. GFOBT does not use sealed sample containers or buffers.

Further, gFOBTs detect the presence of heme, whereas iFOBTs detect hemoglobin protein.

62. Lenhard observes that the combination of the specific “HIC1 methylation analysis” with gFOBT “allowed for the detection of two thirds of CRCs.” Ex. 1004 at 2. Critically, however, there was no increase in the sensitivity for adenomas with the combination. *Id.* at 6. Well before the Priority Date, it was known that advanced adenoma is the most clinically significant endpoint for CRC screening. *See, e.g.*, Ex. 2009 at 1. The Lenhard reference notes that detection of “early disease and precancerous adenomatous lesions leads to a decrease of CRC-related mortality,” which provides a “strong rationale for screening programs.” Ex. 1004 at 1.

63. In Lenhard, “[m]ost patients with CRCs had been referred with a known diagnosis,” with 16 of the 26 CRC patients having symptomatic cases. Ex. 1004 at 2; *see also* Table 1. A POSA would take this into consideration because patients with a known diagnosis are not representative of the screening population. In addition, the “two thirds of CRCs” detected by the specific HIC1 and gFOBT combination discussed in Lenhard were largely late-stage cancers. As shown in Table 1, half of the patients with CRC, 13 of 26, were in stage IV. Ex. 1004 at 2,

Table 1. Of the remaining thirteen patients, seven were in stage III, five in stage II, and only one in stage I. *Id.*

Table 1. Clinicopathologic Data and HIC1 Methylation Status of Patients With CRC

No.	Sex	Age (y)	UICC stage	Localization	Symptoms ^a	HIC1 methylation	FOBT
1	M	71	IV	Sigmoid colon/rectum	1	—	—
2	F	75	III	Sigmoid colon	1,3	—	—
3	M	66	IV	Descending/sigmoid colon	0	—	—
4	M	69	II	Ascending colon	0	+	—
5	M	65	III	Transverse colon	0	+	+
6	M	56	IV	Rectum	1	+	—
7	M	63	IV	Ascending colon	2	—	—
8	F	72	III	Cecum	2	+	+
9	M	74	III	Sigmoid colon/rectum	0	—	+
10	M	68	IV	Rectum	3	+	+
11	M	66	IV	Rectum	1	—	+
12	M	75	III	Cecum	0	—	—
13	M	71	IV	Sigmoid colon	0	+	—
14	M	67	II	Hepatic flexure	3	+	—
15	F	72	IV	Sigmoid colon	1,2	+	—
16	M	59	II	Rectum	0	+	—
17	M	59	II	Rectum	0	—	+
18	M	53	III	Descending colon	0	—	—
19	F	55	IV	Rectum	2	—	+
20	F	61	IV	Sigmoid colon	2,3	—	—
21	M	61	IV	Rectum	0	—	—
22	M	80	II	Transverse colon	2	+	—
23	F	53	IV	Ascending colon	1,3	—	—
24	M	63	I	Cecum	4	NA	+
25	M	76	III	Transverse colon	2	—	+
26	F	60	IV	Ascending colon	1	+	—

UICC, International Union Against Cancer; M, male; F, female; NA, no amplification.

^a0, no symptoms; 1, change in bowel habits; 2, blood admixed with stool; 3, abdominal pain; 4, anemia.

Ex. 1004 at 2 (Table 1). The combined results from HIC1 and gFOBT in Lenhard showed relatively poor sensitivity of only 65% of CRCs that were predominantly late-stage. *Id.*

64. Lenhard states that the “combination of both assays resulted in increased detection rates for CRCs (65%; 95%CI, 44%-83%).” Ex. 1004 at 6. Notably, Lenhard does not state that there was a “significant” increase in sensitivity. *Id.* Lenhard also does not provide any probability (“p”) value when stating that the combination resulted in “increased detection rates for CRCs.” *Id.* The data reported in Lenhard’s Table 4 on its face raises questions about whether

there is any significant difference between HIC1 and the combined HIC1 and gFOBT results reported in Lenhard.

Table 4. Positivity Rates of the Fecal DNA Assay, FOBT, and Combination of the Tests

	HIC1		FOBT		Combined	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
All cancers	11/26 (42)	23%–63%	9/26 (35)	17%–56%	17/26 (65)	44%–83%
Localized cancers	4/6 (67)	22%–96%	2/6 (33)	4%–77%	6/6 (100)	12%–188% ^a
Advanced cancers	5/20 (25)	9%–49%	7/20 (35)	15%–59%	11/20 (55)	32%–77%
Rectum and sigmoid colon	5/13 (39)	14%–68%	5/13 (39)	14%–68%	9/13 (69)	39%–91%
From descending colon to cecum	6/13 (46)	19%–75%	4/13 (31)	14%–68%	8/13 (62)	39%–91%
Asymptomatic cases	4/10 (40)	12%–74%	3/10 (30)	7%–65%	6/10 (60)	26%–88%
Symptomatic cases	7/16 (44)	20%–70%	6/16 (38)	15%–65%	11/16 (69)	41%–89%
Adenomas	4/13 (31)	9%–61%	1/13 (8)	.2%–36%	4/13 (31)	9%–61%

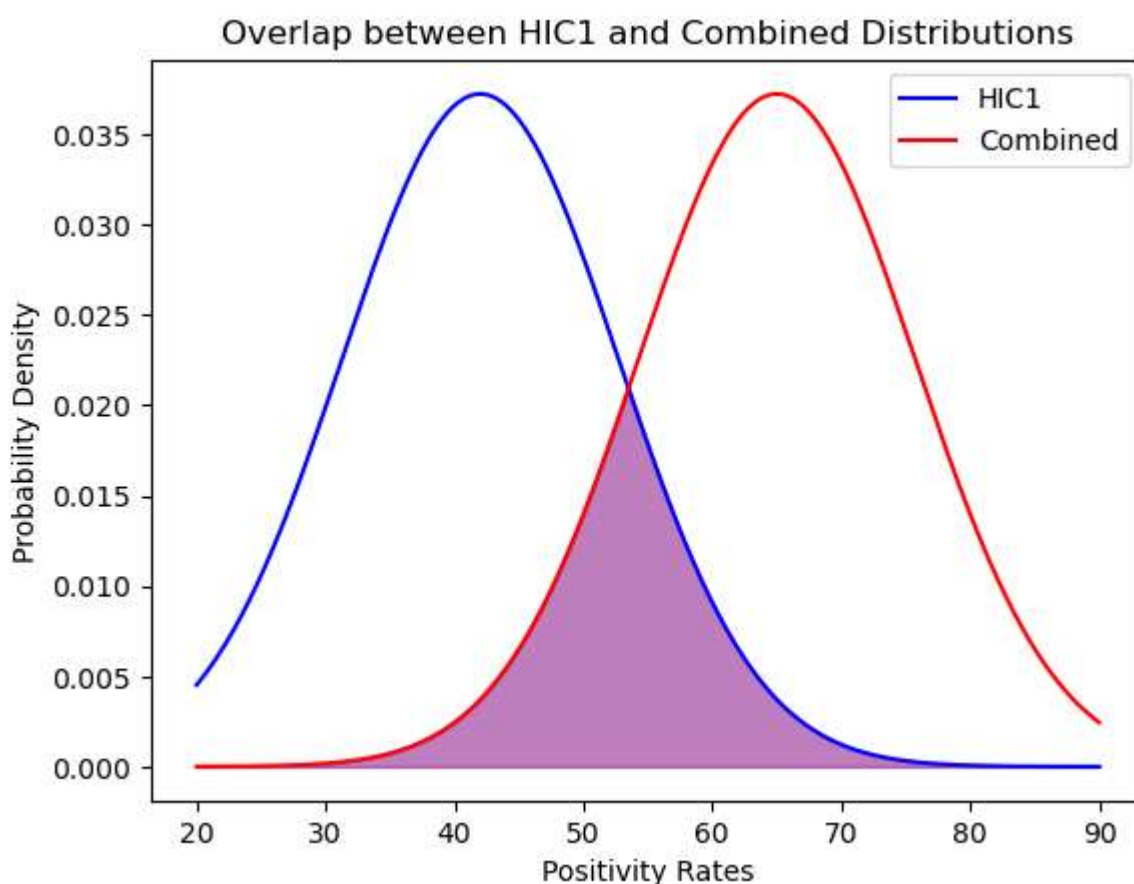
^aEstimated by normal approximation of Poisson distribution.

Calculations based on the data in Table 4 reveal that the results are not statistically significantly different.

65. A POSA in 2009 would not have merely relied on a statement that a combination allowed for detection of “two-thirds of CRCs” or that it “increased detection rates for CRCs” without considering the reported data. One important question that a POSA would consider is whether the findings are statistically significant.

66. In the “n (%)” column, Table 4 shows that the sensitivity for all CRC of HIC1 and the combination of HIC1 and gFOBT as 42% and 65%, respectively. Table 4 also provides 95% confidence intervals (CI). 95% CI indicates that given the statistical distribution of the data, there is 95% chance that the “true” sensitivity of HIC1 for all CRCs should fall between 23% and 63%, and there is

5% probability that the sensitivity would be outside of this range. For the combined results of HIC1 and gFOBT, there is 95% chance that sensitivity would fall between 44% and 83%. The more separated the confidence intervals are, the more confidence one has that the reported estimates of sensitivity are close to their true values. The confidence intervals for HIC1 and the combined results of HIC1 and gFOBT shown in Table 4 of Lenhard overlap as illustrated below:



This data shows that it is possible that the real sensitivity of HIC1 with gFOBT could be lower than that of HIC1 alone.

67. In biostatistics, it is a conventional practice to evaluate statistical significance of data based on p-value. However, as I noted above, although Lenhard reports p-values for certain data, Lenhard does not provide a p-value with respect to the relative sensitivities of HIC1 alone, gFOBT alone, and the combination of HIC1 and gFOBT. To determine a p-value, the corresponding null-hypothesis is that HIC1 and the combined biomarkers have the same sensitivity. P-value is the probability of obtaining the test result (i.e., the sensitivity values) at least as extreme as the result actually observed, under the assumption that the null hypothesis is correct. In other words, P-value is the probability of that an observed effect (e.g., the combined biomarker has higher sensitivity compared to an individual biomarker) is due to random chance when the null hypothesis (e.g., the combined biomarker is not more sensitive than the individual biomarker) is true. Because for a normal distribution, the standard deviation is $(\text{upper 95\% CI} - \text{mean})/1.96$, we can use the Table 4 data to calculate the probability of the sensitivity of the combined marker being the same as that of HIC1 alone and the p-value. This results in $p\text{-value} = 0.13$.

68. By widely accepted convention, a result is said to be statistically significant if the $p\text{-value} < 0.05$, which is considered a loose criterion, or $p\text{-value} < 0.01$, which is a more strict criterion. P-values below 0.1 and higher than 0.05

are considered “marginally significant,” and most observers would not accept a result with $p\text{-value} > 0.05$. The $p\text{-value}$ of 0.13 is not statistically significant according to the conventional definition. Based on this $p\text{-value}$, a POSA would not consider a claim of increased sensitivity for all CRCs for the combination of HIC1 and gFOBT as compared to HIC1 sufficiently substantiated.

69. Moreover, looking at asymptomatic cases only (the cohort that better approximates the clinical scenario as screening is typically intended primarily for asymptomatic individuals), the $p\text{-value} = 0.41$. Based on this $p\text{-value}$, a POSA would not expect a combination of HIC1 and gFOBT to be significantly more sensitive than HIC1 alone. Although Petitioner focuses on statements that the combination of HIC1 and gFOBT allowed for detection of “two-thirds of CRCs,” (Pet. at 8, 14, 21, 49), a more appropriate statement would be that the combined results did not detect enough cancers for the numerically higher sensitivity of the combination to be considered significant.

70. Lenhard also notably does not report or compare the AUC for any of the test results. The data reported in Lenhard show that sensitivity and specificity of HIC1 alone for advanced adenomas are 31% and 98%, respectively. The expected area under the receiver operating characteristic (ROC) curve (AUC, also known as the c-statistic, widely considered as one of the most critical measures of

the diagnostic performance of a biomarker) of HIC1 alone for advanced adenomas is 0.71. The combination of HIC1 with gFOBT would result in a range of sensitivity and specificity values, depending on the cut off points. Based on the data in Lenhard, if this particular combination is optimized for sensitivity, the result is that sensitivity and specificity for advanced adenomas are 31% and 89%, respectively. Here, the sensitivity of the combined test is the same as that of HIC1 alone. At the same time, the specificity is considerably lower. On the other hand, if the combined test is optimized for specificity, the result is sensitivity = 8% and specificity = 98%. This reflects a major drop in sensitivity with no tangible increase in specificity. The expected AUC of the combined test is 0.64, a drop from 0.71 for HIC1 alone. Based on these data, a POSA would conclude that HIC1 should not be combined with gFOBT.

71. That the combined results from HIC1 methylation testing and gFOBT showed no increase in sensitivity for adenomas is also shown in simple form in Table 2. Table 2 of Lenhard reports results for thirteen patients with advanced adenomas. Ex. 1004 at 3 (Table 2). Only four of the thirteen were detected by the HIC1 methylation marker, and only one – one that was also detected by the HIC1 methylation marker – was detected by gFOBT.

Table 2. Clinicopathologic Data and HIC1 Methylation Status of Patients With Adenomatous Polyps

No.	Sex	Age (y)	Diagnosis	HIC1 methylation	FOBT
27	M	72	Tubular adenoma, ascending colon, 3 cm	+	—
28	F	63	Tubulovillous adenoma, ascending colon, hepatic flexure, sigmoid colon, 1–1.5 cm	—	—
29	M	63	Tubulovillous adenoma, ascending colon, 2 cm	—	—
30	M	76	Tubulovillous adenoma, ascending and transverse colon, 1, 3, 4 cm	+	+
31	M	83	Tubulovillous adenoma, transverse colon, 3 cm	—	—
32	F	65	Tubulovillous adenoma, sigmoid colon, 1.5 cm	—	—
33	M	72	Tubulovillous adenoma, ascending colon, 1 cm	—	—
34	F	60	Tubular adenoma, sigmoid colon, 1.5 cm	—	—
35	M	69	Tubular adenoma, 1.5 cm, ascending colon	—	—
36	M	70	Tubulovillous adenoma, sigmoid colon, 1 cm	—	—
37	M	64	Tubulovillous adenoma, rectum, 1 cm	—	—
38	M	72	Adenoma, cecum, 2 cm	+	—
39	F	63	Tubulovillous adenoma, sigmoid colon, 2 cm	+	—

M, male; F, female.

Ex. 1004, Table 2 (highlighting added). The importance of these results to a POSA is highlighted by Lenhard’s observation that the specific combination of HIC1 and gFOBT showed “no increase in the sensitivity for adenoma.” *Id.* at 6. It is also worth noting that the patients with adenomatous polyps discussed in Lenhard had particularly large polyps, all a centimeter or more. *Id.* at Table 2. Further, the only advanced adenomas detected by the HIC1 methylation marker were 2 centimeters or larger (*id.*) which a POSA would recognize were rare.

72. Lenhard’s teachings are also consistent with my opinion that a POSA would not consider effects on sensitivity without also considering any effects on specificity. Lenhard repeatedly states that markers must have **both** high sensitivity and specificity. *See, e.g.,* Ex. 1004 at 1, Background & Aims (“markers with high sensitivity and good specificity are needed”), 2 (“identification of both sensitive and highly specific methylation markers is required ...”), 6 (“Highly sensitive,

specific, and easily analyzable markers are required for noninvasive stool-based CRC screening.”), 7 (“methylation markers as well as genetic markers need to be selected carefully to achieve both high sensitivity and specificity.”). Lenhard further explains that “low specificity of a test results in a low positive predictive value” and “in high rates of unnecessarily performed colonoscopies.” *Id.* at 7. Notably, the increased sensitivity on which Petitioner relies came with a reduction in specificity. *See id.* at Table 3 (showing additional false positives for control subjects 40, 47, 82 and 84 from FOBT testing).

73. The data in Lenhard also show that sensitivity and specificity of HIC1 alone for cancers are 44% and 98%, respectively. The expected area under the receiver operating characteristic (AUC) of HIC1 alone for cancers is 0.80. The combination of HIC1 with gFOBT would result in a range of sensitivity and specificity values, depending on the cut off points. Based on the data in Lenhard, if this particular combination is optimized for sensitivity, the result is that sensitivity and specificity for cancers are 65% and 89%, respectively. Here, although the sensitivity of the combined test is numerically higher, the specificity is considerably lower. On the other hand, if the combined test is optimized for specificity, the result is sensitivity = 12% and specificity = 98%. This reflects a major drop in sensitivity with no tangible increase in specificity. The expected

AUC of the combined test is 0.76, a drop from 0.80 for HIC1 alone. These data would also cause a POSA to conclude that HIC1 should ***not*** be combined with gFOBT. This is consistent with the conclusion in Lenhard.

74. A POSA in 2009 seeking to improve CRC screening tests and having knowledge of Lenhard would have considered whether the results were statistically significant as well as whether the reported combined results showed overall improved test performance. For the reasons described in detail above, a POSA in 2009 seeking to improve non-invasive CRC-screening and considering Lenhard would not have expected improved performance from a test combining nucleic acid testing and FOBT.

75. Table 3 of Lenhard provides a simple illustration of the increase in number of false positives, which, stated differently is a decrease in specificity.

Table 3. HIC1 Methylation Status of Healthy Controls and Patients With Nonneoplastic Disease

No.	Sex	Age	Diagnosis	HIC1 methylation	FOBT
40	F	61	Normal	—	+
41	F	61	Normal	—	—
42	F	73	Normal	—	—
43	M	63	Normal	—	—
44	M	47	Normal	—	—
45	F	41	Normal	—	—
46	M	53	Normal	—	—
47	F	59	Normal	—	+
48	F	73	Normal	—	—
49	M	36	Normal	—	—
50	M	71	Normal	—	—
51	F	65	Normal	—	—
52	F	60	Normal	—	—
53	F	66	Normal	—	—
54	M	80	Normal	—	—
55	M	70	Normal	—	—
56	F	27	Normal	—	—
57	F	57	Normal	—	—
58	M	55	Normal	—	ND
59	M	23	Normal	—	—
60	F	73	Normal	—	—
61	F	79	Normal	—	—
62	M	68	Normal	—	—
63	F	78	Normal	—	—
64	F	38	Normal	—	—
65	F	62	Normal	—	—
66	M	76	Normal	—	—
67	F	61	Normal	—	—
68	M	23	Normal	NA	—
69	M	74	Normal	—	—
70	M	60	Normal	—	—
71	F	49	Normal	—	—
72	M	59	Hyperplastic polyp	—	—
73	F	66	Hyperplastic polyp	—	—
74	F	67	Hyperplastic polyp	—	—
75	F	65	Hyperplastic polyp	—	—
76	F	58	Hyperplastic polyp	NA	—
77	F	76	Hyperplastic polyp	—	—
78	F	54	Hyperplastic polyp	—	—
79	F	76	Hyperplastic polyp	—	—
80	F	60	Hyperplastic polyp	—	—
81	M	47	Ulcerative colitis	+	+
82	M	64	Ulcerative colitis	—	+
83	M	27	Ulcerative colitis	—	—
84	M	67	Ulcerative colitis	—	+
85	M	53	Ulcerative colitis	—	—
86	M	51	Ulcerative colitis	—	—
87	F	44	Crohn's disease	—	—
88	M	30	Crohn's disease	—	—
89	M	37	Crohn's disease	—	—

F, female; M, male; ND, not determined; NA, no amplification.

76. Ex. 1004 at 4 (Table 3) (highlighting added). As shown in Table 3, there was only one false positive with HIC1 methylation testing, subject number 81. That test was also a false positive using gFOBT. *Id.* Subject numbers 40, 47, 82, and 84 were also false positives with the gFOBT test. *Id.* Using the data in Table 3 data to calculate the probability of the specificity of the combined HIC1

and gFOBT markers being the same as that of HIC1 alone results in p-value = 0.12. This is also not statistically significant.

77. A POSA considering Lenhard and its statement that the specific combination of HIC1 and gFOBT “allowed for detection of two thirds of cancers,” would also consider 65% sensitivity in the context of the sensitivity of other markers. For example, Lenhard discusses other methylation markers found in stool, including SFRP2, which detected 77%–90% of CRCs – more than the 65% detected by HIC1 methylation analysis combined with gFOBT. Ex. 1004 at 2. Lenhard noted, however, that the specificity of SFRP2 methylation was quite poor at 77%. *Id.*

78. Lenhard concludes “combination of HIC1 *with a few additional sensitive and specific methylation markers* may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas. Evaluation of other genes known to be methylated in CRC such as hMLH154 and HPP... identification of other useful methylation markers, prospective screening studies, as well as further simplifications and automatization of the assays used, clearly are indicated.” Ex. 1004 at 7. In other words, Lenhard had the data that they could have used to conclude that FOBT should be used together with HIC1 if the data supported that as an approach. However, the data does not support the combination, and their

conclusion was that the most promising route is to search for other methylation markers and combine them with HIC1. They did not conclude that HIC1 should be combined with FOBT. Lenhard's conclusion is consistent with the direction of the art at the time. A POSA at the time would have expected that, by using different methylation markers, some markers would identify indicia of CRC that other markers would not, thus improving test sensitivity without negatively affecting specificity.

79. A POSA in 2009 would have considered the entire Lenhard reference, including (1) the advanced stage of the known CRC patients tested in Lenhard, and the fact that the combined HIC1 and FOBT results failed to identify 1/3 of those cancers; (2) the lack of any improvement in detecting adenomas; (3) that the improved sensitivity adversely affected specificity; (4) the fact that certain methylation markers were already known to have higher sensitivity than the specific combination of HIC1 and gFOBT; (5) that the difference between the results was not statistically significant; and (6) Lenhard's own conclusions concerning a potential path forward combining "sensitive and specific methylation markers." After reading Lenhard, a POSA would conclude that there was no synergy between HIC1 and FOBT tests. In fact, a POSA would expect a drop in performance of a combination of HIC1 and gFOBT tests and would not see

rationale for combining nucleic acid-based tests with gFOBT, particularly where such a combination would create a more costly and more complex test.

B. Vilkin (Ex. 1005)

80. Vilkin is an article from 2005 that concerns assessing the performance of a specific desktop iFOBT screening test and that compared that specific test to gFOBTs. Ex. 1005. As Vilkin notes, the “standard guaiac fecal occult blood test (G-FOBT) is faulted for its low sensitivity.” *Id.* at 3. Vilkin determined that the specific desktop iFOBT being tested “demonstrated a “high sensitivity of 76.5% for all colorectal neoplasia and acceptable specificity of 95.3%.” *Id.* at 7.

81. Vilkin reported both sensitivity and specificity at differing hemoglobin levels. *Id.* at 7, Table 2. The tested population in Vilkin was “ambulatory persons who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high risk for CRC and invited for colonoscopy.” *Id.* at 4. In the group of “high-risk and symptomatic patients” at issue in Vilkin, “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 at this round of screening.” *Id.* at 8.

82. Vilkin required that the subject prepare three consecutive daily samples. *Id.* at 3 (Methods), 4. Vilkin states that the “best results were obtained when all three tests were performed and utilized for the analysis.” *Id.* at 6. Table 3 of Vilkin reveals a wide range of sensitivities between the three different sample sets and reports results based on the combination of the three samples per subject.

Table 3. Sensitivity for Significant Colorectal Neoplasia (N = 34)*
for Each I-FOBT† Prepared

I-FOBT Positive	Cancer (%)	Cancer + AAP (%)
Sample 1	83.3	52.9
Sample 2	66.7	52.9
Sample 3	100	61.8
Samples 1 and 2	83.3	64.7
Samples 1, 2, and 3	100	76.5

*Six colorectal cancers (CRC) and 28 advanced adenomatous polyps (AAP).

†At the 100 ng Hb/mL threshold.

The Vilkin authors stated that they would continue with three annual fecal tests, as they had “confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” *Id.* at 8.

83. Vilkin required that samples are “kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.” Ex. 1005 at 4. Vilkin discloses the decay per day for samples stored at different temperatures, specifically $0.3\% \pm 0.4$ at 4°C (NS), $2.2\% \pm 1.7$ at 20°C (NS), and $3.7\% \pm 1.8$ at 28°C ($p < 0.05$). Ex. 1005 at 3 (Results). Figure 2

shows substantial decay in hemoglobin after one week's storage at room temperature. *Id.* Fig. 2. Vilkin concludes that “[r]e~~frigerated~~ OC-Sensor samples are stable for 21 days. *Id.* at 3 (Conclusions) (emphasis added). Vilkin also states that “storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability.” *Id.* at 8. Although Vilkin refers to an “Hb stabilizing buffer,” Vilkin does not identify the components of the “Hb stabilizing buffer, and teaches that refrigeration was required to prevent decay.

84. Vilkin also states that providing double zip-lock bags with the tests “answered some of the screeners’ hesitancy about keeping the prepared test transiently in their home refrigerator.” Ex. 1005 at 8.

85. Vilkin states that “[a]t present, we will continue with collecting three annual fecal tests, as we have confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” Ex. 1005 at 8. Vilkin notes that “[t]his is in contrast to the annual 2-day, average-risk population I-FOBT collection, as routinely used in Japan, United States, and Australia, and 1-day biennial testing as performed in Italy.” *Id.*

86. Vilkin concluded “we have found this desktop, automated-developed and quantified Hb version of the immunochemical fecal occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with

an acceptable specificity and consequent high negative predicative value.” Ex. 1005 at 8. In the discussion, Vilkin states that the “clinical evaluation demonstrated a high sensitivity of 76.5% for all significant colorectal neoplasia and acceptable specificity of 95.3%.” Ex. 1005 at 7. The results reported in Table 3 show that the “high sensitivity of 76.5%” reflects the combined results of Samples 1, 2, and 3. *Id.* Table 3.

87. After reading Vilkin, a POSA would conclude that the specific iFOBT and methodology described in Vilkin showed acceptable levels of sensitivity and specificity, and that the results from testing that specific desktop iFOBT were superior to results from standard gFOBT. A POSA would be familiar with iFOBT and gFOBT more generally and would understand that the results disclosed in Vilkin were an outlier. Among other things, a POSA would understand that the results disclosed in Vilkin were based on annual collection and testing of three consecutive daily samples from each patient and that the samples were refrigerated.

C. Itzkowitz (Ex. 1006)

88. Itzkowitz describes testing a specific DNA onlybased screening test for CRC, in particular, Exact Sciences’ version 2 fecal DNA test for CRC. Ex. 1006 at 1. Itzkowitz also discusses improved sensitivity in version 1 of the Exact

Sciences DNA-based screening panel, noting that “sensitivity for the version 1 marker panel is increased from 52% to 72.5%. This improvement was a direct result of an increase in DIA (DNA integrity assay) sensitivity from 3% to 65%, confirming the observation of Olson et al.” *Id.* at 6. Itzkowitz cites to Olson, but Itzkowitz itself does not disclose the components of any buffer use for “stabilizing DNA during specimen transport.” *Id.*

89. With respect to the version 2 panel, Itzkowitz observed that, “[t]he combination of vimentin plus DIA-DY resulted in an optimal sensitivity of 85.5% (95% CI, 73.9%-94.5%). This optimal combination detected most cancers, including early stage (stage I) lesions, regardless of their location in the colon.” Ex. 1006 at 6. Itzkowitz concludes that the “results suggest that with only 2 markers (vimentin + DY) providing a sensitivity of 88%, the assay complexity can be reduced significantly, thereby decreasing cost and facilitating the development of an assay kit that could be managed by local clinical laboratories.” *Id.* at 7; *see also id.* at 1 (Conclusions) (“An improved fecal DNA test that incorporates only 2 markers shows much higher sensitivity for CRC. The new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening.”).

90. Itzkowitz recognized the ongoing need for “availability of a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction” to increase participation in CRC screening. Ex. 1006 at 5. Itzkowitz also states that “[i]nherent in the success of any screening test is patient acceptance. Our preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirms a very high degree of patient satisfaction.” *Id.* at 6-7. “These findings support results from the previous multicenter study in which subjects preferred fecal DNA testing to both the fecal occult blood test and colonoscopy.” *Id.* at 7. Itzkowitz cites to Schroy PC 3rd, Heeren TC, *Patient perceptions of stool-based DNA testing for colorectal cancer screening*, 28(2) Am J. Prev. Med. 208, 208-214 (2005) in support of its statement concerning the previous multicenter study.

91. Itzkowitz emphasizes the importance of reducing both complexity and cost in connection with non-invasive CRC screening. For example, Itzkowitz states in the Conclusions in the abstract that “[a]n improved fecal DNA test that incorporates only 2 markers shows much higher sensitivity for CRC. The new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening.” Ex. 1006 at 1. The concluding paragraph of Itzkowitz states “[o]ur results suggest that with only 2 markers (vimentin+DY)

providing a sensitivity of 88%, the assay complexity can be reduced significantly, thereby decreasing cost and facilitating the development of an assay kit that would be managed by local clinical laboratories.” *Id.* at 7.

92. Itzkowitz does not include any data concerning adenomas. However, Itzkowitz recognizes that a POSA would also want to know how well a screening test detected advanced adenomas, stating in the final sentence of the concluding paragraph that “[h]ow well the new fecal DNA assay might perform for detecting adenomas is not yet known, but will be the subject of future investigations.” Ex. 1006 at 7.

93. Itzkowitz refers to gFOBT tests as a point of comparison, noting that “[f]ecal DNA testing has shown greater sensitivity than guaiac-based occult blood tests” for non-invasive CRC screening. Ex. 1006. at 1. Itzkowitz does not suggest combination of FOBT with nucleic acid testing. *See generally id.*

94. Itzkowitz concludes that “[a]n improved fecal DNA test that incorporates only 2 markers shows much higher sensitivity for CRC. The new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening.” Ex. 1006 at 1.

95. After reading Itzkowitz, a POSA would conclude that DNA-based screening could potentially be improved based on selection and combination of

specific DNA markers. A POSA reading Itzkowitz would also understand that subjects at the time preferred fecal DNA testing to FOBTs.

D. Kanaoka (Ex. 1007)

96. Geneoscopy relies on Kanaoka in connection with certain dependent claims for its disclosure of testing stool sample for the presence of COX-2 RNA. Pet. at 12, 16. Kanaoka describes a “method of detecting a tumor marker for diagnosing colon cancer which comprises collecting biological sample which is immediately frozen using liquid nitrogen in some cases.” Ex. 1007 at Abstract. The object of Kanaoka was to “provide a non-invasive and convenient tumor marker detection method for diagnosing colon cancer, which is superior in sensitivity and specificity to the existing fecal occult blood test.” *Id.* at [0015]. Kanaoka also provides results from FOBT, in this case an iFOBT, “for comparison and reference.” Ex. 1007 at [0057].

97. In the “Background of the Invention,” Kanaoka identifies “an alternative method to the fecal occult blood test” in particular “a method for detecting mRNA of protein kinase C (PKC) or the like” in feces. Ex. 1007 at [0008]. Kanaoka states that this method using RNA “could not have the sensitivity exceeding that of the fecal occult blood test method, because it was impossible to extract RNA easily and efficiently from a small amount of feces.”

Id. at [0009]. Kanaoka also states that “RNA is more unstable compared with DNA and is always subjected to a danger of decomposition by RNA digesting enzymes (RNases) which are ubiquitous in all the biological samples and very stable...” *Id.* at [00011].

98. Example 1 of Kanaoka discloses that the tested COX-2 RNA marker had 90% sensitivity with 100% specificity, while the comparison iFOBT test had 82.1% sensitivity with 86.3% specificity. *Id.* at [0065]-[0066].

99. Example 1 of Kanaoka describes a study involving 30 cases confirmed to have colon cancer and 22 cases having no indication of colon cancer. Ex. 1007 at [0056]. In Example 1, “[a]s soon as possible after sampling feces, the feces were separated into 5 ml tubes about 1 g each, were frozen using liquid nitrogen, and were stored at –80° C.” Ex. 1007 at [0057]. This methodology is consistent with the statement in the abstract that the application intends to provide “a method of detecting a tumor marker for diagnosing colon cancer which comprises collecting biological sample which is immediately frozen using liquid nitrogen in some cases.” *Id.* (Abstract). Kanaoka does not describe any method of preserving RNA in the fecal samples other than freezing. *See generally Id.*

100. From the limited sample size in Kanaoka, COX-2 RNA was detected in 27 of the 30 known cancer cases. *Id.* at [0065]. COX-2 RNA was not detected

in any of the 22 cases in the control group. In other words, COX-2 RNA alone had 90% sensitivity with 100% specificity. *Id.* For the iFOBT test, “23 among 28 colon cancer cases” were positive, and 3 of the 22 control group cases were false-positive. *Id.* at [0066]. Where the iFOBT test also had three false positives among the control cases (specificity 86.3%), the COX-2 RNA test had no false positives in the control cases (specificity 100%). *Id.* at [0066], [0065].

101. Kanaoka observes that “[a]mong three COX-2 negative colon cancer cases, one was positive in the immunochemical fecal occult blood test, and two were negative,” and that “COX-2 was detected in 3 among 5 colon cancer cases negative to the immunochemical fecal occult blood test.” Ex. 1007 at [0067], [0068].

102. The data in Example 1 of Kanaoka show that sensitivity and specificity for colon cancer of COX-2 RNA alone are 90% and 100%, respectively. The expected AUC based on the values of sensitivity and specificity is 0.98. The combination with FOBT would result in a range of sensitivity and specificity values, depending on the cut off points. If the combined test is optimized for sensitivity, the result is sensitivity = 93% and specificity = 86%. Although the sensitivity of the combined test is slightly higher, the specificity is considerably lower. If the combined test is optimized for specificity, the result is

sensitivity = 79% and specificity = 100%. Thus, there is a major drop in sensitivity with no increase in specificity. The expected AUC of the combined test is 0.94, a drop from 0.98 for COX-2 RNA alone. Thus, overall performance of the combined test was worse than COX-2 RNA alone. Based on these data, a POSA would conclude that COX-2 RNA should **not** be combined with FOBT.

103. Looking at the data for the limited sample size in Kanaoka, the increase in sensitivity was not statistically significant. In addition, overall performance declines when the COX-2 RNA and iFOBT sensitivity and specificity are considered together. The following confidence interval (CI) estimates were calculated using the Wilson Score Interval method, a standard method of estimating intervals for proportions:

	Sensitivity	Specificity	AUC	95% CI for sensitivity	p-value for improvement in sensitivity
COX2	25/28=89%	22/22=100%	0.946	73% – 96%	0.68
COX2+iFOBT	26/28=93%	19/22=86%	0.896	77% - 98%	

The one additional true positive test if one adds the iFOBT results to the COX-2 RNA results is an increase in sensitivity from 89% to 93%. This is not statistically significant with p-value = 0.68. In addition, the AUC, calculated for the COX2+iFOBT combination designed to increase sensitivity, is lower than the AUC for COX2 RNA alone, a drop from 0.946 to 0.896 due to the insignificant

increase in sensitivity and the more substantial decrease in specificity, although the decrease in specificity is not statistically significant.

104. I also note that the Kanaoka patent application does not conclude that COX-2 RNA should be combined with FOBT.

105. After reading Kanaoka, a POSA would conclude that there was no synergy between COX-2 RNA and FOBT tests. In fact, a POSA would expect a drop in performance with a combination of COX-2 RNA and FOBT tests and would not see a rationale for the combination as there would be no expectation of improved diagnostic performance.

E. Shuber (Ex. 1008)

106. Shuber is an international patent application assigned to Exact Sciences. *See* Ex. 1008. Like Itzkowitz, Shuber describes certain of Exact Sciences' earlier work concerning nucleic acid-based CRC screening.

107. Shuber discloses a method for stabilizing nucleic acids in biological samples, including stool samples, to facilitate analysis in a nucleic acid integrity assay. Ex. 1008 at 2:5-10. Shuber discusses a "stabilization solution." *E.g.*, Ex. 1008 at 3:8-16. Shuber states that "[w]hen the patient sample is a stool sample, and the stabilization solution is 10 mM Tris-Cl, 1 mM EDTA, and 150 mM NaCL, a suitable ratio of stabilization solution to patient sample is 7 ml/gm." *Id.*

at 3:14-16. Shuber provides ranges for the buffer, chelating agent, and salt in the stabilization solution. *Id.* at 3:25-33. For example, the buffer could be 0.5 mM to 25 mM Tris; the chelating agent could be 0.01 to 2.5 mM EDTA; and the salt could be 75 mM to 225 mM NaCl, although other buffers, chelating agents, and salts could be used. *Id.* Shuber further states that in some embodiments the stabilization solution “is provided at pH 7.0 to 9.0, e.g., pH 7.5 to 8.5, or pH 8.0. However, higher or lower pHs may be used.” *Id.* at 4:1-2.

108. Geneoscopy refers to the disclosure in Shuber that states that the method described in Shuber 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 indicia of adenoma or early stage cancer (e.g., using a DNA integrity assay, a multiple mutation assay, a hypermethylation assay, or any combination thereof.”). Pet. at 17, *citing* Ex. 1008 at 28:18-27. Geneoscopy asserts that this “describes the possibility of using multiple tests in combination to improve the test’s sensitivity for detection of CRC.” Pet. at 17. Each of the tests identified in the cited portion of Shuber is a nucleic acid-based test. Shuber does not disclose or suggest combination of FOBT with nucleic acid testing.

109. Shuber acknowledges that “detecting adenomas is particularly useful for identifying early signs or risks of colorectal cancer (e.g., cancerous and

precancerous lesions or growths in the colon).” Ex. 1008 at 13:7-8. According to Shuber, testing for various combinations of mutations could detect adenomas with 60%, 74%, 90% and even “greater than 95% sensitivity (e.g., greater than 98% sensitivity.)” *Id.* at 14:1-16.

110. With respect to sample collection, Shuber states that “a sample (e.g., a stool sample) may be directly deposited into a container (e.g., a sealable container)” [sic] that either already contains a stabilization solution or to which a stabilization solution may be added. Ex. 1008 at 29:8-19. Shuber does not specifically mention home collection by a patient. *See generally id.*

111. Just as with Itzkowitz, a POSA reading Shuber would conclude that DNA-based screening could potentially be improved based on selection and combination of specific DNA markers. Nothing in Shuber suggests the combination of nucleic acid-based markers with a different type of testing, such as FOBT.

F. Inbar (Ex. 1009)

112. Inbar is an international patent application with a July 24, 1997 International Publication Date. Ex. 1009 (Cover). Inbar describes a “system for collecting, storing and transporting” specimens of a “pasty material” including stool. *Id.*

113. Inbar does not describe at home collection of the fecal sample. In the Petition, Petitioner asserts that a POSA would recognize that the fecal sample collection process described in Inbar “**would** occur at a subject’s home because Inbar states that the specimens obtained from the fecal sample are combined with preservation medium in sealed containers and shipped to a laboratory for testing.” Pet. at 54. Dr. Whitney’s declaration states that a “POSA would appreciate that the toilet **could** be in a person’s home...” Ex. 1002 ¶ 290. The distinction is significant because the location of sample collection is entirely speculative. Nothing in Inbar specifies the location of the toilet at which the sample is collected before being transported to the laboratory for testing. Ex. 1009. A POSA reading Inbar in 2009 would understand that the sample collection and Inbar could occur at a doctor’s office or clinic. Inbar neither describes nor suggests that the sample collection “would” occur at a subject’s home as Petitioner argues.

114. Petitioner relies on Inbar’s one mention of “cryptic blood” and uses that mention in combination with general discussions of preservation media to argue that Inbar discloses a solution that prevents “denaturation or degradation of blood proteins.” Pet. at 55. Inbar’s one mention of blood is in the background of the invention, where Inbar states that “[c]ollection and transportation of a pasty

material, such as stool, food samples, soil samples, and the like for purposes of laboratory manipulation such as detection of microorganism being bacteria or parasites, detection of cryptic blood, preparation of a biochemical profile, etc., is an essential component of modern medicine, health care and environmental management.” Ex. 1009 at 1:7-12. Inbar does not otherwise discuss testing for, or preservation of, blood in stool samples. *See generally* Ex. 1009.

115. Inbar describes the use of “preservation media.” *See, e.g.*, Ex. 1009 at 3:32-4:12. Inbar states that composition of the preservation medium depends on the substance to be preserved, for example, “if the entity is a chemical substance, the medium will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration; if the assayed entity is microorganism or any other living matter, the medium will be designed so as to maintain such microorganisms or other living matter in a viable condition.” 4:4-8. Inbar does not disclose a “solution that prevents denaturation or degradation of blood protein” in a fecal sample. *See generally* Ex. 1009.

116. Inbar states that, at times different entities have to be assayed, and that “[t]his is the case, for example, in stool, where it is generally desired to assay both bacteria and parasites, which as noted above, require different media.” Ex. 1009 at 4:13-16. Where the different entities to be assayed “require different

media,” then the system includes two containers, each with a different “preservation medium.” *Id.* at 16-18. Inbar teaches separating the sample only when the analytes to be assayed require the different media for preservation.

117. Inbar does not say anything about preserving, extracting, and/or testing for nucleic acid in any sample. *See generally* Ex. 1009.

118. Inbar states that the “system of the invention minimize possible contact between a sample and a laboratory technician, which is especially important in cases where the sample may contain hazardous materials or microorganisms.” Ex. 1009 at 6:14-17.

IX. ALL GROUNDS: PETITIONER HAS NOT SHOWN A MOTIVATION FOR AT HOME SAMPLE SEPARATION

119. Geneoscopy does not provide a reason why a POSA with knowledge of the cited art would have developed a method that required separation of the stool sample at home. Dr. Whitney states in that “many assays used different stabilizing buffers to minimize loss of sample integrity.” Ex. 1002 ¶ 75. He also provides examples of references that discussed buffers to prevent degradation of DNA and buffers to stabilize blood protein. *Id.* In particular, Dr. Whitney identifies Olson, Shuber, and Itzkowitz in his footnote concerning his statement that “certain buffers” that “prevent degradation of DNA.” *Id.* ¶ 75 and fn. 85. Dr. Whitney identifies Vilkin, Grow, Karl, and Hirata in his footnote concerning his

statement that [o]ther buffers stabilize blood proteins.” *Id.* Dr. Whitney does not compare formulations of DNA stabilization buffers and blood protein stabilization buffers known in the art at the time.

120. A POSA would not have been motivated to require at-home separation of the sample into two portions, combining the first portion with a stabilizing buffer, and combining the second portion with a solution that prevents denaturation or degradation of blood proteins. Initially, as I discuss above, Lenhard does not disclose either at home collection or user interaction with the sample. *See generally* Ex. 1004. Vilkin does not identify the components of the buffer that is identified as “hB stabilizing buffer.” Ex. 1005 at 4. Itzkowitz describes use of a buffer that it refers to as a “DNA-stabilizing buffer.” Ex. 1006 at 2. Itzkowitz cites to Olson after the reference to “DNA-stabilizing buffer.” Ex. 1006 at 2, fn. 7. Olson identifies a “[s]tabilization buffer” consisting of 0.5 mol/L Tris, 0.15 mol/L EDTA, and 10mmol/L NaCl (pH 9.0). Ex. 1022 at 2.

121. Shuber also discloses stabilization solutions containing Tris, EDTA, and NaCl. According to Shuber, the stabilization solution may include 0.5 mM to 25 mM Tris, 0.01 to 2.5 mM EDTA, and 100mM to 200 mM NaCl, with pH ranging from 7.0 to 9.0, although pH could be higher or lower. Ex. 1008 at 4:19-22, 4:1-2.

122. Tris, EDTA, and NaCl were all common components of buffer solutions by 2009. A POSA in 2009 would have expected that a Tris/EDTA buffer, such as those described in Olson and Shuber, would prevent denaturation or degradation of blood protein in stool. This is because, if two molecules are degraded by similar processes and, therefore, are preserved by similar processes (e.g., both require the same pH), a POSA would expect that the same buffer could be used to preserve both. This is the case with nucleic acids and proteins such as hemoglobin. DNA and proteins may be degraded enzymatically or denatured/aggregated non-enzymatically: when exposed to digesting enzymes or non-ideal pH. In liquid specimens, proteases digest proteins. In turn, many proteases depend on divalent cations such as Mg^{2+} and Ca^{2+} . EDTA inhibits proteases by chelating these metal ions, which helps preserve proteins. DNA degradation is due to the activity of DNases, a class of nucleases. Many DNases require Mg^{2+} as a cofactor for their enzymatic activity. By chelating Mg^{2+} , EDTA inhibits DNases. Tris, on the other hand, is a pH buffer. DNA and proteins are both sensitive to highly acidic or basic environments. In high concentrations, divalent cations screen negatively charged DNA resulting in DNA aggregation and denaturation. Tris maintains neutral pH around 7.0 to 9.0, which is an ideal environment for stable DNA and proteins. Furthermore, many proteases and

nucleases have peak of their enzymatic activity at extreme pH. Indirectly, by maintaining stable, neutral pH, Tris inhibits these enzymes. For these reasons, Tris and EDTA work synergistically to preserve both nucleic acids and proteins including hemoglobin. Importantly, the two most detrimental processes to both DNA and proteins—enzymatic digestion and denaturation/aggregation—depend on the same conditions—non-neutral pH and divalent cations—and both conditions are inhibited by Tris/EDTA.

123. As an example, Japanese Patent Application No H5-99923 dated October 11, 1991 (“Tsuji Application”) supports that, well before 2009, a POSA would have understood that buffers containing Tris and EDTA could be used to stabilize hemoglobin in stool. *See* Ex. 2049. The Abstract of the Tsuji Application states that the objective was to provide a method for detecting human hemoglobin “while preventing the denaturation of human hemoglobin present in a liquid containing feces when left unattended...” *Id.* at Abstract. The Tsuji Application discloses liquids for dissolving feces containing human hemoglobin, including Tris-HCl buffer. *Id.* at [0010]. The Tsuji Application also describes adding a “chelating agent,” specifically EDTA, to the buffer solution “to suppress the denaturation of human hemoglobin.” *Id.* at [0011]. The Tsuji Application states that the preferable amount of chelating agent [EDTA], if the feces concentration is

4 mg/ml, is between 0.1 to 50 mmol/l. *Id.* It further states that adding more than the preferable range does not increase results, would be “uneconomical,” and would make the compound “difficult to dissolve.” *Id.*

124. Prior to 2009 there were also commercially available products, such as RNA later, that were sold as stabilizing “both RNA and protein within tissues or cells.” Ex. 2048; *see also* Ex. 1024 (discussing testing of RNA later as a “preservation method” for DNA in stool sample).

125. Petitioner’s reliance on Inbar is misplaced. As I note above, Inbar does not mention home collection of stool sample. More importantly, even if Inbar did discuss home collection, Inbar supports my opinion that a POSA would be motivated to require separation of the stool sample only when such separation was necessary. Inbar states that, at times different entities have to be assayed, and that “[t]his is the case, for example, in stool, where it is generally desired to assay both bacteria and parasites, which as noted above, ***require different media.***” Ex. 1009 at 4:13-16. (emphasis added). According to Inbar, the “medium required to maintain viable bacteria and the medium required to maintain viable parasites are not only different but are mutually exclusive, i.e., one type of medium damages the other type of microorganism.” *Id.* 2:32-3:3. Thus, where the different entities

to be assayed “require different media,” then the system includes two containers, each with a different “preservation medium.” *Id.* at 16-18.

126. The 1985 “Laboratory Procedures for the Diagnoses of Intestinal Parasites” reference cited by Petitioner also supports my opinion. Pet. at 6-7; Ex. 1010 (Melvin). The Petition includes a Figure from Melvin concerning the use of PVA-fixative and formalin for submitting stool specimens to be examined for parasites. Pet. at 7; Ex. 1010 at 32. Melvin explains that more than one preservative may be needed where “[a] single solution is not available for preserving all of the diagnostic forms ...” Ex. 1010 at 85. Figure 2 of Melvin illustrates putting portions of a sample into two separate glass vials where more than one type of preservative was needed.

127. A POSA would have also recognized a significant difference between Inbar and Melvin on one hand and CRC screening tests on the other. Melvin concerns procedures for diagnoses of intestinal parasites, and Inbar, particularly with respect to sample separation, the need for different media for preservation of parasites and bacteria. Ex. 1010; Ex. 1009 at 4:13-16. In other words, those being tested with Melvin and/or Inbar had a reason to suspect the presence of intestinal bacteria. Screening tests are different, as explained in Young. To begin, “the goal of screening for colorectal cancer is to reduce population mortality from and/or

morbidity due to colorectal cancer, potential screening tests require a rigorous evaluation that goes beyond what is required for diagnostic tests being used in situations where disease prevalence is high.” Ex. 1020 at 1. Further, “[s]creening tests are applied to healthy people where the risk of disease is relatively low.” *Id.* The literature, including Itzkowitz and Vilkin, makes clear that subjects are reluctant to interact with stool samples, which can affect test uptake and compliance. A POSA designing tests using stool samples would understand that a symptomatic subject – such as someone experiencing the symptoms caused by the presence of intestinal parasites – is far more likely willing to interact with the fecal sample if that is necessary for diagnosis than an asymptomatic member of the general screening population would be.

128. A POSA in 2009 seeking to improve CRC screening would have been motivated to pursue a solution that was as simple as possible and that required as little patient interaction with the stool sample as possible. Unless there was a compelling reason why the stool sample had to be separated at home by the user at the time of collection, a POSA as of 2009 would not have been motivated to develop a test that required user interaction with stool sample to separate the sample into two vessels, each with a buffer. There was no such compelling reason here where the references on which Petitioner relies for “DNA-stabilizing” buffers

disclose buffers that would prevent denaturation or degradation of blood protein in stool.

X. GROUND I: LENHARD, VILKIN, AND ITZKOWITZ DO NOT RENDER ANY CHALLENGED CLAIM OBVIOUS

129. The claims of the '746 patent would not have been obvious to a POSA as of the Priority Date in light of the Lenhard, Itzkowitz, and Vilkin combination.

130. As discussed in detail above, Lenhard mentions a specific combination of HIC1 methylation analysis and gFOBT in stool collected in a laboratory setting, where the samples were frozen before testing for DNA markers. Ex. 1004 at 2. Lenhard's discussion is in the context of comparing a single marker with FOBT. *Id.* at 1 (Background & Aims). Lenhard itself concludes that HIC1 should be combined with additional sensitive and specific ***methylation markers***. *Id.* at 7. Itzkowitz discusses only DNA-based tests, and, more specifically, early Exact Sciences DNA-based tests. Ex. 1006. Vilkin is limited to a particular, desktop iFOBT and the reported results are based on testing of three samples per subject. Ex. 1005. A POSA at the time seeking to develop a non-invasive CRC screening test with sufficient diagnostic accuracy that would also be acceptable to patients would not have been motivated to combine any

FOBT with DNA-based testing, let alone the particular aspects of these specific references on which Geneoscopy relies.

1. The Direction of the Prior Art Was to Improve Sensitivity by Improving Tests for Individual Marker Classes

131. A POSA would not have been motivated to combine Lenhard with the iFOBT of Vilkin and the DNA-based testing of Itzkowitz. To the contrary, Lenhard would have discouraged a POSA from such a combination. Geneoscopy focuses on Lenhard's statement that "[t]he combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs." Pet. at 13, 19. However, Lenhard also found no increase in the sensitivity for adenomas with the combination. Ex. 1004 at 2, 6. In other words, the combination showed no improvement in the critical detection of advanced adenomas which is important for cancer prevention. Lenhard itself noted that the combination of HIC1 and gFOBT showed no increase in sensitivity for adenomas. *Id.* at 6. Lenhard also acknowledge that the "majority of CRCs follow the adenoma-carcinoma sequence," and that the detection of "early disease and precancerous adenomatous lesions leads to a decrease of CRC-related mortality." *Id.* at 1. Lenhard's disclosures are consistent with the importance that a POSA would have placed on the ability of a screening test to detect early disease and precancerous adenomas.

A screening test without good sensitivity for advanced adenomas does not serve the purpose of trying to *prevent* cancer.

132. Importantly, the portions of Lenhard on which Geneoscopy relies tell only part of the story. As discussed above, the increase in sensitivity for CRC with the specific HIC1/gFOBT combination was not statistically significant and was accompanied by a decrease in specificity. Based on the data in Lenhard, including that the combination did not improve sensitivity for adenomas, a POSA would conclude from this that HIC1 should *not* be combined with gFOBT.

133. The 65% sensitivity for CRC of the specific HIC1/gFOBT combination of Lenhard was significantly worse than the sensitivity of other types of tests, including a single-marker test discussed in Lenhard. Lenhard states that SFRP2 was “found to be the most sensitive fecal methylation marker, detecting 77%-90% of CRCs. However, specificity of SFRP2 methylation was quite poor, at 77%.” Ex. 1004 at 2.

134. Vilkin describes analysis of a particular, desktop iFOBT. Vilkin concludes: “we have found this desktop, automated-developed and quantified Hb version of the immunochemical fecal occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with an acceptable specificity and consequent high negative predictive value.” Ex. 1005 at 8. Vilkin

reports that its results mean “that in this group of high-risk and symptomatic patients, 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 at this round of screening.” *Id.* Using an iFOBT “threshold of 100 ng Hb/mL” and three tests per subject allowed the Vilkin authors to achieve 100% sensitivity for CRC and sensitivity of 76.5% for all significant colorectal neoplasia with “acceptable specificity” of 95.3%. *Id.* A POSA in 2009 would have understood that the sensitivity and specificity reported in Vilkin were the result of Vilkin’s testing methodology. Vilkin taught, and was limited to, specific improvements in iFOBT. It does not teach or suggest combination of iFOBT with any other type of screening test.

135. Itzkowitz focuses on improvements in a DNA-based screening test. Itzkowitz described an increase in sensitivity from 52% to 72.5% in version 1 of Exact Sciences’ DNA-only based test attributed to the improved methods of stabilization and extraction. Ex. 1006 at 6. Itzkowitz noted that the improvement in the version 1 test was achieved at a “relatively minor decrease in specificity from 94.4% to 89.3%.” *Id.* Itzkowitz focused on Exact Science’s version 2 DNA panel. With the version 2 panel “[t]he combination of vimentin plus DIA-DY resulted in an optimal sensitivity of 85.5% (95% CI, 73.9%-94.5%). This optimal

combination detected most cancers, including early stage (stage I) lesions, regardless of their location in the colon.” *Id.* The Itzkowitz “results suggest that with only 2 markers (vimentin + DY) providing a sensitivity of 88%, the assay complexity can be reduced significantly, thereby decreasing cost and facilitating the development of an assay kit that could be managed by local clinical laboratories.” *Id.* At 7. Itzkowitz concluded that a combination of DNA-based markers could achieve acceptable sensitivity with reduced complexity. Itzkowitz does not suggest the combination of DNA-based markers with other types of tests.

136. If a POSA were to be motivated by increased sensitivity, as Geneoscopy contends, each of Lenhard, Vilkin, and Itzkowitz disclose significantly better than the 65% sensitivity of the HIC1/gFOBT combination ***without*** the combination of DNA-based testing and FOBT.

137. Lenhard concludes that the study shows “HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 ***with a few additional sensitive and specific methylation markers*** may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas.” Ex. 1004 at 7 (emphasis added). Lenhard had the benefit of Lenhard’s own analysis of both gFOBT and specific DNA markers. Based on that, Lenhard

expressly suggests using multiple methylation markers, not combining methylation marker testing with FOBT.

138. The individual disclosures of both Vilkin and Itzkowitz further confirm that a POSA would have been motivated to improve a specific type of test, not to combine two differing types of tests. This is consistent with the other art on which Petitioner relies, art that is generally focused on improving tests for a single class of markers and that, to the extent that it discusses more than one class of markers, typically does so for comparison and reference. *See, e.g.*, Ex. 1004; Ex. 1007; Ex. 1042; Ex. 1043; *see also* Ex. 1020 at 6-7 (stating that “fecal DNA tests require much more work before it is clear what the best markers are, how they compare to GFOBT and FIT, and what the relative costs will be.”)

2. A POSA Would Have Considered the Diagnostic Performance Metrics of Sensitivity and Specificity Together

139. Lenhard would not have motivated the combination of the iFOBT of Vilkin with nucleic acid-based testing in this unpredictable field. Lenhard is limited to one specific combination of a gFOBT with one particular methylation marker and reports results for a relatively small number of subjects – 26 CRC patients, 13 individuals with advanced adenomas, and 50 healthy controls. A POSA at the time would have understood that there was no way to predict without

testing whether a combination of different tests would result in improved performance. By 2009, it was very well known in the field that a combination of biomarkers rarely leads to improved diagnostic performance. A POSA would have known that improved diagnostic performance with a combined test is unlikely, and any attempt to show improved performance would need to be validated. A POSA also would have known that, rather than improving performance, a combination might reduce performance.

140. The fact that combinations of biomarkers frequently do not lead to improved diagnostic performance and may decrease it was known in the biomarker and disease diagnostics field well before 2009. In many cases, a combination of two or more biomarkers has lower diagnostic performance than the most diagnostically accurate individual biomarker from the combined set. For example, if two biomarkers are highly correlated, their combination may not add new discriminatory power, leading to no gain in diagnostic performance. Further, each individual biomarker invariably carries a certain level of noise, which is generally additive when biomarkers are combined. Combining several biomarkers that together increase the noise without increasing discriminatory power leads to degradation of overall performance.

141. Many biomarker combinations use either AND or OR rules. With the AND rule, the test is positive if both biomarkers are positive. With the OR rule, the test is positive if any of the biomarkers is positive. The use of the AND rule may increase true negatives, which leads to a higher specificity, but it also increases false negatives, thus sacrificing sensitivity. The use of the OR rule on the other hand can increase true positives, resulting in a higher sensitivity, but this can also increase false positives, lowering specificity. The OR rule was used in reporting the combined results in Lenhard. Depending on the conditional independence of biomarkers, their joint distribution may not yield additive value, and the combined AUC can be lower than that of the best individual marker. For either the AND or the OR rule, there is a compromise between sensitivity and specificity, which means that AUC can decrease or increase depending on the mutual statistics of combined biomarkers.

142. Petitioner relies on an increase in sensitivity for CRCs of the combined HIC1 and gFOBT biomarker in Lenhard's study as evidence of the improved performance of the combination. A POSA would have known that it was not necessary to combine biomarkers to attain a higher sensitivity. Attaining a higher sensitivity is always possible by lowering the positivity threshold—the value at which a biomarker test result is considered positive—of any individual

biomarker. In case of Lenhard's HIC1 for example, by sufficiently lowering the positivity threshold of HIC1, one would achieve the same sensitivity as the combined HIC1 and gFOBT results - two thirds of CRCs being detected.

Extrapolating this further, perfect 100% sensitivity could always be achieved within any individual biomarker if a sufficiently low positive threshold is chosen.

Improvement in either sensitivity or specificity alone is not the reason why biomarkers are combined. Biomarkers are combined to increase their overall performance, which includes both sensitivity and specificity. For example, if two biomarkers offer robust synergy, their OR combination should improve sensitivity without substantially degrading specificity. The data in both Lenhard and Kanaoka clearly show that this is not the case with their biomarkers.

143. Moreover, each combinable biomarker adds a degree of freedom to the biomarker signal, which translates into a larger number of patients needed to first develop and then validate the prediction rule. If the number of patients is not sufficiently high, there is a risk of overfitting the data. For example, consider 10 biomarkers combined into a single prediction rule and only two cases and two controls in the prediction rule development study. There is a very high likelihood that one would be able to design a prediction rule using these 10 biomarkers that would be able to correctly assign the status of all four patients. However, this rule

is likely to be overfitted and would be unlikely to withstand an independent validation in a larger dataset. The number of patients needed to be recruited in either development or validation study increases with the number of biomarkers. Therefore, there are additional risks of combining biomarkers.

144. For the reasons explained above, when combined, most individual biomarkers would not show improved overall diagnostic performance but would result in lower performance and higher complexity of their implementation. This fact is well known in the field. To give one example, the National Institutes of Health, the largest federal funding agency supporting biomedical research in the country, reviews more than 66,000 grant applications to support studies, including those to develop new biomarkers. I am familiar with the NIH grant review process from having both reviewed and submitted multiple grant applications. A critical step in the review process is peer review by a “study section,” a panel consisting of experts in the field. In addition to my serving on multiple study sections, I have been a standing member of two NIH study sections whose portfolios included a large number of grant applications focused on cancer biomarkers, including multimodal biomarkers. A study section reviewing an application proposing to combine biomarkers would require experimental evidence that the biomarkers proposed to be combined are synergistic and the proposed combination is

expected to have a higher diagnostic performance. A grant proposal that does not provide such evidence but states that the investigators expect their combination to have a higher diagnostic performance merely because several biomarkers are combined would not be considered justified by an NIH study section. In other words, the main reason the NIH put the burden of proof on investigators proposing to combine biomarkers is due to the well-recognized fact that, frequently, a biomarker combination does not offer benefits or even degrades diagnostic performance compared to individual biomarkers comprising the proposed combination.

145. Lenhard shows the increased sensitivity of the HIC1/gFOBT combination for cancers was at the expense of a drop in specificity from 98% for HIC1 alone to 89% for the HIC1/gFOBT combination. And, as discussed above, the increased CRC sensitivity of the HIC1/gFOBT combination of Lenhard was not statistically significant and the combination had no effect on sensitivity for adenomas. Lenhard would not have motivated a POSA to pursue the more complicated path of combining two classes of markers to try to increase sensitivity, particularly a limited increase in sensitivity for only cancers but not for adenomas, where the one set of combined data in Lenhard also shows a decrease

in specificity. A screening test with a high rate of false positives does not serve the goal of reducing the burden, and disadvantages, of unnecessary colonoscopies.

146. Even minor reductions in specificity could have a large negative impact on the overall cost-effectiveness of screening using the test. False positives also have significant patient impact. *See, e.g.*, Ex. 1034 at 12-13. If a screening test has low specificity, then both health care providers and patients would understand that a positive test result may not be indicative of disease. This, in turn, may reduce incentive to follow up with the recommended colonoscopy after a positive screening test result. On the other hand, when a patient does follow-up as recommended, in addition to the risks and costs of the colonoscopy procedure outlined above, there is also the intangible impact on the patient of the stress of waiting for the results of the follow-up colonoscopy, only to eventually learn that the initial test result was a false positive and that the patient does not have cancer or precancerous lesions. *See id.* Lack of confidence in the test results could lead to true positives not following up on their positive tests thus not receiving the necessary treatment.

3. A POSA Would Have Considered all of the Requirements of Vilkin and Would Not Have Been Motivated to Combine the iFOBT of Vilkin With Tests for Nucleic Acid Markers

147. As discussed above, the iFOBT of Vilkin required that the subject prepare three consecutive daily fecal samples. Ex. 1005 at 3 (Methods), 4. Vilkin discloses that the “best results were obtained when all three tests were performed and utilized for the analysis.” *Id.* at 6. Vilkin further reports that they would “continue with collecting three annual fecal tests” as they had “confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” *Id.* at 8. To the extent that one of the perceived advantages of iFOBT over gFOBT was collection of fewer samples (*see* Ex. 1020 at 4 (states that most branded versions of iFOBT “require fewer than three fecal samples, the recommended number for gFOBT”)), Vilkin did not provide that advantage. I understand that Geneoscopy has argued that Vilkin does not require the collection of three samples over three consecutive days. A POSA would have understood that the diagnostic results reported in Vilkin are a direct result of the methods followed in Vilkin – the reported 76.5% sensitivity reflects the testing of all three samples. Ex. 1005 (Table 3). Further, even if one assumes that a POSA would have been motivated to use the iFOBT of Vilkin based on Vilkin’s sensitivity and specificity, but would have rejected Vilkin’s methodology, 2-day iFOBT

collection was routinely used at the time in Japan, the United States, and Australia for average-risk populations. Ex. 1005 at 8. Geneoscopy does not explain how or why a POSA would combine a test requiring 2 (or 3) consecutive daily samples with nucleic acid testing the sensitivity of which is not dependent upon the presence of blood in stool.

148. Vilkin also relies on refrigeration for sample preservation. Ex. 1005 at 4 (“samples are kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.”), 3 (Conclusions) (“[r]efrigerated OC-Sensor samples are stable for 21 days.”). According to Vilkin, “storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability.” *Id.* at 8. While Vilkin refers to an “Hb stabilizing buffer,” Vilkin teaches that refrigeration was required to prevent decay.

149. I understand that Geneoscopy has also argued that “clinical” use of the iFOBT of Vilkin would not require refrigeration. Even if Geneoscopy were correct, that still would not support Geneoscopy’s position that, when using the iFOBT of Vilkin, a single sample would be taken and shipped without refrigeration. As previously noted, Vilkin’s discussion of other test methodologies states that Japan, the United States, and Australia all used an “annual 2-day, average-risk population I-FOBT collection.” Ex. 1005 at 8. The

references cited in Vilkin include Nakama, “Colonoscopic Evaluation of Immunochemical Fecal Occult Blood Test for Detection of Colorectal Neoplasia.” Ex. 1005, fn. 16. Nakama was a study to “assess the validity of three testing methods of immunochemical occult blood according to the number of collection times as a mean for colorectal cancer screening.” Ex. 2047 at 228 (Abstract: Background/Aims). Nakama concluded that collection over two consecutive days “is the most desirable in immunochemical occult blood testing as a means of screening for colorectal cancer.” *Id.* at 231. Thus, even if collection over three consecutive days were not necessary, a POSA would expect at least collection over two days, which would require refrigeration.

150. Vilkin’s requirement that three samples be collected over three separate days and refrigerated also made the test less acceptable to potential users. Vilkin noted “screeners’ hesitancy about keeping the prepared test transiently in their home refrigerator.” Ex. 1005 at 8. Using the “routinely used” two samples over two days would also have required this undesirable at-home refrigeration of the samples.

151. Geneoscopy does not describe why or how a POSA at the time would have been motivated to combine only specific features of the Vilkin test, a test that required both collection of three different samples and refrigeration of those

samples, with a separate nucleic acid-based test that requires neither collection of multiple samples nor refrigeration. The collection of three different samples and refrigeration of those samples for the iFOBT of Vilkin would have dissuaded a POSA from combining Vilkin with a separate nucleic-acid based test. Even if the Vilkin methodology were ignored, the fact that the routine methodology for iFOBT for the average-risk population involved 2-day sample collection would have also dissuaded combination of nucleic acid testing with iFOBT for at-home collection by the subject.

4. A POSA Would Have Considered Complexity, Patient Acceptance, and Cost

152. Itzkowitz also discourages use of FOBT. Itzkowitz recognized the well-known need for patient acceptability. Itzkowitz states “[i]nherent in the success of any screening test is patient acceptance. Our preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirms a very high degree of patient satisfaction.” Ex. 1006 at 6-7. Itzkowitz observed that its “findings support results from the previous multicenter study in which *subjects preferred fecal DNA testing to both the fecal occult blood test and colonoscopy.*” *Id.* at 7 (emphasis added). A POSA would not have been motivated to combine the patient-preferred, improved DNA-based tests of Itzkowitz with FOBT.

153. A POSA at the time would have tried to minimize both cost and complexity of CRC screening tests. Particularly considering the separate advancements for each of FOBT and nucleic acid-based tests, a POSA would have had no reason to increase both the cost and complexity of a test by combining two differing types of tests. A POSA would have understood that screening using two types of tests for two different classes of markers would only increase the cost. A test for nucleic acid markers, even if multiple nucleic acid markers, could use the single, direct-defecation sample collection device of Itzkowitz. However, combining a nucleic acid test with an FOBT test as claimed requires, among other things, more collection components. The claimed invention requires a sealable vessel containing a first portion of fecal sample and a stabilizing buffer and a second sealable containing a second portion of the fecal sample and a solution that prevents denaturation or degradation of blood proteins. The claimed invention thus requires twice the containers and twice the buffers of a single-marker-class test.

154. Requiring a patient to remove a portion of stool from the sample for the FOBT test also increases complexity at the collection site and significantly reduces the advantage of the direct defecation device of Itzkowitz that avoids the patient having to interact with their stool. A POSA in 2009 would have been

aware of user reluctance concerning previous home fecal collection tests. *See, e.g.*, Ex. 2036 at 1-2 (observing that “[s]tool-based DNA testing received higher ratings for simplicity of the stool collection process and comfort, presumably attributable to the use of a specimen collection container that could be directly mounted onto the toilet seat, thus obviating the need for direct manipulation of stool as required for FOBT.”); Ex. 1005 at 8 (noting participant “hesitancy about keeping the prepared test transiently in their home refrigerator”). That knowledge concerning user reluctance would have further discouraged the collection method claimed in the ’746 patent in this area where patient acceptance is critical to success. *See, e.g.*, Ex. 1006 at 6 (“Inherent in the success of any screening test is patient acceptance.”); Ex. 1007 at [0003] (noting that “[f]or the mass screening of cancer, it is important that the detection method is easy and non-invasive.”); Ex. 1020 at 4 (“Population participation is essential for cancer detection.”)

155. Combining multiple diagnostic tests that each require different analytical platforms also introduces significant logistical and operational complexity at the laboratory, which can hinder the efficiency and scalability of diagnostics. One can see this in the practice of laboratory medicine, where combining diagnostic tests that require different specimens, workflows, equipment, and technical expertise is rarely done. Using both FOBT, which relies

on immunochemical detection, and nucleic acid testing, which requires molecular analysis, demands separate equipment, workflows, and technical expertise. This not only increases costs and turnaround time but also raises the risk of errors across platforms. Such complexity can be especially detrimental in routine screening, where simplicity, speed, and reliability are critical. This fragmentation is not only resource-intensive but also complicates standardization and automation—key principles in modern lab operations. As a result, such combinations are typically avoided unless the clinical benefit clearly outweighs the added complexity.

156. Individually or together, there would have been an expectation of lower uptake if cost, complexity, or both were increased. A POSA would have considered combining two tests for two different classes of markers, which increases complexity for both the patient and the laboratory, only if there were a significant chance of a substantial increase in diagnostic performance. However, considering the fact that combining biomarkers does not typically increase performance, and the fact that by 2009 there were multiple studies (including by Lenhard and Kanaoka) that illustrated the problems with combining tests, a POSA would have been deterred from exploring combined FOBT and nucleic acid analysis.

157. The invention of the '746 patent requires at-home sample collection, sample separation, addition of a stabilizing buffer to the first portion, and addition of a solution that prevents denaturation or degradation of blood proteins to the second portion. Each portion of the sample must then be analyzed separately, one for nucleic acid markers and the other for blood protein. Each of these steps adds both cost and complexity. The understanding that a combination would have increased both cost and complexity would have discouraged combination, particularly considering that the likelihood of improved diagnostic performance from a combination was unpredictable, and considering that the cited references indicate that a combination would reduce specificity.

158. Finally, there is also no motivation in the cited art to select the specific elements of the claims from the different references and combine them to arrive at the claimed invention. Geneoscopy pulls select aspects of each reference to assert that each element of the claimed invention can be found in the prior art without explaining why or how a POSA at the time would have selected those particular features and combined them in exactly the configuration of the claimed invention. Lenhard describes using a gFOBT test and testing frozen samples for nucleic acids. Vilkin describes a particular iFOBT desktop device with specific sample collection and handling requirements, including that a subject must collect

three samples over three consecutive days, and that the samples must remain refrigerated. Geneoscopy ignores those, and other, aspects of the references on which it relies in choosing specific, limited disclosures from each reference.

159. The art on which Geneoscopy relies provides no basis for the specific combination of the at-home sample collection of the claims which require that a single fecal sample be separated such that there is one portion of the sample in one sealable vessel and a second portion in a second sealable container, where the first portion is combined with stabilizing buffer and the second is combined with a solution to prevent denaturation or degradation of blood protein, and where the freshly-collected fecal samples are not frozen. First, the cited art provides no motivation to combine nucleic acid-based tests with FOBT. Second, even if there were such a motivation, combining the disparate teachings of the cited references would not result in the claimed method.

XI. GROUND III: SHUBER AND VILKIN DO NOT RENDER ANY CHALLENGED CLAIM OBVIOUS

160. The challenged claims of the '746 patent also would not have been obvious to a POSA as of the Priority Date in light of the Shuber and Vilkin combination. As described in more detail above, Shuber discusses DNA-based tests, with a focus on the use of DNA-stabilization solutions. *See* Ex. 1008 at 2:5-9. Vilkin discusses a specific, desktop iFOBT with specific sample-handling

requirements. Ex. 1005. Nothing in either reference teaches or suggests the combination of nucleic acid-based testing with iFOBT.

161. As discussed above, a POSA at the time would not have been motivated to combine any FOBT with nucleic acid-based testing. In fact, the references on which Geneoscopy relies, either alone or in combination, would have discouraged the combination of FOBT and nucleic acid-based tests.

162. Geneoscopy asserts that Shuber “describes the possibility of using multiple tests in combination to improve the test’s sensitivity for detection of CRC.” Pet. at 17. The portion of Shuber on which Geneoscopy relies suggests the potential combination of nucleic acid-based tests. *Id.* Nothing in Shuber discloses or suggests combining any nucleic acid-based test with any FOBT, or with any other form of test other than those that are nucleic acid based.

163. Shuber discloses that testing for various combinations of nucleic acid markers could detect adenomas with 60%, 74%, 90% and even “greater than 95% sensitivity (e.g., greater than 98% sensitivity).” Ex. 1008 at 14:1-16. A POSA seeking to maximize sensitivity would therefore understand from Shuber that sensitivity of 95% or even greater than 98% could be achieved using a test for a single class of markers.

164. Shuber says little about sample collection and contains no specific mention of at-home collection by a patient. *See* Ex. 1008 at 29:8-19.

165. As discussed above, Vilkin describes using stool probes to collect samples over three consecutive days and refrigeration of those samples. Vilkin does not describe where the stool is located when a portion is collected with the stool probe. Ex. 1005 at 4.

166. Neither Shuber nor Vilkin discloses or suggests a combined test in which a patient would separate one stool sample such that there is a first portion and a second portion, both in sealable containers, to be tested for two different classes of markers as required by the claims.

167. The other references on which Geneoscopy relies also do not teach or suggest the combination of nucleic acid-based testing, as discussed in Shuber, with the iFOBT test of Vilkin. Taken in the context of the references as a whole, and in the context of the knowledge in the art as of the Priority Date, the statements on which Petitioner relies would not have motivated a POSA to combine Shuber with the iFOBT of Vilkin, and certainly not in a way that would result in the claimed invention.

168. Among other things, Geneoscopy relies on a sentence from Nishikawa, a reference from 2002. Pet. at 38-39, citing Ex. 1011. Nishikawa

concludes that the tested method of detecting *K-ras* point mutations “is highly specific, noninvasive, and cost-effective, and 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.” Ex 1011 at 6. Nishikawa does not identify data in support of this statement. *Id.* I also find it informative that seven years passed between Nishikawa and the invention of the ’746 patent, yet no one else in this active field came up with the combination before Exact Sciences’ claimed invention.

169. Geneoscopy also cites to Lenhard in its argument that a POSA would have been motivated to combine Shuber with Vilkin. Pet. at 39. As I discuss in detail above, consideration of the full Lenhard disclosure would have discouraged, not motivated, any combination of FOBT with nucleic acid-based testing. As I also discuss above, Lenhard concludes that it shows “HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 *with a few additional sensitive and specific methylation markers* may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas.” Ex. 1004 at 7 (emphasis added). That is, Lenhard expressly teaches the

combination of methylation markers. Lenhard neither teaches nor suggests the combination of nucleic-acid marker testing with blood protein testing.

170. Geneoscopy also relies on Kutzner. Pet. at 39. Kutzner, which describes a retrospective study of frozen samples, poses the question of “whether both [MD and gFOBT] methods should be used together in broad diagnostic screening programs.” Ex. 1012 at 8. The Kutzner authors state that their “retrospective data ***do not allow*** any conclusion on the potential of this approach in diagnostic screening. Prospective comparative studies, which include a very high number of individuals, have to prove the value of the combined application of MD and FOBT.” *Id.* (emphasis added). By posing the question, Kutzner confirms my opinion that the answer was not obvious and was also not predictable. Instead, Kutzner supports the opinion that – absent testing of a specific combination – it would not have been obvious to a POSA to combine nucleic acid-based testing with any form of FOBT with any reasonable expectation of improved diagnostic performance. I also note that the FOBT discussed in Kutzner was gFOBT, not iFOBT.

171. Geneoscopy also relies on Levin. Pet at 40. Levin poses a question for potential investigation: “[a]nother question worthy of consideration is ***whether or not*** including a sensitive gFOBT or FIT at the time of [sDNA] testing would

improve sensitivity without adversely affecting specificity.” Ex. 1013 at 9 (emphasis added). Levin cites to Kutzner. *Id.* Petitioner cites both Kutzner and Levin to argue that it would not have been obvious to a POSA to combine DNA testing with FOBT. To the contrary, Levin’s teachings indicate that a POSA, aware of Lenhard and Kanaoka and that they both show adverse effects on specificity, would have expected that the answer to Levin’s “whether or not” question would be “not.” In context, a POSA therefore would not have been motivated by Kutzer and/or Levin to include any form of FOBT with nucleic acid testing.

172. I also note that Levin concluded that there were “no clear patterns of superior performance between a high-sensitivity guaiac-based test (Hemoccult SENSE) and a variety of FIT.” Ex. 1013 at 7. In addition, Levin notes “higher costs associated with FIT compared with gFOBT.” *Id.*

173. I further note that Petitioner relies on Kanaoka in connection with certain dependent claims. As with Lenhard, and as discussed in more detail below, analysis of the data in Kanaoka shows that Kanaoka would have discouraged, not encouraged, a combination. Example 1 of Kanaoka shows that testing for COX-2 RNA and using an iFOBT test resulted in one additional positive test from the iFOBT what was not identified with the COX-2 RNA test. Ex. 1007 at [0067].

The iFOBT test also had three false positives among the control cases (specificity 86.3%), where the COX-2 RNA test had no false positives in the control cases (specificity 100%). *Id.* at [0066], [0065]. Accordingly, based on the small sample size in Kanaoka, the combination resulted in an insignificant increase in sensitivity, with a more significant decrease in specificity. A POSA would not have been motivated to combine the tests based on this data. And, as with Lenhard, Kanaoka does not suggest proceeding with any combined test approach.

174. None of the references Petitioner cites as supposed motivation describe at home sample collection. *See generally* Ex. 1004, Ex. 1007, Ex. 1011-1013; Pet. at 35-36; 38-40;

175. The references on which Geneoscopy relies confirm that, a POSA at the time seeking to improve the sensitivity of CRC screening would have focused on improving either nucleic acid-based analysis or FOBT analysis. This is particularly true where, as is also discussed above, combining different types of tests would also add cost and complexity.

176. As is also discussed above, a POSA also would not have had a reasonable expectation that combining iFOBT with nucleic acid-based testing would have improved diagnostic performance.

177. Finally, just as with the Lenhard, Itzkowitz, and Vilkin combination Geneoscopy identifies no reason why a POSA would have selected the specific elements of the claims from Shuber and Vilkin and combined them to arrive at the precise configuration of the claimed invention. Even if the two references were combined, the combination would not result in the claimed invention that requires at-home collection without freezing, separation of the sample into two separate sealable containers, and adding buffers to each of the containers.

XII. GROUND VI: INBAR, SHUBER, AND VILKIN DO NOT RENDER ANY CHALLENGED CLAIM OBVIOUS

178. The challenged claims of the '746 patent also would not have been obvious to a POSA as of the Priority Date in light of the Inbar, Shuber, and Vilkin combination. As described in more detail above, Shuber discusses DNA-based tests, with a focus on the use of DNA-stabilization solutions. *See* Ex. 1008 at 2:5-9. Vilkin discusses a specific, desktop iFOBT with specific sample-handling requirements. Ex. 1005. Nothing in either reference teaches or suggests the combination of nucleic acid-based testing with iFOBT. Nothing in the Inbar reference changes the discussion above and the fact that a POSA in February of 2009 would not have had any motivation to combine Shuber with Vilkin, with or without the addition of Inbar.

XIII. GROUNDS II, IV, AND VII: NO MOTIVATION TO COMBINE THE FROZEN SAMPLES OF KANAOKA; NO REASONABLE EXPECTATION OF SUCCESS; AND NO REASON TO SEPARATE THE SAMPLE IF COMBINATION CONSIDERED

179. I understand that, if an independent claim is not obvious, then the dependent claims relying on the independent claim also are not obvious.

Geneoscopy's Grounds II, IV, and VII address only dependent claims 12 and 13.

Those claims also would not have been obvious to a POSA at the time for the same reasons discussed above.

180. In each of Grounds II, IV, and VII, Petitioner adds the COX-2 RNA analysis of Kanaoka to the proposed combinations discussed above. Based on the disclosures of Kanaoka, a POSA would have understood that the fecal sample to be tested for the presence of COX-2 RNA should be frozen immediately after collection. Example 1 of Kanaoka describes a process where "[a]s soon as possible after sampling feces, the feces were separated..., were frozen using liquid nitrogen, and were stored at -80° C." Ex. 1007 at 5. Kanaoka also states in the Abstract that the method involves "collecting biological sample which is immediately frozen using liquid nitrogen in some cases." Ex. 1007 at Abstract. The only method for stabilizing RNA in the fecal sample discussed in Kanaoka is immediate freezing. Ex. 1007.

181. In his background discussion of Kanaoka, Dr. Whitney points out that Kanaoka states that the sample “can be “used as they are, or, in some cases, after frozen.” Ex. 1002 ¶ 131, citing Ex. 1007 at ¶¶0040-0041. The statement in paragraph 41 of Kanaoka does not concern stabilization of the sample. A POSA would understand the statement in Paragraph 41 of Kanaoka to indicate that the fecal sample could be processed either “as they are” or frozen. Dr. Whitney appears to agree that Kanaoka requires that the only method of stabilization taught in Kanaoka is freezing. *See, e.g.*, Ex. 1002 at ¶¶ 220-223. Specifically, Dr. Whitney turns to a separate reference, Nechvatal, to assert that, in his opinion, “[a] person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing...” *Id.* at ¶ 223. I disagree for the reasons discussed below. However, even before considering whether there would have been a reasonable expectation of success, a POSA in 2009 would not have been motivated to incorporate the COX-2 RNA testing of Kanaoka – which requires freezing – in a method of processing a freshly collected fecal sample that excludes freezing.

182. In addition, as discussed above, the results reported in Example 1 of Kanaoka show that testing for COX-2 RNA and using an iFOBT test resulted in one additional positive test from the iFOBT that was not identified with the COX-

2 RNA test. Ex. 1007 at [0067]. However, the iFOBT test also had three false positives among the control cases (specificity 86.3%), where the COX-2 RNA test had no false positives in the control cases (specificity 100%). *Id.* at [0066], [0065]. Based on the small sample size in Kanaoka, the combination resulted in an insignificant increase in sensitivity, with a more significant decrease in specificity. *Id.*

183. Analyzing the data for the limited sample size in Kanaoka, the increase in sensitivity was not statistically significant. In addition, overall performance declines when the COX-2 RNA and iFOBT sensitivity and specificity are considered together. The following confidence interval (CI) estimates were calculated using the Wilson Score Interval method, a standard method of estimating intervals for proportions (and the method that is identified in Lenhard as having been used to calculate confidence intervals reported in that reference):

	Sensitivity	Specificity	AUC	95% CI for sensitivity	p-value for improvement in sensitivity
COX2	25/28=89%	22/22=100%	0.946	73% – 96%	0.68
COX2+iFOBT	26/28=93%	19/22=86%	0.896	77% - 98%	

The one additional true positive test when iFOBT results were added to the COX-2 RNA results is an increase in sensitivity from 89% to 93%. This is not

statistically significant with $p\text{-value} = 0.68$. In addition, the AUC, calculated for the COX2+iFOBT combination designed to increase sensitivity, is lower than the AUC for COX2 alone, a drop from 0.946 to 0.896 due to the insignificant increase in sensitivity and the more substantial decrease in specificity.

184. Like Lenhard, Kanaoka suggests that the combination would result in worse overall performance and consideration of the Kanaoka reference as a whole would have discouraged a combination of nucleic acid-based and FOBT tests.

185. A POSA in 2009 also would not have had any expectation that they could successfully incorporate the RNA analysis of Kanaoka into an at-home collection methodology that expressly excludes freezing.

186. Kanaoka includes background discussion where it states that a prior art attempt to use RNA as an alternative to an FOBT did not have sufficient sensitivity “because it was impossible to extract RNA easily and efficiently from a small amount of feces.” Ex. 1007 at [0008]-[0009]. Kanaoka also states that “RNA is more unstable compared to DNA.” *Id.* at [0011].

187. Petitioner relies on Nechvatal to argue that a POSA would have had a “reasonable expectation of successfully incorporating the RNA assay of Kanaoka” into the asserted combinations. Pet. at 36; Ex. 1024 at 8. I disagree that a POSA would have had a reasonable expectation of successfully incorporating Kanaoka’s

analysis of frozen samples based on Nechvatal's statement that "[i]n conclusion, this study suggests that preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible."

Ex. 1024 at 8. Nechvatal also states that it "focuses on DNA preservation, extraction, and quality, the methods studied were also chosen for their likely suitability for preserving RNA as well. *Id.* at 2. That statement also would not have supported a reasonable expectation of success where Nechvatal contains no data from any analysis of RNA, and considering Kanaoka's discussion of RNA being "more unstable compared with DNA." *See generally* Ex. 1024; Ex. 1007 at [0011].

188. Nechvatal tested "multiple methods for fecal preservation and DNA extraction." Ex. 1024. The tested preservation methods included using commercially available products such as RNeasyTM and PaxgeneTM, drying sample on cards then placing it in pouch with silica gel desiccant packs, drying sample over silica beads, and flash freezing in liquid nitrogen. Ex. 1024 at 2. Nechvatal then combines various of these "preservation methods" with extraction methods and reports on DNA recovery, PCR inhibition, and extraction time for the combinations. Ex. 1024. Of the tested "preservation" methods, only two were tested on human DNA: a) the commercial RNeasy product, and b) freezing with

liquid nitrogen. Ex. 1024 at 130. Nechvatal includes extraction data for human DNA for only the RNAlater approach. Ex. 1024 at 130. Nechvatal contains no data from any analysis of RNA using any of these “preservation” methods. *Id.*

189. There are several limitations of Nechvatal as relevant to human DNA or RNA collection. First, most of the provided data are for bacterial DNA not human DNA. Bacterial DNA is prevalent in stool and does not present the same level of stability concerns as human DNA. Second, the metrics used in Nechvatal to evaluate suitability of a given preservation protocol are PCR inhibition and total amount of DNA. These metrics are not suitable to assess whether extracted DNA or RNA are suitable for cancer biomarker analysis. The reported ability to extract some amount of bacterial DNA does not tell us how much human DNA could be extracted and whether it could be used for biomarker analysis. As noted above, Nechvatal includes only limited discussion of any human DNA found in stool samples. *See* Ex. 1024 at 130, Fig. 5. And there is no indication that this amount of DNA is adequate for any kind of analysis or how much DNA was lost. *See generally* Ex. 1024.

190. Nechvatal does not present sufficient data to support that any of the described protocols could be used to stabilize and extract sufficient human DNA or RNA for biomarker analysis.

191. Nechvatal's conclusion, without reporting any RNA data, that the reported study of DNA, and primarily bacterial DNA, "suggests that preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible" (Ex. 1024 at 8) does not support a reasonable expectation that collection for the COX-2 RNA analysis of Kanaoka could be done at home and without freezing, and particularly not where the RNA would later be extracted from the fecal sample and an amount of RNA expressed from the human gene measured. *See* Ex. 1001, claims 12 and 13.

192. After testing various combinations of "preservation" and "extraction" methods (*see, e.g.*, Table 1), Nechvatal concluded that the best combination of the examined stool sample preservation and DNA extraction methods was "QS-R" which used RNAlater as the preservation method. Ex. 1024 at 3, 8; RNAlater was a commercially available product sold to stabilize both RNA *and* protein. Ex. 2048.

193. As previously discussed, Kanaoka does not describe at home collection and describes immediately freezing the sample, and a POSA in 2009 would not have been motivated to try to incorporate Kanaoka in an at-home collection method without freezing. A POSA likewise would not have pursued a combination COX-2 RNA and iFOBT screening method based on the data in

Kanaoka. However, assuming that, relying on Nechvatal, a POSA would have sought to develop an at-home collection method without freezing for a CRC screening method that would test for both COX-2 RNA and fecal occult blood, there would have been no reason to require the additional container, second buffer, and separation steps of the patented method. The RNeasy product used in the best combination (for DNA preservation and extraction) according to Nechvatal stabilized both nucleic acid and protein, so a POSA relying on Nechvatal would have had no reason to separate the sample into two containers with buffers in each container.

XIV. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

194. Dr. Whitney states that, it is his “opinion that the purported invention of the challenged claims is, at best, a minor component of the Cologuard Product.” Ex. 1002 ¶ 334. Dr. Whitney goes on to state his opinion that “to the extent that any of the challenged claims possess novel features, those features have little or nothing to do with the success of the Cologuard product.” *Id.* I disagree. As discussed below, the Cologuard product practices the innovative combination of features – including convenient at home collection and testing for both nucleic acids and blood proteins – claimed in the ’746 patent. As discussed in detail above, nothing in the prior art disclosed or suggested the particular configuration

set forth in the challenged claims. I note that Dr. Whitney does not assert that the Cologuard product does not practice the claims, only that, in his incorrect opinion, that there is no nexus between secondary indicia and those claims.

195. As I note above, I understand that there is a presumption of nexus when the product is co-extensive with the claims, that this, when the product is essentially the claimed invention. I also understand that nexus can be shown by establishing that the secondary considerations are the direct result of the unique characteristics of the claimed invention. In my opinion, there is strong objective evidence that the '746 patent would not have been obvious at the relevant time.

196. As explained below, use of the Cologuard test practices at least claim 3 of the '746 patent, and the Cologuard product is essentially the invention of claim 3. The Cologuard test met the long-felt need for a sufficiently sensitive and specific CRC screening test that was also acceptable to users, thus addressing the uptake problem. The Cologuard test met this need by combining two different types of tests – nucleic acid and fecal occult blood – in a test that allowed for convenient, at home sample collection. Exact Sciences' Cologuard test has been widely adopted and successfully used by millions of people notwithstanding that its combined home test to screen for two classes of biomarkers increased the complexity of the test and the potential for error.

197. In my opinion, the secondary indicia are a direct result of the specific combination of convenient at home collection of a sample that is not frozen, use of a nucleic acid stabilizing buffer with the first portion of the sample, use of a solution that prevents denaturation or degradation of blood proteins, and testing for both nucleic acid and blood protein. Imperiale 2014, discussed above, describes benefits of the Cologuard test over FIT. Among other things, Imperiale 2014 reported that the Cologuard test achieved 42.4% sensitivity for detecting advanced precancerous lesions; 69.2% sensitivity for polyps with high-grade dysplasia; and 42.4% sensitivity for serrated sessile polyps measuring 1 cm or more. *Id.* In comparison with FIT, Imperiale reported that “[a]s measured by the area under the ROC curve (AUC), the discrimination between colorectal cancer and the combination of nonadvanced neoplasia and lesser findings was significantly higher with DNA testing than with FIT (0.94 vs. 0.89, $P = 0.04$) (Fig. 3A); the AUC values for discrimination between advanced colorectal neoplasia (colorectal cancer plus advanced precancerous lesions) and all other findings were 0.73 and 0.67, respectively ($P < 0.001$) (Fig. 3B).” Ex. 1077 at 8.

198. In discussing Cologuard’s improved sensitivity for detecting CRC and precancerous lesions over FIT alone, Imperiale states “[t]his difference may be 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.” Ex. 1077 at 1295. As clearly stated, the noted improved sensitivity over FIT alone was not attributable to an improved hemoglobin component of the combination test. *Id.* Rather, the improved sensitivity is based on the overall test, which tests for a combination of DNA markers and hemoglobin. *Id.* at 1289-90, 1295.

A. The Claimed Invention is Fundamental to the Cologuard Test

199. In my opinion, Cologuard practices at least Claim 3 of the ’746 patent, and the invention claimed in Claim 3 is fundamental to the diagnostic accuracy and patient uptake of Cologuard, thus the secondary considerations are the direct result of the unique characteristics of the claimed invention.

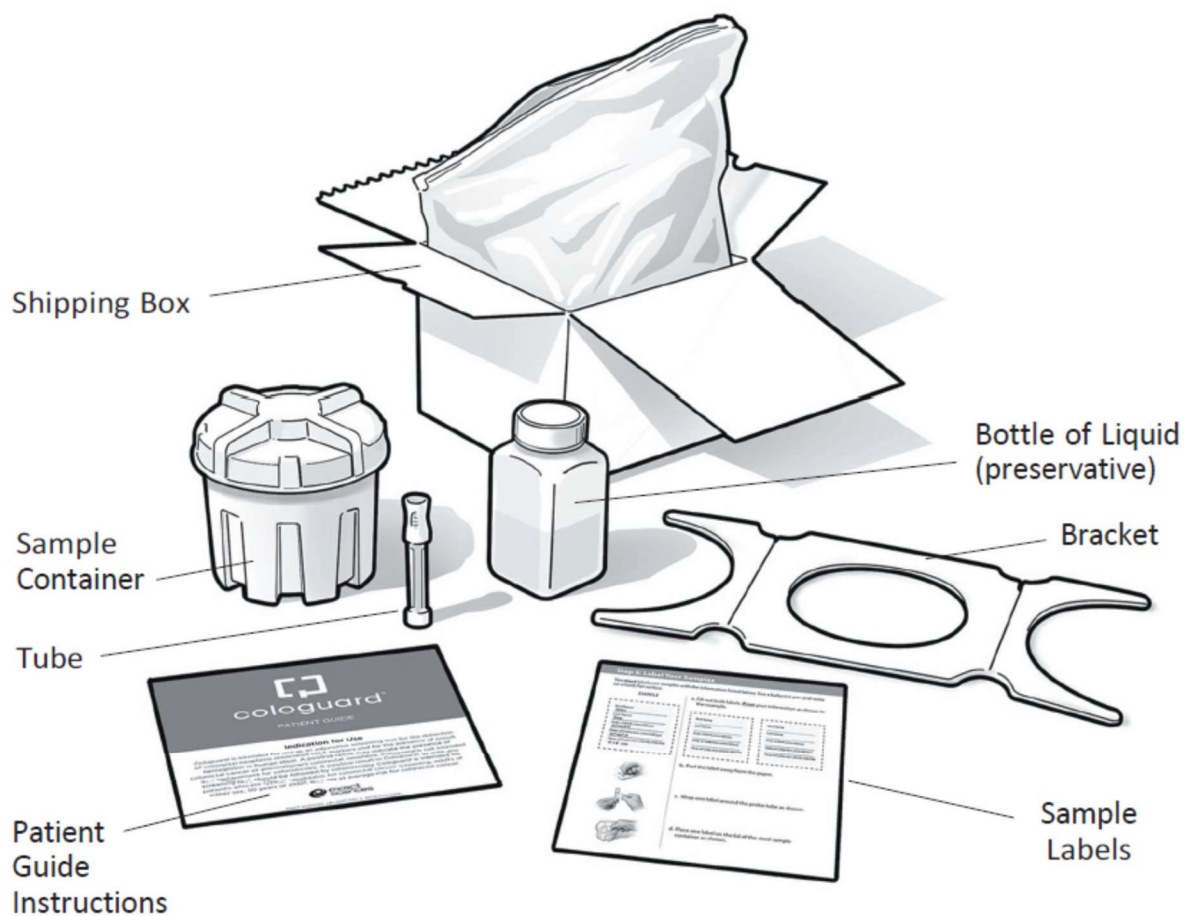
200. As I describe in detail below, the Cologuard Patient Guide (the “Patient Guide”) tracks the at home collection process, including addition of stabilizing buffer and solution to prevent denaturation or degradation of blood protein, of the claimed invention. Convenient home collection without freezing is important to patient acceptance of the test and therefore its uptake. Addition of buffers to the freshly collected samples so that they are preserved without the inconvenience of freezing contributes to both patient acceptance and the diagnostic accuracy of testing. The critical testing steps of subsequent receipt by a

laboratory of the pair of portions of the fecal sample, extraction of nucleic acid from the first portion, testing of the extracted nucleic acid, and testing of the second portion for an amount of blood protein track the elements of Claim 3.

1. [pre]: A method of processing a freshly-collected fecal sample without freezing, the method comprising:

201. The Patient Guide provides detailed instructions for the collection of a fecal sample that is shipped without freezing. Ex. 1076 at 24-28, 30-31. The patient receives a Cologuard Collection Kit (the “Collection Kit”) that includes everything that the patient needs:

What Is Inside the Cologuard Collection Kit



- The bottle of liquid contains a preservative (less than 10% EDTA in Tris buffered solution).
- The tube contains a 10% albumin in Tris buffered detergent solution with an antimicrobial agent.

Ex. 1076 at 8.

2. 1[a]: collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;

202. The Patient Guide includes instructions for the patient to collect a fecal sample by defecating directly into a sealable container in the privacy of their own home. Ex. 1076 at 14, 17-18, 23.

3. 1[b]: in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and;

203. The Collection Kit includes a sealable tube – a separate sealable container – that contains a probe. Ex. 1076 at 14, 20. The probe is used to remove a second a portion of the fecal sample from the sealable collection vessel, leaving a first portion in the vessel. *Id.* at 20-22.

204. The Collection Kit also contains a bottle containing a stabilizing buffer – the “bottle of liquid contains a preservative (less than 10% EDTA in Tris buffered solution).” Ex. 1076 at 8. The Patient Guide instructs the patient to pour all of the contents of the bottle containing the stabilizing buffer over the first portion of the sample in the sealable collection vessel and to seal the vessel after adding the stabilizing buffer. *Id.* at 22-23.

4. 1[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.

205. The probe with the second portion is returned to the separate sealable tube. Ex. 1076 at 20-21.

206. The separate sealable tube in the Collection Kit contains a buffer that prevents denaturation or degradation of blood proteins – a 10% albumin in Tris buffered detergent solution with an antimicrobial agent. Ex. 1076 at 8. The

Patient Guide instructs the user to place the probe with the second portion of stool sample into the tube that contains the buffer and turn the cap. *Id.* at 21. Placing the probe in the buffer-containing separate sealable tube combines the fecal sample with the buffer, and turning the cap seals the container. *Id.* at 21.

5. 3[pre]: A method of processing a fecal sample, the method comprising:

207. The Cologuard test is a method of processing a fecal sample. *See, e.g.,* Ex. 1076 at 6 (“After you collect your stool sample following the instructions in this Patient Guide, the collection kit will be delivered to a lab. The lab will test your stool sample...”).

6. 3[a]: obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising;

208. The pair of portions of the fecal sample are collected from a human subject pursuant to the instruction in the Patient Guide, as set forth in connection with claim elements 1[a] - 1[c] above. The pair of portions is sent to a lab that obtains and tests the portions. *See* Ex. 1076 at 6, 24-28.

7. 3[a][i]: a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and

209. The pair of portions includes a sealed sealable vessel containing the first portion of the fecal sample and stabilizing buffer. Ex. 1076 at 8, 17-18, 22-26.

8. 3[a][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;

210. The pair of portions is obtained by the method of claim 1, as described above. The second portion is obtained by the lab in a sealed sealable container containing the second portion of the fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample.

Ex. 1076 at 8, 20-21, 25.

9. 3[b]: extracting nucleic acid from the first portion of the fecal sample;

211. After obtaining the first portion of the fecal sample from the patient, the lab extracts nucleic acid from that first portion. Ex. 1080 at 4 (“patient stool samples are processed at the laboratory to isolate the DNA for testing.”).

10. 3[c]: testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and

212. After obtaining the first portion of the fecal sample from the patient, the lab tests the first portion for an amount of human nucleic acid. *See, e.g.*, Ex. 1076 at 6 (“Cologuard is designed to detect the DNA and hemoglobin released from these abnormal cells in your stool.”), Ex. 1080 at 4 (“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.”)

11. 3[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.

213. After obtaining the second portion of the fecal sample from the patient, the lab tests the second portion for hemoglobin. Ex. 1076 at 6 (“Cologuard is designed to detect the DNA and hemoglobin released from these abnormal cells in your stool.”); Ex. 1080 at 4 (“The hemoglobin stool sample is prepared and analyzed in a quantitative Enzyme-Linked Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.”)

B. The Cologuard Test Has Been Widely Adopted

214. In my opinion, the Cologuard test would not have been adopted to the extent that it has been if it did not satisfy two critical aspects of screening tests: diagnostic accuracy and uptake. As illustrated in the discussion of the claims above, the claimed invention of the ’746 patent is essential to both of these criteria that are necessary for both clinical and commercial success of a diagnostic product such as a CRC screening test. The addition of buffers to each of the first and second portions of the sample and the fact that the sample is tested for both nucleic acids and fecal occult blood all contribute to the test’s diagnostic performance. In addition, the Cologuard test kit itself, which uses the ’746

patented method, allows convenient, at-home collection in a way that patients have accepted.

215. The product literature directed at patients and physicians describe Cologuard as testing for both DNA markers and hemoglobin. For example, the first sentence of the first page of the Cologuard Patient Guide states “Cologuard is intended for the qualitative detection of colorectal neoplasia associated with DNA markers and for the presences of occult hemoglobin in human stool.” Ex. 1078 at 1. In describing how Cologuard works, the Patient Guide states that “Cologuard is designed to detect the DNA and hemoglobin released from these abnormal cells in your stool.” *Id.* at 6. The press release upon launch of Cologuard noted that Cologuard was “the first noninvasive screening test for colorectal cancer that “analyzes both stool DNA and blood biomarkers and has been proven to find 92 percent of cancers and 69 percent of the most advanced precancerous polyps in average risk patients.” Ex. 1025 at 1. The press release continues by noting that Cologuard provides “an easy-to-use screening test” that people “can do in the privacy of their own home.” *Id.* These materials confirm that critical aspects of the test are that it is multitarget, testing for both DNA and blood, and that it is easy to use.

216. The Cologuard Physician Brochure similarly begins with the statement that “Cologuard is intended for the qualitative detection of colorectal neoplasia associated with DNA markers and for the presence of occult hemoglobin in human stool.” Ex. 1080 at 1. The Physician Brochure explains that Cologuard is “a statistically superior noninvasive stool test for detecting CRC and AA.” *Id.* at 3. The Physician Brochure also explains that “[b]ased on combined results of all the DNA markers and hemoglobin, a single Cologuard result is determined.” *Id.* The Physician Brochure reports details of the DeeP-C Study showing Cologuard’s diagnostic performance for both CRC and AA. *Id.* at 4-9.

217. The adoption and use of the Cologuard test is particularly noteworthy considering the landscape for CRC screening into which it was launched. By the time that Cologuard received FDA approval and was launched in 2014, the poor performance and/or lack of patient acceptability of other CRC screening tests were well known.

218. In 2005, Schroy and Heeren published a study designed to “assess and compare the perceptions of asymptomatic, mostly average-risk subjects undergoing stool-based DNA testing, FOBT, and colonoscopy as part of one of the large multicenter trials.” *See* Schroy PC 3rd, Heeren TC, *Patient perceptions of*

stool-based DNA testing for colorectal cancer screening, 28(2) Am. J Prev Med 208, 208-214 (2005) (Ex. 2036). The Schroy article is cited in footnote 16 of Itzkowitz on which Geneoscopy relies. *See* Ex. 1006 at fn. 16. Schroy observed that “[p]oor patient adherence has been a major barrier to CRC screening.” Ex. 2036 at 1. Schroy went on to note that previous studies had identified “practical reasons (e.g., conflicts with work or family commitments, inconvenience, lack of interest, and cost), lack of current health problems or worrisome symptoms, and most importantly, lack of a physician recommendation as the major reasons for nonparticipation.” *Id.* Schroy also pointed out that “[n]egative attitudes toward the tests themselves are also prevalent.” *Id.* Among other things “[f]ecal occult blood testing (FOBT) is widely perceived as embarrassing or distasteful.”

219. Itzkowitz also recognized the existing barriers to screening as of 2007, observing that “[c]oncerns about test discomfort, invasiveness, embarrassment, and self-efficacy have been identified as important barriers to more effective screening.” Ex. 1006 at 5. As Itzkowitz states, “[i]nherent in the success of any screening test is patient acceptance.” *Id.* at 6.

220. For a CRC screening test to be prescribed by doctors and used by patients, both doctors and patients would have to be aware of the test and willing to prescribe or use it, respectively. This requires education of both doctors and

patients in the best of circumstances so that they are aware of diagnostic performance and usability, among other things. As the authors of the Levin reference observed, there was in 2008, and there remains “suboptimal awareness and engagement of primary care in supporting adherence with screening recommendations.” Ex. 1013 at 3.

221. In addition to the need to educate prescribers and users generally, the Cologuard test faced the barriers and bias that were highlighted in literature such as Schroy and Itzkowitz concerning at-home collection and handling of stool samples. In fact, considering that the Cologuard test requires at-home interaction with the stool sample to remove a portion of the sample to the separate sealable container, adoption of the Cologuard test required effort and education to overcome the reluctance described in the literature.

C. Failure of Others and Long Felt Need

222. By February of 2009, it was known that early screening and detection reduced CRC mortality. *See, e.g.*, Ex. 1004 at 1 (“Detection of early disease and precancerous adenomatous lesions leads to a decrease of CRC-related mortality.”); Ex. 1012 (“The diagnosis and the therapy of early-stage tumours have the potential to decrease morbidity and mortality of colorectal cancer patients.”).

223. The references included as exhibits with Geneoscopy's Petition provide an overview of the extensive work that had been done before 2009 to try to address the problem. As discussed in Geneoscopy's Exhibit 1013, those efforts included gFOBT, iFOBT (referred to as "FIT" in that reference), and sDNA tests, among others. Ex. 1013 at 4-10.

224. However, as discussed in the background above as well as in the background in the '746 patent, the technologies that existed at the time of the invention, such as colonoscopy and noninvasive tests including gFOBT and FIT, each had their own limitations and had not adequately reduced the numbers of unscreened individuals. Both the background discussion in the '746 patent and the references on which Geneoscopy relies in challenging the '746 patent discuss the limitations with the existing technology. *See, e.g.*, Ex. 1001 at 1:56-3:40; Ex. 1013.

225. As I also discuss above, although colonoscopy was considered the gold standard for testing as of 2009, it has significant drawbacks. It is an invasive procedure that carries a risk, although a low one, of complications including perforation that would require surgery; it requires preparation through colonic purge before the procedure; and it must be performed at a medical facility which requires patient time and potential travel as well as availability of trained medical

personnel to perform the procedure. *See, e.g.*, Ex. 1021 at 1 (noting potential harm from colonoscopy, availability of qualified endoscopists, and costs); Ex. 1034 at 13 (noting the need to travel and the physical hazards, discomfort, and pain of unnecessary colonoscopies).

226. FOBT, FIT, and previous nucleic-acid based tests also failed to satisfy the existing, long-felt need. For example, the sensitivity and predictive value of FOBT were suboptimal with approximately 10% sensitivity for advanced adenomas. Ex. 1042 at 7-8. FOBT was also widely perceived as embarrassing or distasteful. Ex 2036 at 1.

227. Fecal DNA analysis had also been explored by 2009. DNA analysis at the time offered only marginal increase in sensitivity for advanced neoplasia, including advanced adenomas and CRC, to 18.2%, the benefit of which was offset by increased cost per test. *See* Ex. 1042 at 7-8.

228. Exact Sciences' own history highlights failed efforts to develop CRC screening tests with sufficient diagnostic accuracy and that would be used by patients prior to the Cologuard test. Exact Sciences' previous attempts to develop a non-invasive CRC screening test with sufficient diagnostic accuracy and user uptake were well known in the field. By 2004, a team at Exact Sciences had developed the company's first non-invasive, DNA based test used for screening

for CRC. *See, e.g.*, Ex. 1042; *see also* Ex. 1006. That test, which is identified as version 1 in Itzkowitz, was the subject of the 2004 Imperiale article comparing fecal DNA testing with gFOBT. *See* Ex. 1042; Ex. 1006. Although the sensitivity of that first Exact Sciences test was far superior to gFOBT, the overall sensitivity for invasive cancers plus adenomas was only 40.8%. Ex. 1042 at 1.

229. As is described in Itzkowitz, and was also known in the field at the time, by 2007 a team at Exact Sciences had developed the second-generation DNA-based stool. *See* Ex. 1006. As discussed above, Itzkowitz notes, among other things, that how well the “new fecal DNA assay might perform for detecting adenomas is not yet known, but will be the subject of future investigation.” Ex. 1006 at 7. That version 2 Exact Sciences test also failed to satisfy the long-felt need for a CRC screening test with sufficient diagnostic accuracy.

230. As of the Priority Date, a high proportion of individuals within the group for whom guidelines recommended screening still had not undergone CRC screening and there remained a longstanding, unmet need. *See, e.g.*, Ex. 1006 at 1 (“fewer than half of eligible individuals older than age 50 have undergone CRC screening.”); Ex. 1013 at 2 (“a majority of US adults are not receiving regular age- and risk-appropriate screening or have never been screened at all.”)

231. The low screening levels of individuals within the recommended screening group persisted until the introduction of the Cologuard test by Exact Sciences, which through the combination of fecal DNA analysis and identification of blood proteins in the stool offered excellent sensitivity and specificity for early-stage CRCs and robust sensitivity and excellent specificity for advanced adenomas. The test had excellent uptake by patients and patient accessibility due to its non-invasive nature and lack of complications, thus addressing all major limitations of the other attempts at CRC screening.

232. The Cologuard test has been responsible for significant increases in CRC screening rates and patient adherence.

233. One publication observed that in 2019 alone, 1.7 million patients were successfully screened using Cologuard. *See Lesley-Ann Miller-Wilson et al., Cross-sectional adherence with the multi-target stool DNA test for colorectal cancer screening in a large, nationally insured cohort*, 36 International Journal of Colorectal Disease 2471, 2471-2480 (2021) (Ex. 2037) at 2.

234. Another study described better adherence from patients using the Cologuard test where, in the Medicare population, 71% of beneficiaries who had a Cologuard test order completed the test, with 91% completing the test within 60 days, far exceeding the 45% adherence rate for other fecal CRC tests. John B.

Kisiel et al., *Multitarget Stool DNA for Average Risk Colorectal Cancer Screening Major Achievements and Future Directions*, 30 *Gastrointest Endoscopy Clin N Am* 553, 553-568 (2020) (Ex. 2038) at 10.

235. Other studies have confirmed that the Cologuard test is being used by a patient population whose needs were previously unmet by the then-available screening options. A study published in 2020 found that 24% of patients with a positive Cologuard test who subsequently had a screening colonoscopy were over 10 years overdue for screening. Jason D. Eckmann et al., *Multi-Target Stool DNA Testing for Colorectal Cancer Screening: Emerging Learning on Real-world Performance*, 18 *Curr Treat Options Gastro* 109, 109-119 (2020) (Ex. 2039) at 4. I also understand that internal studies by Exact Sciences have shown that approximately 40% of surveyed Cologuard users were previously unscreened for CRC. Exact Sciences Form 10-K for the year ending December 31, 2023 at 5 (Ex. 2029).

236. That Cologuard has met the long-felt need for a non-invasive CRC screening test with sufficient diagnostic accuracy and patient uptake is reflected by the percent of the screenable population that is now using the Cologuard test. I understand that roughly 4 million Cologuard tests were used in the United States in 2023. Ex. 2029 at 4; Ex. 2021 at 11. This represents a significant portion of the

number of people who are eligible to be screened and who are screened in a single year, particularly of those being screened by non-invasive means.

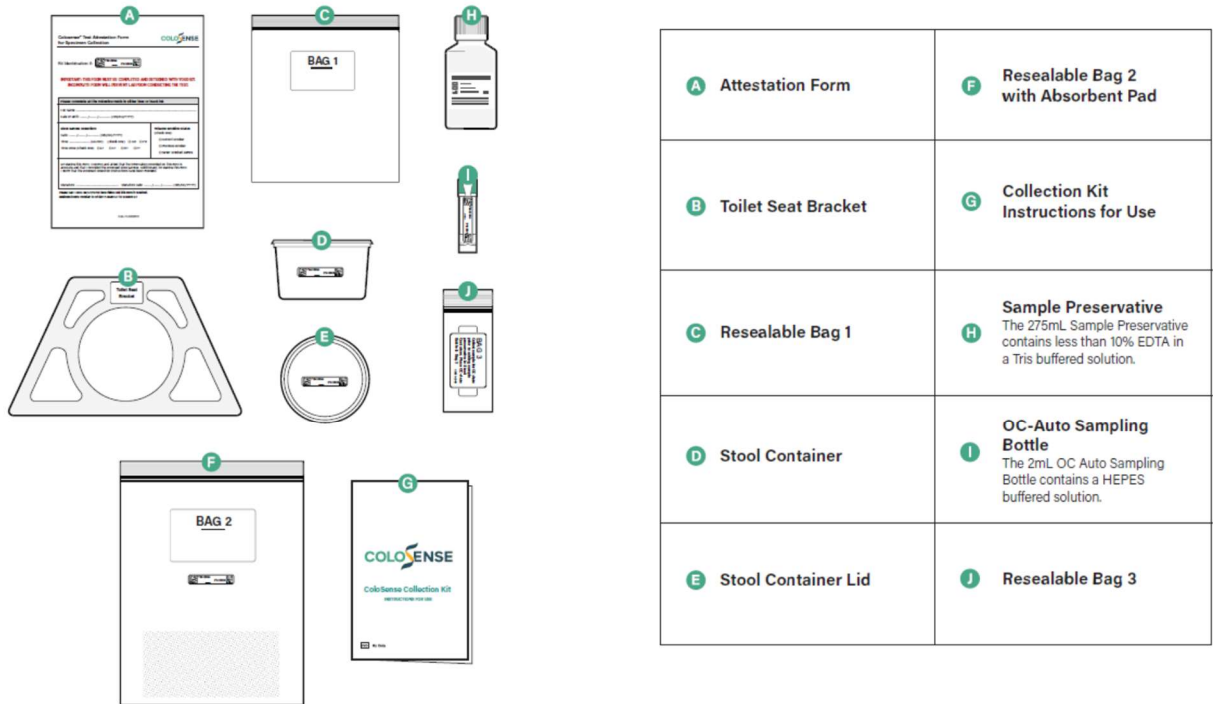
237. The volume of Cologuard test sales, increased screening rates overall, and the number of Cologuard test users who were never previously screened or were well overdue for screening all demonstrate that the Cologuard test is meeting the previously unmet need.

D. Copying by Geneoscopy

238. Like the patient instructions of Cologuard, the instructions for Petitioner Geneoscopy's ColoSense™ track the steps of Exact Sciences' patented method as claimed in the '746 patent. Product information for ColoSense is available at https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001C.pdf. A true and correct copy of the information downloaded from this link to the FDA website is marked as Exhibit 2040.

239. Geneoscopy's kit contains the same general components as Exact Sciences' Cologuard collection kit.

ColoSense Collection Kit Contents



Ex. 2040 at 34.

240. As instructed by Geneoscopy, a patient using the ColoSense kit collects a fresh fecal sample in the privacy of their own home. Ex. 2040 at 36-37.

241. The patient removes a portion of the sample from the Stool container with a sample probe that is housed in what Petitioner calls a “sampling bottle,” creating a first portion and a second portion of the sample. Ex. 2040 at 36-37.

242. The patient adds a stabilizing buffer to the first portion of the sample in the sealable sample container, and seals the container. Ex. 2040 at 38-40.

243. The sampling bottle contains “liquid Sample Preservative” – a buffer that prevents denaturation or degradation of blood proteins. Ex. 2040 at 37-38.

244. The patient returns the probe that is covered with the second portion of the stool sample to the sampling bottle and seals it. Ex. 2040 at 38.

245. Both containers are shipped to a lab at room temperature. Ex. 2040 at 38-40.

246. The lab obtains the two containers with the two portions. Nucleic acid is extracted from the first portion and the nucleic acid is tested for an amount of human nucleic acid. *Id.* at 54-55. The second portion is tested for an amount of blood protein. Ex. 2040 at 56.

XV. CONCLUSION

247. For all of the reasons set forth above, the challenged claims of the ’746 patent would not have been obvious to a POSA as of the Priority Date.

248. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for

cross-examination within the United States during the time allotted for cross-examination.

249. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on the information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: May 30, 2025



Vadim Backman