UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

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

DECLARATION OF VADIM BACKMAN, Ph.D.
IN SUPPORT OF PATENT OWNER'S RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT 11,634,781

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 11,634,781 and exhibits thereto, including the '781 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 '781 patent and the materials cited in this declaration. I have also reviewed the Board's Institution Decision and the transcript of the October 10, 2024 deposition of Dr. Duncan Whitney. I am also aware that Geneoscopy has filed a Petition for *Inter Partes* Review of Exact Sciences' U.S. Patent No. 11,970,746 (the "'746 patent") and that the '746 patent

issued from a continuation of the application that resulted in the ’781 patent. I am further aware that Exact Sciences has filed a continuation application in the same patent family, Application No. No. 18/919,170. I will consider Geneoscopy’s petition for *inter partes review* concerning the ’746 patent and/or Exact Sciences’ ongoing patent prosecution in the same patent family to the extent that such information becomes relevant to my opinions.

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 ’781 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 claims of the ’781 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”) of Vilkin with nucleic acid-based testing. 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 tests 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 claims of the ’781 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. 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. Finally, 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.

18. 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 '781 patent would not have been obvious to a POSA as of the Priority Date.

19. 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

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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

28. 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.

29. 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 1 ("It is the strong opinion of this expert panel that *colon cancer prevention* should be the primary goal of CRC screening.").

30. 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. 1024 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 too 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.

31. 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.

32. 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.

33. 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.

34. 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. 1043 at 5; *see also* Ex. 1033 at 12-13.

35. 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.

36. 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. 1033 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. 1010 at 1; *see also* Ex. 1033 at 13.

37. For all of these reasons, considerably less than half of the eligible population received regular colonoscopic screening before 2009. *See, e.g.,* Ex. 1043 at 2; Ex. 1044 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. 2020). 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.

38. 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.

39. 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.

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. 1043 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).

40. 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.

41. 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) (Ex. 2008). The 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 '781 PATENT

42. As explained in the detailed description of the invention, the invention of the '781 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 6:40-45. 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 6:45-53.

43. The Background of the Invention in the '781 patent is consistent with my experience and the discussion above concerning CRC and CRC screening. Ex. 1001 at 1:40-3:67.

44. Claim 1 of the '781 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 by direct defecation into a sealable container; (b) removing a portion of the fecal sample to a separate sealable container, at which point there is a removed portion and a remaining portion; (c) combining the removed portion in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins in the fecal sample, and sealing the separate container; and (d) combining the remaining portion of the sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel. Ex. 1001 at 45:21-38.

45. Claim 3 of the ’781 patent describes a method of processing a fecal sample, the method comprising: (a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: (i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and (ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions obtained by the method of claim 1; (b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion; (c) extracting nucleic acid from the remaining portion of the fecal sample; and (d) testing the nucleic acid for an amount of a human nucleic acid. Ex. 1001 at 45:45-61.

VII. LEVEL OF ORDINARY SKILL IN THE ART

46. 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.

47. 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.

48. I have reviewed the declaration of Dr. Whitney, including his opinion concerning a POSA. Specifically, Dr. Whitney opines that "a POSA relevant to the '781 Patent would have a Ph.D. in chemistry, biochemistry, biology, or a related field and at least five years of experience designing and performing diagnostic assays on fecal samples." 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.

49. I have also reviewed the level of ordinary skill in the field that Geneoscopy included in its request for reexamination of the '781 patent, and that it attributed to Mr. Anthony Shuber, who submitted a declaration in that proceeding. Ex. 1021 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.

50. 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 Ph.D., Dr. Whitneys adds an extraordinary requirement of at least five years of experience with the narrow focus of designing and performing diagnostic assays on fecal samples.

51. 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.

52. I understand that, in the Institution Decision, 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 9 at 8.

53. 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.

54. No matter which of the three different levels of skill is applied, it does not change my opinion that the claims of the '781 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)

55. 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.

56. 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.

57. 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.

58. 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.

59. 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.

60. 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. 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.
[a]0, 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.*.

61. The data 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.

62. That the specific 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.

63. Lenhard's teachings are 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).

64. 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 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.

65. 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.

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.*

66. A POSA considering Lenhard and its statement that the specific combination of HIC1 and gFOBT "allowed for detection of two thirds of

cancers," would 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.*

67. 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." In other words, Lenhard had the data they could have used to conclude that FOBT should be used together with HIC1. Instead, 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.

68. A POSA in 2009 would have considered the entire Lenhard reference, including (1) the advanced stage of the known CRC patients tested in Lenhard; (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; and (5) Lenhard's own conclusions. 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)

69. 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. 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. Vilkin required that the subject prepare three consecutive daily samples. *Id.* at 1 (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.

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.

70. 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% ± 0.4 at 4°C (NS), 2.2% ± 1.7 at

20°C (NS), and 3.7% ± 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]efrigerated*** 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 teaches that refrigeration was required to prevent decay.

71. Vilkin also states that providing double zip-lock bags with the tests "answered some of the screenees' hesitancy about keeping the prepared test transiently in their home refrigerator." Ex. 1005 at 8.

72. 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.

73. 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. A POSA would also understand that the results disclosed in Vilkin were based on annual collection and testing of three separate samples from each patient and that the samples were refrigerated.

C. Itzkowitz (Ex. 1006)

74. Itzkowitz describes testing a specific DNA-based 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 sensitivity from 3% to 65%, confirming the observation of Olson et al." *Id.* at 6.

75. 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.").

76. 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.

77. Itzkowitz does not include any data concerning adenomas. Itzkowitz states 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.

78. Itkowitz 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*.

79. 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.

80. 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)

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

82. 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]. Of this limited sample size, COX-2 was detected in 27 of the 30 known cancer cases. *Id.* at [0065]. COX-2 was not detected in any of the 22 cases in the control group. In other words, COX-2 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 test had no false positives in the control cases (specificity 100%). *Id.* at [0066], [0065].

83. 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].

84. The data in Kanaoka show that sensitivity and specificity for colon cancer of COX-2 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 alone. Based on these data, a POSA would conclude that COX-2 should ***not*** be combined with FOBT.

85. I also note that the Kanoaka patent application does not conclude that COX-2 should be combined with FOBT.

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

E. Derks (Ex. 1008)

87. Geneoscopy relies on Derks only in Grounds III and VI for its discussion of particular markers. Derks is a 2006 article that explores "the timing of promoter methylation and relationship with mutations and chromosomal alterations" in CRC. Ex. 1008 at 1. Derks evaluated the promoter methylation status of hMLHl , O^6MGMT, APC, $pl4^{ARF}$, $pl6^{INK4A}$, RASSFJA, GATA -4, GATA-5, and CHFR. Derks concludes that "[s]ince promoter methylation was already present in nonprogressed adenomas without chromosomal alterations. . .promoter methylation can be regarded as an early event preceding TP53 mutation and chromosomal abnormalities in colorectal cancer development." *Id.*

88. Consistent with the other references on which Petitioner relies and the knowledge in the art at the time, Derks also emphasizes the potential for early detection. In summarizing its conclusions, Derks states that the "association between gene methylation and pre-malignant lesions is highly relevant for methylation-marker based colorectal cancer screening." Ex. 1008 at 10. Derks states that its observations suggest that "methylation levels in normal colonic mucosa could serve as a marker of the risk of development of CRC." *Id.* Derks concludes that "[g]iven that aberrant DNA methylation can also be detected in stool DNA, studying methylation as common event in pre-malignant lesions is

promising to provide novel specific biomarkers for risk assessment and secondary prevention." *Id.*

F. Shuber (Ex. 1009)

89. Shuber is an international patent application assigned to Exact Sciences. *See* Ex. 1009. Like Itzkowitz, Shuber describes certain of Exact Sciences' earlier work concerning nucleic acid-based CRC screening.

90. Shuber discloses a method for stabilizing nucleic acids in biological samples, including stool samples, to facilitate analysis in a nucleic acid integrity assay. Ex. 1009 at 2:5-10. 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 20, *citing* Ex. 1009 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 20. 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.

91. 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. 1009 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.

92. 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 conatiner)" [sic] that either already contains a stabilization solution or to which a stabilization solution may be added. Ex. 1009 at 29:7-19. Shuber does not specifically mention home collection by a patient. *See generally id*.

93. 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.

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

94. The claims of the '781 patent would not have been obvious to a POSA as of the Priority Date in light of the Lenhard, Itzkowitz, and Vilkin combination.

95. 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 testing of three samples per subject. Ex. 1005. A POSA at the time 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

96. Lenhard would not have motivated the combination of any FOBT with 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 14, 21. 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.

97. 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 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.

98. 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.

99. 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 predicative 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" allowed the Vilkin authors to achieve sensitivity of 76.5% with "acceptable specificity" of 95.3%. *Id.* 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.

100. 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.

101. Itzkowitz described a series of improvements in DNA-based testing and concluded that a combination of DNA-based markers could achieve acceptable sensitivity with reduced complexity.

102. 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.

103. 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.

104. 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. 1043; Ex. 1044; *see also* Ex. 1024 at 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

105. 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.

106. 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 HIC1/gFOBT combination of Lenhard 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.

107. 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. 1033 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*.

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

108. As discussed above, the iFOBT of Vilkin required that the subject prepare three consecutive daily fecal samples. Ex. 1005 at 1 (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. 1024 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.

109. 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.

110. 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 "screenees' hesitancy about keeping the prepared test transiently in their home refrigerator." Ex. 1005.

111. 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 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.

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

112. Itzkowitz also discourages use of FOBT. Itzkowitz recognized the well-known need for patient acceptability. Ex. 1006. at 6-7. 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." 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.

113. 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 with a combination of two types of tests would only increase the cost. Combining a nucleic acid test with an FOBT test as claimed requires, among other things, more collection components for the separated sample and separate testing once the sample is delivered to the lab. The samples, once delivered, must then be analyzed using separate technology platforms and different sets of equipment. The analysis of the two separate classes of biomarkers produces two sets of results. All of these factors result in added cost, complexity, and increased potential for error and would have weighed against combination of tests for two different classes of biomarkers.

114. Requiring a patient to remove a portion of stool from the sample for the FOBT test 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. 2048 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 '781 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. 1024 at 4 ("Population participation is essential for cancer detection.")

115. 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.

116. The invention of the ’781 patent requires at-home sample collection, sample separation, and the addition of buffers to each sample in different containers. Each 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.

117. 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 his declaration that “many assays used different buffers to minimize loss of sample integrity.” Ex. 1002 ¶ 74. He also provides examples of references that discussed buffers to prevent degradation of DNA and buffers to stabilize blood protein. *Id.* Dr. Whitney does not compare formulations of DNA stabilization buffers and blood protein stabilization buffers known in the art at the time to reach any opinion as to whether or not it would

have been possible to use a DNA stabilization buffer to also stabilize blood proteins. A POSA at the time 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 the Priority Date 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.

118. Finally, there is 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. 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. For example, Lenhard describes testing frozen samples. As another example, 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.

119. 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 sample in two separate sealable containers, where each sample is combined with buffer, 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.

X. GROUND IV: SHUBER AND VILKIN DO NOT RENDER ANY CLAIM OBVIOUS

120. The claims of the ’781 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. 1009 at 2:5-10. 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.

121. 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.

122. 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 20. 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.

123. 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. 1009 at 14:1-15.

124. Shuber says little about sample collection and contains no specific mention of at-home collection by a patient. *See* Ex. 1009 at 29:8-19.

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

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

127. 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.

128. Among other things, Geneoscopy relies on a sentence from Nishikawa, a reference dated 2002. Pet. at 48, 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 '781 patent, yet no one else in this active field came up with the combination before Exact Sciences' claimed invention.

129. Geneoscopy also cites to Lenhard in its argument that a POSA would have been motivated to combine Shuber with Vilkin. Pet. at 49. 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.

130. Geneoscopy also relies on Kutzner. Pet. at 49. 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. 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 success. I also note that the FOBT discussed in Kutzner was gFOBT, not iFOBT.

131. Geneoscopy also relies on Levin. Pet at 49-50. 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.* Both references support that it would not have been obvious to a POSA to combine DNA testing with any form of FOBT with any reasonable expectation of success. To the contrary, Levin indicates that a POSA would not be motivated to combine tests in light of data such as that in Lenhard and Kanaoka, both of which show adverse effects on specificity.

132. I also note that Levin concluded that there were "no clear patterns of superior performance between a high-sensitivity guaiac-based test (Hemoccult SENSA) and a variety of FIT." *Id.* In addition, Levin notes "higher costs associated with FIT compared with gFOBT." *Id.*

133. I further note that, in its later combination relying on Kanaoka in connection with certain dependent claims, Geneoscopy argues that Example 1 of Kanaoka provides further motivation to combine. *See* Pet. at 63. As with Lenhard, analysis of the data in Kanaoka shows that Kanaoka would have discouraged, not

encouraged, a combination. Example 1 shows that testing for COX-2 and using an iFOBT test resulted in one additional positive test from the iFOBT what was not identified with the COX-2 test. Ex. 1007 at [0067]. The iFOBT test also had three false positives among the control cases (specificity 86.3%), where the COX-2 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.

134. The references on which Geneoscopy relies confirm that, a POSA at the time seeking to "improve the sensitivity of CRC diagnosis" 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.

135. As is also discussed above, a POSA also would not have had a reasonable expectation of success of combining iFOBT with nucleic acid-based testing.

136. 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.

XI. GROUNDS II, III, V, AND VI ALSO FAIL

137. 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 and V address only dependent claims 12 and 13. Geneoscopy's Grounds III and VI address only dependent claim 10. Those claims also would not have been obvious to a POSA at the time for the same reasons discussed above.

138. With respect to Claims 12 and 13, Petitioner argues that Kanaoka provides further motivation to combine to increase sensitivity. Pet. at 44, 63. As discussed above, the results reported in Example 1 of Kanaoka shows that testing for COX-2 and using an iFOBT test resulted in one additional positive test from the iFOBT that was not identified with the COX-2 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 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.* As with Lenhard, consideration of the Kanaoka reference as a whole would have discouraged a combination of nucleic acid-based and FOBT tests.

XII. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

139. In my opinion, there is strong objective evidence that the ’781 patent would not have been obvious at the relevant time. Patent Owner Exact Sciences successfully developed a CRC screening test, sold commercially as Cologuard, that embodies at least claims 1 and 3 of the ’781 patent.

140. As explained below, 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. 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.

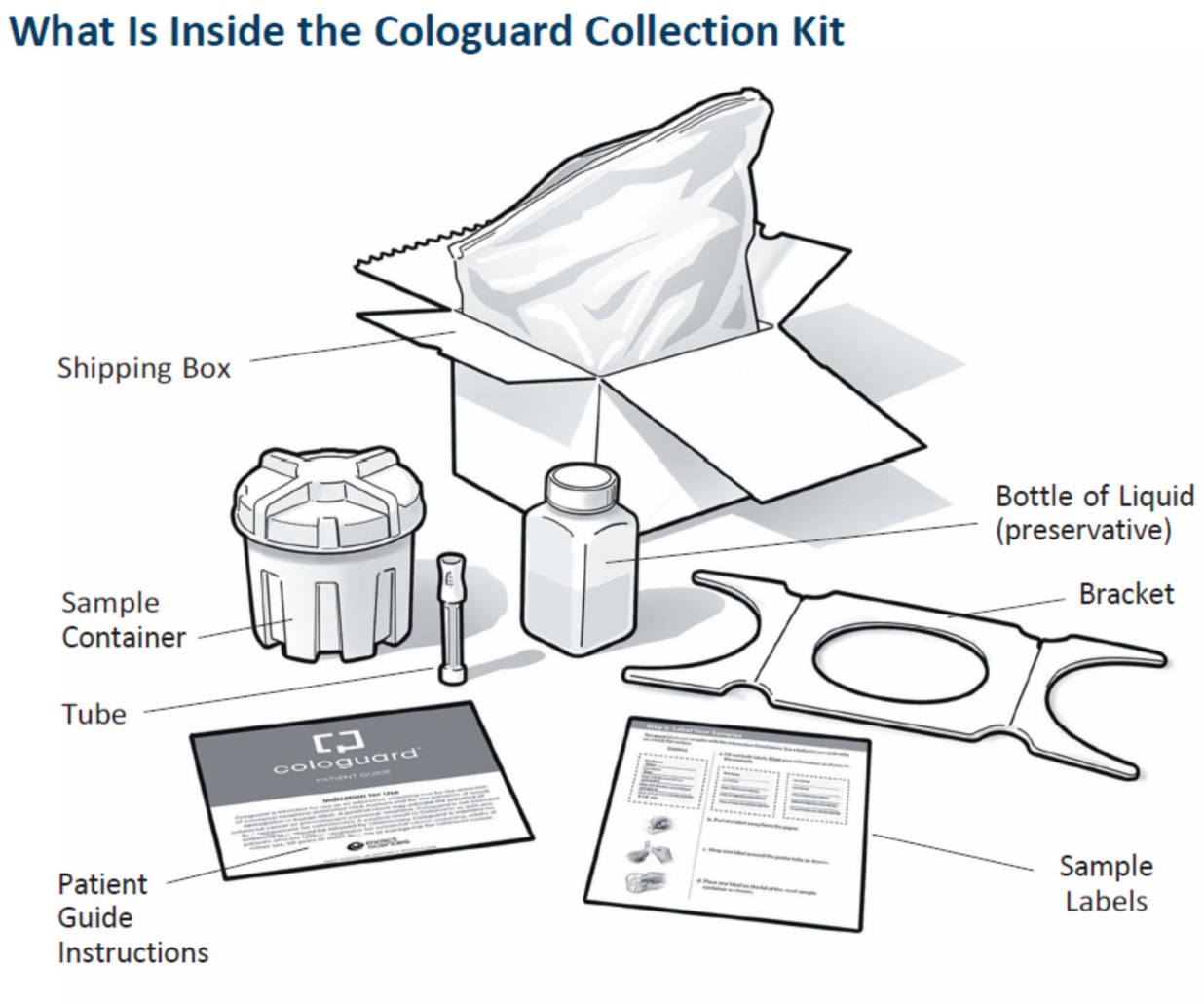
A. The Claimed Invention is Fundamental to the Cologuard Test

141. In my opinion, Cologuard practices at least claims 1 and 3 of the ’781 patent, and the invention claimed in claims 1 and 3 is fundamental to the diagnostic accuracy and patient uptake of Cologuard.

142. As described below, the Cologuard Patient Guide (the “Patient Guide”) tracks the sample processing method of Claim 1 and the collection and subsequent laboratory testing of the collected sample practices of Claim 3.

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

143. The Patient Guide provides detailed instructions for the collection of a fecal sample that is shipped without freezing. Ex. 2032 at 24-28, 30-31. The patient receives a Cologuard Collection Kit (the “Collection Kit”) that includes everything that the patient needs:



- 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.

Patient Guide 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 by defecation directly into a sealable collection vessel;

144. The Collection Kit includes a sealable sample container and the Patient Guide includes instructions for the patient to defecate directly into that sealable container in the privacy of their own home. Ex. 2032 at 14, 17-18, 23.

3. 1[b]: removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;

145. The Collection Kit also includes a sealable tube – a separate sealable container – that contains a probe. Ex. 2032 at 14, 20. The probe is used to remove a portion of the fecal sample from the sealable collection vessel. *Id.* at 20-21. The probe is then returned to the separate sealable tube. *Id.* Removal of a portion of the fecal sample with the probe results in a removed portion in the tube and a remaining portion of the fecal sample in the collection vessel. *Id.* at 20-22.

4. 1[c]: combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and

146. 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. 2032 at 8. The Patient Guide instructs the user to place the probe with the removed 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. 1[d]: combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.

147. 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. 2032 at 8. The Patient Guide instructs the patient to pour all of the contents of the bottle containing the stabilizing buffer over the sample in the sealable collection vessel and to seal the vessel after adding the stabilizing buffer. *Id.* at 22-23.

6. 3[pre]: A method of processing a fecal sample, the method comprising:

148. The Cologuard test is a method of processing a fecal sample. *See, e.g.,* Ex. 2032 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…").

7. 3[a]: obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising;

149. 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] and 1[b] above. The pair of portions is sent to a lab that obtains and tests the portions. *See* Ex. 2032 at 6, 24-28.

8. 3[a][i]: a sealed sealable container containing a removed portion of a fecal sample and a buffer; and

150. The pair of portions includes a sealed sealable container, the tube, containing a removed portion of the fecal sample and a buffer. Ex. 2032 at 8, 20-21, 25.

9. 3[a][ii]: a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer,

the pair of portions obtained by the method of claim 1;

151. The pair of portions is obtained by the method of claim 1, as described above. The pair of portions includes a sealable container containing a remaining portion and a stabilizing buffer. Ex. 2032 at 8, 17-18, 22-26.

10. 3[b]: testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;

152. After obtaining the removed portion of the fecal sample from the patient, the lab tests the removed portion for hemoglobin. Ex. 2032 at 6 ("Cologuard is designed to detect DNA and hemoglobin released from these abnormal cells in your stool."), 46 ("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.")

11. 3[c]: extracting nucleic acid from the remaining portion of the fecal sample; and

153. After obtaining the remaining portion of the fecal sample from the patient, the lab extracts nucleic acid from that remaining portion. Ex. 2032 at 46 ("patient stool samples are processed at the laboratory to isolate the DNA for testing.).

12. 3[d]: testing the nucleic acid for an amount of a human nucleic acid.

154. After obtaining the remaining portion of the fecal sample from the patient, the lab tests the remaining portion for an amount of human nucleic acid. *See, e.g.,* Ex. 2032 at 6 ("Cologuard is designed to detect the DNA and hemoglobin released from these abnormal cells in your stool."), at 46 ("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.")

B. Cologuard Has Been Widely Adopted

155. 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 ’781 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 remaining and removed 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 ’781 patented method, allows convenient, at-home collection in a way that patients have accepted.

156. 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.

157. 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. 2048). 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. 2048 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."

158. 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.

159. 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.

160. 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

161. 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.").

162. 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 3-9.

163. However, as discussed in the background above as well as in the background in the '781 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 '781 patent and the references on which Geneoscopy relies in challenging the '781 patent discuss the limitations with the existing technology. *See, e.g.,* Ex. 1001 at 1:56-3:40; Ex. 1013.

164. 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. 1010 at 1 (noting potential harm from colonoscopy, availability of qualified endoscopists, and costs); Ex. 1033 at 13 (noting the need to travel and the physical hazards, discomfort, and pain of unnecessary colonoscopies).

165. 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. 1043 at 7-8. FOBT was also widely perceived as embarrassing or distasteful. Ex 2048 at 1.

166. 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. 1043 at 7-8.

167. 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. 1043; *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. 1043; 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. 1043 at 1.

168. 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.

169. 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.")

170. 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.

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

172. 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. 2049) at 2.

173. 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 at 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. 2050) at 10.

174. 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. 2052) at 3. 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 2023 Form 10-K at 5 (Ex. 2040).

175. 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. 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.

176. 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.

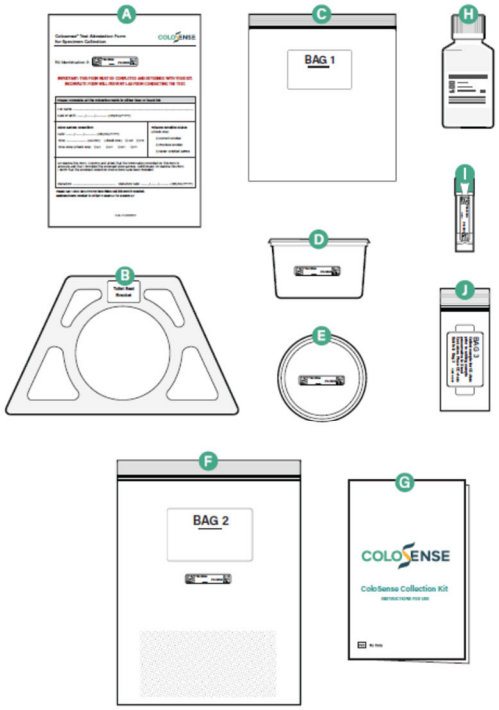
D. Copying by Geneoscopy

177. 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 '781 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 2053.

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

ColoSense Collection Kit Contents



A Attestation Form	F Resealable Bag 2 with Absorbent Pad
B Toilet Seat Bracket	G Collection Kit Instructions for Use
C Resealable Bag 1	H Sample Preservative The 275mL Sample Preservative contains less than 10% EDTA in a Tris buffered solution.
D Stool Container	I OC-Auto Sampling Bottle The 2mL OC Auto Sampling Bottle contains a HEPES buffered solution.
E Stool Container Lid	J Resealable Bag 3

Ex. 2053 at 33.

179. As instructed by Geneoscopy, a patient using the ColoSense kit collects a fresh fecal sample by direct defecation into a stool container in the privacy of their own home. Ex. 2053 at 36-37.

180. 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." Ex. 2053 at 36-37.

181. The sampling bottle contains "liquid Sample Preservative" – a buffer that prevents denaturation or degradation of blood proteins. Ex. 2053 at 37.

182. The patient returns the probe that is covered with a removed portion of the stool sample to the sampling bottle and seals it. Ex. 2053 at 37.

183. The patient also adds a stabilizing buffer to the remaining sample in the sample container. Ex. 2053 at 38.

184. The patient seals that container as well, and both containers are shipped to a lab at room temperature. Ex. 2053 at 38-40.

185. The lab obtains the two containers with the two portions and tests the removed portion for a blood protein. Ex. 2053 at 56 . Nucleic acid is extracted from the remaining portion and the nucleic acid is tested for an amount of nucleic acid. *Id.* at 54-55.

XIII. CONCLUSION

186. For all of the reasons set forth above, the claims of the ’781 patent would not have been obvious to a POSA as of the Priority Date.

187. 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.

188. 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: October 24, 2024

Vadim Backman

Vadim Backman