

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 PRELIMINARY 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 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 colorectal cancer 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 program 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.

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 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 of field 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 the background discussion of this declaration. 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.

12. 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 as of the February 3, 2009 (“Priority Date”).

13. In connection with that request, I was also asked to provide my opinion concerning the level of skill of a person of ordinary skill in the art (“POSA”) in the relevant field as of the Priority Date.

III. SUMMARY OF OPINION

14. The claims of the ’781 patent are not rendered obvious by the Lenhard, Itzkowitz, and Vilkin combination. A person of ordinary skill in the art at the time would not have been motivated to combine FOBT 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 of success of combining iFOBT with nucleic acid-based testing. Further, even if there had been a motivation to combine the two types of 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.

15. 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 FOBT 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 of success of combining iFOBT with nucleic acid-based testing. Finally, there is no motivation in the art to select the specific elements of the

claims for the different references and combine them to arrive at the claimed invention.

16. 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

17. 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.

18. 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 person having ordinary skill in the art.

19. I understand that to prove that prior art, or a combination of prior art, renders a patent obvious, it is necessary to: (1) identify the particular references

that singly, or in combination, make the patent 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.

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

21. I also understand that a reference may be said to teach away when a person of ordinary skill, 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 skilled artisan would be motivated to combine that reference with another reference.

V. TECHNOLOGY BACKGROUND

22. Colorectal cancer (CRC) is 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.

23. 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). 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. *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).

24. 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 has 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.

25. 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.

26. 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 need to be followed 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.

27. 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., Thomas F. Imperiale et al., Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population, 351(26), N. Engl. J. Med. 2704, 2708 (2004) (Ex. 1043).*

28. 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 in part due to pain and a higher complication rate, minorities, patients residing in rural areas, and underserved patient populations.

29. There is also a significant financial cost and there are limitations to access. The societal cost of screening the entire at-risk population 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.

30. 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. The prevalence has improved since then, to approximately 59% in 2021, but is still far from capturing 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.

31. 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.

32. Before the introduction of the Exact Sciences' 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 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 the 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 CT colography 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).

33. 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.

34. 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. The test offered 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.

VI. OVERVIEW OF THE '781 PATENT

35. 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." Ex. 1001 at 6:45-53.

36. 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.

37. Claim 1 of the '718 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.

VII. LEVEL OF ORDINARY SKILL IN THE ART

38. 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.

39. 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.

40. I have reviewed the declaration of Dr. Whitney, including his opinion concerning the person of ordinary skill in the art. 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. Ex. 1002 at ¶¶11, 12.

41. 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. 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.

Ex. 1021 at 7.

42. 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's 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.

43. 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.

44. Whichever of the three levels of skill is used, I satisfy at least the level of skill of a person of ordinary skill. 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. I further note that, by 2009 I had more than twenty years of experience concerning CRC biomarkers.

45. 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)

46. Lenhard is focused on the exploration of a single epigenetic marker in comparison with guaiac fecal occult blood testing for purposes of distinguishing between patients with CRCs and those without. Lenhard concludes that the single “epigenetic marker HIC1 promoter methylation carries high potential for the remote detection of CRCs.” Ex. 1004 at 1.

47. 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.

48. The FOBT test used in Lenhard is a guaiac FOBT. Guaiac FOBT involve application of sample to test cards. Guaiac FOBT does not use sealed

sample containers or buffers. Further, guaiac FOBTs detect the presence of heme, whereas iFOBTs detect hemoglobin protein.

49. 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. 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 measure 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.

50. 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.

51. 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.

52. 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 FOBT.

B. Vilkin (Ex. 1005)

53. Vilkin assessed the performance of a specific desktop iFOBT screening test and 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.” Ex. 1005 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%.” Ex. 1005 at 7. 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.” Ex. 1005 at 8.

54. 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 decay/day for samples stored at different temperatures, specifically $0.3\% \pm 0.4$ at 4°C (NS), $2.2\% \pm 1.7$ at 20°C (NS), and $3.7\% \pm 1.8$ at 28°C ($p < 0.05$). Ex. 1005 at 3 (Results). Figure 2 shows substantial decay in hemoglobin after one week’s storage at room temperature. Ex. 1005 Fig. 2. Vilkin concludes that “[r]efrigerated OC-Sensor samples are stable for 21 days. Ex. 1005 at 3 (Conclusions) (emphasis added). Although Vilkin refers to an “Hb stabilizing buffer,” Vilkin teaches that refrigeration was required to prevent decay.

55. Vilkin also discloses that the subject prepared three consecutive daily samples. Ex. 1005 at 1 (Methods); *Id.* at 4. As noted above, the samples were kept in the refrigerator until the three were returned to the developing laboratory, which also kept them refrigerated until development. *Id.* at 4. Vilkin discloses that the “best results were obtained when all three tests were performed and utilized for the analysis.” *Id.* at 6.

56. 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 predictive value.” *Id.* at 8.

57. 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.

C. Itzkowitz (Ex. 1006)

58. 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.

59. 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.”).

60. 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.

61. 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 fecal occult blood tests.

D. Kanaoka (Ex. 1007)

62. 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 17. 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].

63. Example 1 of Kanaoka describes a study involving 30 cases confirmed to have colon cancer and 22 cases to have indication of colon cancer. *Id.* 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 case 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].

64. 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.” *Id.* at [0067], [0068].

65. 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.

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

67. 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 of a combination of COX-2 and FOBT tests and would not see rationale for a significant increase in diagnostic performance.

E. Derks (Ex. 1008)

68. Geneoscopy relies on Derks only 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 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.*

F. Shuber (Ex. 1009)

69. 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.

70. 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, “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.

71. 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

72. 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. As discussed in detail above, Lenhard mentions a very specific combination of HIC1 methylation analysis and gFOBT in stool collected in a laboratory setting, where the samples were frozen before testing. 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. Ex. 1005. A person of ordinary skill in the art 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.

73. Lenhard would not have motivated the combination of any FOBT with the DNA-based testing of Itzkowitz. To the contrary, Lenhard would have discouraged 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. 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.

74. In addition, the portion of Lenhard on which Geneoscopy relies tells only part of the story. As discussed above, the increase in sensitivity with the 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.

75. It is also worth noting that 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. In Vilkin, using an iFOBT “threshold of 100 ng Hb/mL” allowed them to achieve sensitivity of 76.5% with “acceptable specificity” of 95.3%. Ex. 1005 at 8. In Itzkowitz, the “optimal combination of vimentin methylation plus DIA resulted in 87.5% sensitivity and 82% specificity.” Ex. 1006 at 1. 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.

76. 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.

77. 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.

78. 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.

79. In addition, Vilkin relies on refrigeration for sample preservation. *Id.* at 4 (“samples are kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.”); *Id.* at 3 (Conclusions) (“[r]efrigerated OC-Sensor samples are stable for 21 days.”) Vilkin refers to an “Hb stabilizing buffer,” Vilkin teaches that refrigeration was required to prevent decay.

80. Vilkin also required collection of three samples over three consecutive days. *Id.* at 4. 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.

81. 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.

82. Itzkowitz also discourages use of FOBT. Itzkowitz recognized the well-known need for patient acceptability. *Id.* at 6-7 ("Inherent 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.

83. 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. In addition, more complex fecal matter handling by a patient would increase the complexity. 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 different tests, 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.

84. The invention of the '781 requires home sample separation and the addition of buffers to each sample in different containers by the patient. 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 a POSA would not have expected increased performance from the combination.

85. A POSA also would not have had a reasonable expectation of success of combining iFOBT with nucleic acid-based testing. Lenhard is limited to one specific combination of a gFOBT with one particular methylation marker. 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. However, as discussed above, by 2009, it is very well known in the field that a combination of biomarkers rarely leads to improved diagnostic performance. A person of skill in the art would have known that an improved diagnostic performance of a combined test is unlikely, and any attempt to show improved performance would need to be validated. A person of skill in the art also would have known that, rather than improving performance, a combination might reduce

performance. For example, as shown in Lenhard, the increased sensitivity of the HIC1/gFOBT combination for cancers was at the expense of a drop in specificity. And the HIC1/gFOBT combination of Lenhard had no effect on sensitivity for adenomas. A POSA would have considered all aspects, including sensitivity, specificity, and complexity. A POSA would not have been motivated by an increase in sensitivity, particularly a limited increase in sensitivity for only cancers but not for adenomas, at the expense of 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. Further, a screening test without good sensitivity for advanced adenomas does not serve the purpose of trying to *prevent* cancer.

86. 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.

87. In summary, 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 by the subject such that there is sample in two separate sealable containers, where each sample is combined with buffer, and where the samples are processed without freezing. First, there was 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

88. 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.

89. As discussed above, a person of ordinary skill in the art 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.

90. 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 fecal occult blood test, or with any other form of test other than those that are nucleic acid based.

91. 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.

92. 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.

93. 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.

94. 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.

95. 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 1578 (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.

96. 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 positives among the control cases (specificity 86.3%), where the COX-2 test had no 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.

97. 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 test would also add cost and complexity.

98. 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.

99. 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

100. 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.

XII. CONCLUSION

101. For all of the reasons set forth above, the claims of the '781 patent would not have been obvious to a person of ordinary skill in the art as of the Priority Date.

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

Declaration of Dr. Vadim Backman

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: April 30, 2024



Vadim Backman