

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

U.S. Patent 11,634,781

SECOND DECLARATION OF DUNCAN WHITNEY, Ph.D.

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I. INTRODUCTION

1. As set forth in the declaration I submitted on January 10, 2024 (EX1002, my “Opening Declaration”), I have been retained by counsel for Geneoscopy, Inc. (“Geneoscopy”) to offer my opinions as to whether the claims of U.S. Patent No. 11,634,781 (EX1001; the “’781 patent”) would have been obvious to the person of ordinary skill in the art (“POSA”) as of February 3, 2009, which I understand is the earliest priority date claimed by the ’781 patent (the “Priority Date”).

2. I understand that my opinions in this Declaration will be submitted as evidence in an inter partes review (“IPR”) proceeding before the Patent Trial & Appeal Board in the U.S. Patent & Trademark Office concerning the ’781 patent. I understand Geneoscopy is the Petitioner in this proceeding and that Exact Sciences Corporation (“Exact”) is the Patent Owner.

3. In my Opening Declaration I set forth my relevant background and experience and provide my independent expert opinions concerning the validity of the claims of the ’781 patent. I have now been asked to respond to the opinions concerning validity of the claims of the ’781 patent set forth in the October 24, 2024 declaration of Dr. Vadim Backman (the “Backman Declaration”). My opinions and conclusions I express herein are based on my review of the materials cited herein, in my Opening Declaration, and in Dr. Backman’s declaration. I have

also relied on my general knowledge and experience in the field of cancer diagnostics, including my experience developing fecal CRC diagnostic assays.

II. OVERVIEW OF OPINIONS

4. In my Opening Declaration, I opined that the claims of the '781 patent are invalid as obvious over prior art. After reading the Backman Declaration, my opinions regarding the obviousness of the claims of the '781 patent are unchanged.

5. Nothing in the Backman Declaration has altered my opinion that the claims of the '781 patents are not inventive. The claims of the '781 patent are directed to a straightforward application of two known assays—one detecting blood proteins and the other detecting nucleic acids—to a single fecal specimen. Dr. Backman does not dispute that tests for detecting blood proteins and nucleic acids in fecal samples were well known by the Priority Date. It was also well known that separating a fecal sample into multiple portions so that different assays could be performed on each portion was routine well before the Priority Date.

6. The Backman Declaration does not effectively rebut my opinion that the Challenged Claims are obvious in view of Lenhard (EX1004), Vilkin (EX1005) and Itzkowitz (EX1006). As explained in my Opening Declaration, Lenhard discloses the performance of a fecal CRC diagnostic assay in which both a DNA biomarker and a blood protein biomarker are detected in the same fecal sample. A POSA would have been motivated to improve the Lenhard test by

replacing its gFOBT assay with the superior automated iFOBT assay of Vilkin and the fecal collection by incorporating the fecal collection and DNA stabilization process of Itzkowitz, and, in doing so, would arrive at the methods of the claims of the '781 patent.

7. In his declaration, Dr. Backman's challenges to my opinion regarding Lenhard, Vilkin, and Itzkowitz focus on his assertion that a POSA would be dissuaded from combining fecal nucleic acid tests with fecal blood protein tests because such a combination could potentially reduce assay specificity and would result in a more complicated test. Dr. Backman's opinion ignores the fact that Lenhard already discloses the performance of an assay that combines a fecal nucleic acid test with a fecal blood protein test. As I explain in my Opening Declaration, a POSA would recognize that incorporation of the iFOBT of Vilkin and the sample stabilization and stabilization processes of Itzkowitz would further improve both diagnostic performance and patient convenience of the combined nucleic acid/blood protein test disclosed in Lenhard, and in doing so would arrive at the methods of the Challenged Claims.

8. Dr. Backman has also not effectively rebutted my opinion that the Challenged Claims are obvious in view of Shuber (EX1009) and Vilkin. Here, again, Dr. Backman argues that a POSA would be dissuaded from combining fecal nucleic acid tests with fecal blood protein tests because such a combination could

potentially reduce assay specificity and would result in a more complicated test.

Dr. Backman's arguments ignore the importance a POSA places on improved test sensitivity. For example, Exact acknowledges in their publication of the Cologuard clinical trial that "[s]ensitivity is the most important characteristic for screening tests because the primary role of such testing is to rule out diseases such as cancer."¹ A POSA would have been willing to sacrifice some assay specificity, cost and complexity if the result was a test with markedly better sensitivity.

9. Thus, I explain in my Opening Declaration, a POSA would have been motivated to combine existing fecal nucleic acid tests, such as the ones disclosed in Shuber, with established fecal blood protein tests, such as the one disclosed in Vilkin, to improve test sensitivity, and, in doing so, would arrive at the methods of the claims of the '781 patent. By the Priority Date combining fecal nucleic acid assays with fecal blood protein assays was a known strategy for improving assay sensitivity, and well before that date it was routine to separate a fecal sample into multiple portions so that different assays could be performed on each portion.

10. Finally, the secondary considerations identified by Dr. Backman should be accorded little or no weight because there is no nexus between the Cologuard product and the methods claimed in the '781 patent. Dr. Backman does

¹ Imperiale (EX2008), at p. 1295.

not contend that Cologuard is coextensive with the Challenged Claims, which I understand is a requirement for a presumption of nexus. As I explain in this Declaration, the methods of the Challenged Claims are, at best, a minor component of the Cologuard assay.

11. Dr. Backman has also not demonstrated that Cologuard's purported success is a direct result of any unique characteristics of the Challenged Claims, which I understand is a requirement to establish nexus where there is no presumption. Instead, Dr. Backman makes the conclusory and unsupported assertion "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."² Dr. Backman does not demonstrate that the diagnostic accuracy and patient uptake of Cologuard are products of the claimed method, as opposed to the other Cologuard features covered by the more than 60 unrelated patents Exact identifies on its website or the more than \$3 billion that Exact admits it spent marketing Cologuard. Dr. Backman's conclusory assertions do not satisfy Exact's burden of demonstrating nexus, so his alleged secondary considerations deserve no weight.

² Backman Declaration (EX2022), ¶141.

III. THE PERSON OF ORDINARY SKILL IN THE ART

12. I provided my opinions concerning the definition of a POSA in my Opening Declaration.³ The Backman declaration does not change those opinions. I further note that I am a POSA under both my proposed POSA definition and the definition proposed by Exact. The opinions I offer herein would not change if I applied Exact's definition of a POSA in place of my own.

IV. LEGAL STANDARDS

13. I provided my understanding of the legal standards of obviousness in my Opening Declaration.⁴ I have applied the same standards to the analysis set forth in this declaration.

V. THE CHALLENGED CLAIMS ARE OBVIOUS

A. The Backman Declaration Misreads the Prior Art

14. As discussed below, the summaries of prior art references provided in the Backman Declaration are incomplete, at times are inaccurate, and generally do not reflect how a POSA would understand the disclosures of these references.⁵

15. What is more, throughout his Declaration, Dr. Backman consistently attacks the prior art references I cite in my obviousness analysis individually,

³ Opening Declaration (EX1002), ¶¶9-12 .

⁴ *Id.*, ¶¶88-94.

⁵ Backman Declaration (EX2022), ¶¶55-93.

rather than considering their collective teachings in combination, as I understand is required in an obviousness analysis.

1. Lenhard

16. In his Declaration, Dr. Backman contends that a POSA reading Lenhard, would “not see a rationale for combining nucleic acid-based tests with FOBT.”⁶ Dr. Backman’s analysis ignores the explicit and repeated teachings in Lenhard that combining the methylation marker test with FOBT **increased** CRC assay sensitivity, which Exact acknowledges is the most important characteristic for screening tests.⁷

17. The opinions asserted by Dr. Backman cannot obscure the explicit teaching of Lenhard that “[t]he combination of both assays resulted in increased detection rates for CRCs.”⁸ Lenhard’s results demonstrate that the combined application of both the DNA methylation assay and the FOBT detected CRC with significantly greater sensitivity than either assay alone.⁹ Indeed, Lenhard twice notes that “[t]he combination of H1C1 methylation analysis with FOBT allowed

⁶ Backman Declaration (EX2022), ¶68.

⁷ Imperiale (EX2008), at p. 1295

⁸ Lenhard (EX1004), p. 147 (emphasis added).

⁹ *Id.*, pp. 143, 147.

for the detection of two thirds of CRCs.”¹⁰ Specifically, Lenhard determined that while HIC1 methylation alone detected 42% of CRCs and FOBT alone detected 35% of CRCs, the combination of the two tests was able to detect 65% of CRCs.¹¹

18. Dr. Backman notes that Lenhard’s analysis was performed in a population that included late-stage CRC patients (some with a known diagnosis, others asymptomatic).¹² In my opinion, this does not discredit Lenhard’s findings, particularly because Lenhard also includes early-stage cancers. Also, a POSA would be motivated for their fecal test to identify **any** patient with CRC, regardless of the cancer stage. A POSA would want their CRC diagnostic assay to detect as many instances of cancer as possible to minimize the number of patients with cancer who are left untreated and risk death. Lenhard teaches that a way to achieve this goal is to combine a methylation marker test with a blood protein-based test because “[t]he combination of both assays resulted in increased detection rates for CRCs.”¹³

¹⁰ *Id.*

¹¹ *Id.*, Table 4, and p. 147.

¹² Backman Declaration (EX2022), ¶60

¹³ Lenhard (EX1004), p. 147.

19. Dr. Backman states that Lenhard discloses that “the specific combination HIC1 and gFOBT showed ‘no increase in the sensitivity for adenoma’.”¹⁴ This is not completely accurate—while the combined test and the DNA test were equally sensitive for adenomas, the combined assay did have a higher sensitivity for adenomas compared to the gFOBT.¹⁵

20. Moreover, the equal sensitivity for adenomas between the DNA test and the combined test does not detract from the fact that the combined test was much more sensitive for detecting CRCs. Detection of CRC in a non-invasive way is an important feature of CRC screening, particularly in cases where subjects may be unwilling or unable to get a colonoscopy. In contrast, adenomas are potential indicators of future cancer, but, as Dr. Backman acknowledges in his declaration, only about 10% of adenomas progress to invasive cancer.¹⁶ I strongly disagree with Dr. Backman’s opinion that detection of adenomas would be more important to a POSA than detection of cancer.

21. Indeed, as of the priority date, a POSA would recognize that the primary goal for fecal CRC screens was the detection of CRC, not advanced

¹⁴ Backman Declaration (EX2022), ¶¶61-62.

¹⁵ Lenhard (EX1004), Table 4.

¹⁶ Backman Declaration (EX2022), ¶29.

adenomas. For example, as explained the 2008 Colorectal Cancer Screening Guidelines from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (Levin, EX1013):

Individuals and health care professionals should also understand that screening tests for CRC broadly fall into 2 categories. ***In one category are the fecal tests (ie, gFOBT, FIT, and sDNA), which are tests that primarily are effective at identifying CRC.*** Some premalignant adenomatous polyps may be detected, providing an opportunity for polypectomy and the prevention of CRC, but ***the opportunity for prevention is both limited and incidental and is not the primary goal of CRC screening with these tests.***¹⁷

22. A POSA would therefore be motivated to use the combined test because of its increased effectiveness of identifying CRC, even if it were only equally sensitive for detection of advanced adenomas.

23. Dr. Backman further notes that the methylated HIC1 test alone exhibited a specificity of 98%, while the combined test exhibited a specificity of 89%, so “although the sensitivity of the combined test is higher, the specificity is considerably lower.”¹⁸ I note, however, that as of the Priority Date the most

¹⁷ Levin (EX1013), pp. 1572-1573.

¹⁸ Backman Declaration (EX2022), ¶64.

important feature of fecal CRC screening test was its ability to detect CRC (i.e., its sensitivity, not its specificity). As I noted in my opening declaration, sensitivity is particularly important in fecal CRC tests, or any other CRC screening test, because “the consequence of false-negative results is that CRC patients do not receive needed cancer treatment, leading to a worse prognosis and potentially death.”¹⁹ Thus, while specificity was also important, a POSA would be willing to sacrifice some specificity in exchange for increases in sensitivity. The slight reduction in specificity in Lenhard to 89% would be acceptable to a POSA, particularly in exchange for the substantial increase in sensitivity seen in the combined assay. Indeed, the 89% specificity for the combined test in Lenhard is at least as good as Cologuard’s 86.6% specificity,²⁰ which Dr. Beckman qualifies as being “excellent.”²¹

24. A POSA’s willingness to sacrifice some specificity for improved sensitivity is illustrated, for example, in Exact’s 2007 Itzkowitz publication, where it describes development of a “second generation” of its fecal DNA CRC test with

¹⁹ Opening Declaration (EX1002), ¶28.

²⁰ Imperiale (EX2008), Table 1.

²¹ Backman Declaration (EX2022), ¶41.

improved sensitivity for CRC.²² Notably, whereas Exact’s “first generation” test had a specificity of 94%, the specificity of the “second generation” test decreased to only 82%.²³ In comparison, as noted above, the specificity of the combined test in Lenhard is 89%.²⁴ Exact’s sacrifice of specificity for improved sensitivity in their 2007 Itzkowitz publication is consistent with the recognition in the art at the time that sensitivity is the most important characteristic of a fecal CRC diagnostic test.

25. In his declaration, Dr. Backman provides calculated values for “expected area under the receiver operating characteristic (ROC) curve (AUC)” for the combined HIC1 with gFOBT of Lenhard. However, it is not clear how these values are calculated and there are no references cited. Furthermore, any calculation of an AUC from a single pair of sensitivity and specificity values, which was all that was provided in the Lenhard study, can provide only a rough estimation at best, and therefore is an inexact method for comparing test performance. The AUC of a ROC curve is typically calculated based on considering a full range of decision-thresholds, which provides a representation of

²² Itzkowitz (EX1006), abstract.

²³ *Id.*

²⁴ Backman Declaration (EX2022), ¶61.

all possible sensitivity and specificity values for any assay. As an example, if we were to consider the FOBT assay itself, varying a decision-threshold across a broad range of hemoglobin values for different samples would provide a continuum of positive and negative samples corresponding to each of those thresholds which could be used to construct a ROC curve whereby an AUC could be calculated. In the Lenhard paper, samples were labeled as either positive or negative, indicating that only a single threshold was used. Calculating an AUC from a single pair of sensitivity/specificity values is not typically done. In my opinion, the expected AUC values provided by Dr. Backman would be seen as having little relevance to a POSA assessing Lenhard, and are likely to be inaccurate.

26. Notably, Lenhard does not itself provide AUC values associated with its assays and Dr. Backman does not disclose the methodology he used to calculate the “expected” AUC figures he provided in his declaration. This is particularly important because Lenhard only provides single sensitivity and specificity points for HIC1 and gFOBT, which are insufficient to construct a true ROC curve across multiple thresholds. While there are statistical methods available through which an AUC can be roughly estimated from a single operating point, such AUC estimates are unreliable and would not be used by a POSA as a basis for comparing fecal CRC screening assays. When comparing the various versions of its own fecal DNA assay in Itzkowitz, Exact never refers to any expected AUC values derived from

the single sensitivity and specificity points it provides for the different versions of its own assays.²⁵ In contrast, Vilkin, which, unlike Lenhard or Itzkowitz, includes numerous sensitivity and specificity data points at different assay thresholds, is able to provide ROC curves in figure 4.²⁶

27. It is also unclear how Dr. Backman derived the “expected AUC” values he provides in his declaration (an “expected AUC” of 0.80 for the HIC1 assay alone and an “expected AUC” of 0.76 for HIC1 combined with FOBT for CRC detection).²⁷ Different methods can be used to estimate AUC from single data points, and each method can yield different estimated values. For example, one method for estimating AUC from a single point that was used as of the Priority Date estimates AUCs of 0.838 for the HIC1 test alone, 0.741 for the gFOBT test alone, and 0.847 for the combined test for detection of CRC.²⁸ Thus, when this method is used to approximate AUC values from the Lenhard data, **the result is a**

²⁵ Itzkowitz (EX1006).

²⁶ Vilkin (EX1005), Figure 4.

²⁷ Backman Declaration (EX2022), ¶64.

²⁸ Described in Zhang and Mueller, “A note on ROC analysis and non-parametric estimate of sensitivity” *Psychometrika*, 70:203-212 (2005). Online calculator made available by Kevin Tsang, Assistant Professor at University College London, at <https://kevinchtsang.github.io/auc-roc-calc/index.html>.

slightly higher estimated AUC for the combined test than either the HIC1 test alone or the gFOBT alone. As discussed below, when two fecal CRC tests have a similar AUC, as here, a POSA would favor a test with higher sensitivity.

28. A more straightforward mathematical method that was commonly used to combining sensitivity and specificity to arrive at a single comparative metric is to calculate test accuracy. Test accuracy is calculated at the sum of true-positive and true-negative samples, divided by the sum of the complete sample set. This calculation can be derived from single sensitivity and specificity scores and does not require any estimation. With respect to the Lenhard assays, the HIC1 assay itself has a test accuracy of 80% while the addition of the FOBT test improves the test accuracy to 81.3%. Dr. Backman did not consider the test accuracy values in his declaration. Thus, when test accuracy is calculated from from the Lenhard data, the result is also a slightly higher estimated accuracy for the combined test than either the HIC1 test alone or the gFOBT alone. This metric therefore provides a POSA with further motivation to use the combined test.

29. Moreover, even if Dr. Backman's expected AUC calculations were accurate and relevant, his position overlooks the fact that a numerical drop in the expected AUC (or even a drop in test accuracy) when HIC1 is combined with gFOBT would not necessarily mean the combination is clinically inferior. AUC or test accuracy alone cannot fully capture the practical trade-offs between sensitivity

and specificity, which can be tailored to different clinical needs. In many screening contexts, including fecal CRC screens, some loss in specificity is acceptable if it translates to substantially better detection rates and earlier interventions.

Dismissing the combined approach outright overlooks the potential complementary benefits of using both tests together. In this case although the combined test shows a small drop in specificity compared to the HIC1 test alone, the sensitivity for CRC detection is greatly increased, consistent with the recognition in the art at the time that sensitivity is the most important characteristic of a fecal CRC diagnostic test.

30. Dr. Backman notes that Lenhard discloses that the methylation marker SFRP2 was known to have a higher sensitivity (but substantially lower specificity) for CRC than the combination of the HIC1 and FOBT tests.²⁹ Dr. Backman does not clarify the alleged import of the existence of this methylation marker, and Lenhard appears to disfavor it as a biomarker to be used as part of a panel due to its “poor” specificity of only 77%.³⁰

31. I also note that it is the complementary nature of candidate biomarkers that leads to improvements in assay sensitivity when biomarkers are combined. In other words, for a combination of biomarkers to improve assay sensitivity, it is

²⁹ Backman Declaration (EX2022), ¶66.

³⁰ Lenhard (EX1004), p. 143.

necessary that each biomarker detects instances of CRC that the other would miss. Because DNA biomarkers and blood protein biomarkers have different sources (one is from changes to the DNA in certain CRC cells and the other is due to with a more generalized phenomenon of bleeding lesions in the patient's digestive tract often associated with CRC), such biomarkers would be expected to pick up different instances of CRC and therefore be complementary and additive. Indeed, the data presented in Lenhard confirms that they are.³¹ By contrast, it is unclear whether SFRP2 would complement HIC1 in a way that improved sensitivity. That is because it is possible that all CRC cells that have HIC1 methylation also have SFRP2 methylation. Indeed, based on the data as described by Lenhard, it is not clear that sensitivity would have been improved if HIC1 were combined with SFRP2 as biomarkers, but given SFRP2's low specificity alone, specificity almost certainly would have been significantly reduced, in fact much more so than by combining HIC1 with FOBT. Therefore, combining two or more different DNA biomarkers may not have improved assay sensitivity, or at a minimum a POSA would not be able to predict whether or not two DNA-methylation markers would be additive leading to improved sensitivity.

³¹ *Id.*, Table 1.

32. Regardless, by the Priority Date, combining FOBT with fecal DNA tests was recognized as a general strategy for improving assay sensitivity that was not limited to any single DNA biomarker, including methylation of HIC1.³² Thus, even if a POSA were motivated to use methylated SFRP2 in place of or in addition to HIC1 in the Lenhard assay, they would also be motivated to further improve that DNA test by also combining it with a FOBT.

33. Dr. Backman quotes Lenhard as saying that “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.”³³ Lenhard does not suggest that the additional methylation markers would be added in place of the FOBT test. Indeed, a POSA would understand that the logical starting point for further improving the Lenhard CRC test would be through the addition of more biomarkers to the combined test, which has a sensitivity of 65%, and not to the test for HIC1 alone, which has a sensitivity of only 42%. As noted above, by the Priority Date, combining FOBT with fecal DNA tests was recognized as a general strategy for improving assay sensitivity that would be

³² Opening Declaration (EX1002), ¶¶63, 241-244.

³³ Backman Declaration (EX2022), ¶67.

applicable to tests that included additional DNA biomarkers in combination with HIC1.³⁴

2. Vilkin

34. In his Declaration, Dr. Backman mischaracterizes Vilkin as requiring three consecutive daily samples and storage of those samples in a patient's refrigerator.³⁵ A POSA, however, would recognize that these features were only applied to the specific experiment performed in Vilkin to allow the researchers to assess assay reproducibility using multiple samples, and are not reflective of how Vilkin's iFOBT test would be used in clinical practice. Consistently, Vilkin's first aim was to determine "test-development reproducibility" and its third aim was to determine "inpatient daily I-FOBT test variation."³⁶

35. Vilkin is clear that it did not view the collection of three consecutive daily samples as a requirement when its iFOBT is used clinically. Vilkin explains that "[t]he **decision on the number of fecal samples** to be obtained and optimal fecal Hb threshold chosen for screening an average risk population will also **involve an evaluation of cost-benefit.**"³⁷ At his deposition, Dr. Backman admitted

³⁴ Opening Declaration (EX1002), ¶¶63, 241-244.

³⁵ Backman Declaration (EX2022), ¶¶69, 73.

³⁶ Vilkin (EX1005), p. 2519

³⁷ *Id.* p. 2524 (emphasis added).

that Vilkin does **not** require collection of three consecutive daily samples when its assay is used in clinical practice.³⁸

36. Consistently, the Vilkin authors state that they elected to continue “collecting three **annual** sample fecal tests” in certain high-risk populations. Vilkin further recognizes that different standards would apply to an “average-risk population.”³⁹ Vilkin notes that different countries screen with different frequencies screening criteria, such as “2 annual samples...in Japan *versus* 1 biennial [i.e., every other year] sample...in Italy.”⁴⁰ **None** of the countries discussed in Vilkin tested samples collected on three consecutive days.

37. A POSA would also understand that, in clinical practice, a patient would not need to refrigerate stool samples at home when using the iFOBT described in Vilkin. In particular, a POSA would understand that patients only needed to refrigerate the stool samples in the Vilkin experiment because the experiment required the patient to collect three daily samples to test for test reproducibility. As discussed above, in clinical practice, the disclosed iFOBT test does not require collection of three consecutive daily samples. Accordingly, a

³⁸ Backman Dep. Tr. (EX1090), 141:4-142 :19.

³⁹ Vilkin (EX1005), p. 2524.

⁴⁰ *Id.*

patient using the Vilkin iFOBT device in clinical practice can ship the stool sample back to the diagnostic laboratory immediately after collection, without refrigeration.⁴¹ Indeed, it is my opinion that the data presented in Vilkin indicates that a fecal sample would be sufficiently stable at room temperature to allow for the convenient shipment of a freshly collected fecal sample to the diagnostic laboratory either at room temperature or packaged with a cold-pack. Upon receipt at the laboratory, the stool sample can then be refrigerated until tested.

38. Vilkin determined that, over the course of three full weeks of storage, degradation was lower in refrigeration (4°C, 39°F) than at approximately room temperature (20°C, 68°F) or a relatively hot temperature (28°C, 82°F), by several percentage points per day (0.3% decay/day at 4°C, versus 2.2% decay/day at 20°C or 3.7% decay/day at 82°F).⁴² It is my opinion that three weeks is a relatively long storage time that would not be necessary in clinical practice. It is further my opinion that Vilkin shows that storage without freezing (e.g., at room temperature, or refrigerated), for a reasonable period of time, such as several days, would be reasonable as an option to facilitate home use. Moreover, Vilkin clearly demonstrates that freezing is not required for sample stability, as acknowledged by

⁴¹ *Id.* p. 2520

⁴² Vilkin (EX1005), Abstract

Dr. Backman's assertion that refrigeration alone is an example of storage that would prevent decay.⁴³ To put Dr. Backman's assertions in the context of the patent, the claims of the '781 patent notably do not require, or exclude, refrigeration; the claims only exclude freezing. At no point were samples frozen in the Vilkin study.

3. Itzkowitz

39. Dr. Backman asserts that “[a]fter reading Itzkowitz, a POSA would conclude that DNA-based screening could potentially be improved based on selection and combination of specific DNA markers” and that “subjects at the time preferred fecal DNA testing to FOBTs.”⁴⁴ It is my opinion that this statement misinterprets the disclosure in Itzkowitz regarding patient preferences among fecal DNA testing, fecal occult blood testing, and colonoscopy.

40. As noted by Dr. Backman, Itzkowitz discusses “the need for a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction,” as well as the importance of “patient acceptance.”⁴⁵ In his declaration, Dr. Backman notes a passing reference in Itzkowitz to a study regarding patient preference in CRC testing that was

⁴³ Backman Declaration (EX2022), ¶70.

⁴⁴ *Id.*, ¶80.

⁴⁵ *Id.*, ¶76.

reported in a publication by Schroy *et al* (EX2048), but he does not discuss the underlying reference in detail.⁴⁶

41. In the Schroy study, patients were surveyed who had experienced three types of testing: DNA testing, gFOBT, and colonoscopy—but not FIT. In particular, Schroy asked patients to (1) submit a stool sample in a “plastic bucket-type container” for DNA testing, (2) prepare three gFOBT cards by “two smears from each stool on 3 connective days,” subject to dietary and medication restrictions, and (3) undergo a colonoscopy.⁴⁷ Thus, Schroy’s survey was based on a particular protocol for a gFOBT test that was particularly unpleasant, using six total steps of actively smearing one’s own feces onto gFOBT cards after dietary restriction (none of which would be required for FIT). Schroy’s patients were then asked to compare this particularly unpleasant gFOBT regimen with a single-sample DNA test. These results predictably show that the single-bucket test was preferred to a six-smear test or outpatient colonoscopy, though no test was selected by a majority of the patients. Schroy also shows that ***a substantial fraction of***

⁴⁶ *Id.*

⁴⁷ Schroy (EX2048), pp. 208-209

*patients still preferred the six-smear gFOBT test (32%), and some preferred colonoscopy (preferred by 15%).*⁴⁸

42. Consistent with the above, Schroy summarizes that:

Conceptually, stool-based DNA testing and FOBT share many similarities from the patient perspective. Both are safe, noninvasive stool-based tests with sample collection performed conveniently at home. ***Thus, the finding that most patients rated both tests comparably with respect to most prep- and test-related features is not unexpected.***⁴⁹

43. Thus, a POSA reading Schroy would not draw a general conclusion that all DNA tests would be preferable to all FOBT tests for all patients. Indeed, as acknowledged by Dr. Backman at his deposition, even under the testing procedures applied in Schroy, there were significant numbers of patients who preferred each.⁵⁰

4. Kanaoka

44. Dr. Backman asserts that since Kanaoka's data show 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", and then states, "[a]lthough the sensitivity of the combined test is slightly higher, the specificity is

⁴⁸ *Id.*, abstract.

⁴⁹ *Id.*, pp 211-212 (emphasis added).

⁵⁰ Backman Dep. Tr. (EX1090), 160:16-162:2.

considerably lower.”⁵¹ As with Lenhard, Dr. Backman again provides calculated expected AUC estimates for the individual RNA test and the combined test without stating how these values are calculated and then, based on these expected AUC calculations, opines that “a POSA would conclude that the COX-2 should **not** be combined with FOBT.”⁵²

45. As discussed above in the context of Lenhard, Dr. Backman’s purported expected AUC values derived using an undisclosed methodology from single specificity and sensitivity data points are, at best, unreliable and would have minimal significance to a POSA when assessing the data presented in the examples of Kanaoka.⁵³ What would be important to a POSA is that Kanaoka shows that the COX-2 assay and the FIT assay are complementary—the COX-2 assay identified positive fecal samples the FIT missed and the FIT assay identified positive fecal samples that the COX-2 assay missed.⁵⁴

⁵¹ Backman Declaration (EX2022), ¶¶81, 84.

⁵² *Id.*, ¶84.

⁵³ Unlike with his analysis of the Lenhard data, Dr. Backman’s expected AUC calculations based on the Kanaoka data do match those calculated using the Zhang and Mueller method.

⁵⁴ Opening Declaration (EX1002), ¶¶ 126, 129.

46. Dr. Backman further asserts that “the Kanaoka patent application does not conclude that COX-2 should be combined with FOBT.” I disagree with Dr. Backman’s assertion. As I explain in my Opening Declaration, Kanaoka notes that “[a]mong three COX-2 negative colon cancer cases, one was positive in the immunological fecal occult blood test” while “COX-2 was detected in 3 among 5 colon cancer cases negative to the immunological fecal occult blood test,” indicating that the combination of the two tests had a higher sensitivity than either test alone.⁵⁵ Far from indicating “no synergy” as Dr. Backman contends,⁵⁶ these complementary findings demonstrate to the potential for a combined testing approach to improve overall detection rates by reducing false negative results.

5. Shuber

47. Dr. Bachman asserts that “Shuber does not specifically mention home collection by a patient.”⁵⁷ This view does not fairly reflect what would be understood by a POSA reading Shuber. Dr. Backman acknowledges that Shuber teaches “that ‘a sample (e.g., a stool sample) may be directly deposited into a container (e.g., a sealable container)’ that either already contains a stabilization

⁵⁵ *Id.*, ¶129.

⁵⁶ Backman Declaration (EX2022), ¶86.

⁵⁷ *Id.*, ¶92

solution or to which a stabilization solution may be added.”⁵⁸ The sample can be “freshly isolated.”⁵⁹ In some instances, samples were “shipped to EXACT Sciences,” indicating at least that samples were collected at a site remote from a testing facility.⁶⁰ Shuber explains that “stabilization solution may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center” as opposed to when a sample is “processed on-site at a medical center.”⁶¹ A POSA reviewing Shuber would have understood that the most likely off-site location where a patient might defecate to produce a sample would be at the patient’s home, from which a sample could be shipped to a testing facility or medical center. In addition, nothing in Shuber is contrary to collection at home by a patient, which would be a standard location for stool collection as of the Priority Date, as evidenced by numerous other references discussed above and in my Opening Declaration.

⁵⁸ *Id.*

⁵⁹ Shuber (EX1009), at 9:1-3.

⁶⁰ *Id.*, 14:27-28.

⁶¹ *Id.*, 10:12-15.

B. Lenhard, Vilkin, and Itzkowitz Render the Challenged Claims Obvious

48. As discussed in my Opening Declaration, a POSA would have been motivated by the express teachings of the cited references themselves and the knowledge in the art to improve the fecal screening method of Lenhard by replacing its gFOBT with the iFOBT of Vilkin and by incorporating the fecal collection and DNA stabilization process of Itzkowitz to arrive at the methods of the Challenged Claims.

49. I disagree with Dr. Backman's assertion that "[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."⁶² As I explain in my Opening Declaration, Lenhard discloses a method for performing a noninvasive CRC detection assay in which a portion of a patient's fecal sample is removed and tested for blood proteins using gFOBT, and then the remainder of the sample is tested for tumor-derived DNA using DNA methylation as a biomarker.⁶³ Thus, Lenhard itself, the primary reference in this obviousness combination, alone already discloses an assay combining a FOBT with DNA-based testing. As set forth in my Opening Declaration, a POSA would be motivated to

⁶² Backman Declaration (EX2022), ¶95.

⁶³ Opening Declaration (EX1002), ¶139.

further improve this combined assay disclosed by Lenhard to incorporate the iFOBT of Vilkin and the sample collection and stabilization buffer of Itzkowitz to improve the performance and patient convenience of Lenhard's assay.⁶⁴

50. Dr. Backman also incorrectly alleges that "even if there were such a motivation, combining the disparate teachings of the cited references would not result in the claimed method."⁶⁵ In fact, as I explain in my Opening Declaration, the result of these obvious and straightforward improvements to the Lenhard assay would be a method for processing a freshly-collected fecal sample in which a patient defecates directly into a sealable container (as in Itzkowitz), removes a portion of the stool sample and combines it with a buffer that stabilizes blood proteins in a separate sealable container (as in Vilkin), and then adds DNA stabilization buffer to the remaining fecal sample before sealing the original sealable container (as in Itzkowitz).⁶⁶ The patient would then send both sealed containers to a diagnostic laboratory for analysis of DNA methylation and FOBT, which Lenhard teaches provides improved assay sensitivity compared to either test

⁶⁴ *Id.*, ¶¶143-158.

⁶⁵ Backman Declaration (EX2022), ¶119.

⁶⁶ Opening Declaration (EX1002), ¶159.

alone.⁶⁷ When the resulting obvious fecal processing methods are performed the assay meets each and every limitation of the Challenged Claims.⁶⁸

1. Lenhard Discloses a Fecal CRC Test That Combines a Fecal DNA Assay and an FOBT

51. I disagree with Dr. Backman's assertion that "Lenhard would not have motivated the combination of any FOBT with the DNA-based testing of Itzkowitz."⁶⁹ First, the primary reference Lenhard already **discloses** the use of a fecal test that combines DNA analysis and FOBT, so no further motivation to combine tests for such biomarkers is required to render the claims obvious. What is more, if such motivation were necessary, it is abundantly provided by the repeated express statements in Lenhard that the combined assay detected more CRC than either test alone, as well as by the numerous disclosures in the art indicating that combining DNA-based fecal tests with FOBT tests was a known method for improving test performance.⁷⁰

52. Dr. Backman's argument that "Lenhard would have discouraged a POSA from such a combination ... [because] the combination showed no

⁶⁷ *Id.*

⁶⁸ *Id.*, ¶¶148-162.

⁶⁹ Backman Declaration (EX2022), ¶96.

⁷⁰ Opening Declaration (EX1002), ¶¶63, 241-244.

improvement in the critical detection of advanced adenomas”⁷¹ even though it did show an increase in sensitivity for CRC is contrary to the state of the art and defies common sense. As I discuss above, Lenhard shows that combining its methylated DNA assay with an FOBT resulted in a test that had equal sensitivity for adenomas but greatly improved sensitivity for CRC. A POSA would **clearly** be motivated to use such a test that had higher sensitivity for detection of CRCs, even if that test were only equally sensitive for the detection of adenomas.

53. Indeed, cancer detection is of primary importance in fecal CRC diagnostic assays. For example, when comparing different versions of its fecal DNA assay in Itzkowitz, Exact based its assessment entirely on each assay’s ability to detect cancer—its ability to detect advanced adenomas was not investigated.⁷² Consistently, the 2008 Colorectal Cancer Screening Guidelines from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (Levin, EX1013) explains:

Individuals and health care professionals should also understand that screening tests for CRC broadly fall into 2 categories. ***In one category are the fecal tests (ie, gFOBT, FIT, and sDNA), which are tests that primarily are effective at identifying CRC.*** Some premalignant

⁷¹ Backman Declaration (EX2022), ¶¶96-98.

⁷² Itzkowitz (EX1006); Backman Dep. Tr. (EX1090), 73:15-21.

adenomatous polyps may be detected, providing an opportunity for polypectomy and the prevention of CRC, but ***the opportunity for prevention is both limited and incidental and is not the primary goal of CRC screening with these tests.***⁷³

54. Indeed, when Exact ran its clinical trial of Cologuard, “[t]he primary aim was to determine the performance characteristics of [Cologuard] in the detection of colorectal cancer.”⁷⁴

55. Dr. Backman argues that a POSA would not have been motivated to combine a DNA methylation test with FOBT because the sensitivity for CRC of the specific HIC1/gFOBT combination of Lenhard was lower than the sensitivity of the single-marker SFRP2 as well as because both Vilkin and Itzkowitz report sensitivities higher than reported in Lenhard for the HIC1 and gFOBT combination.⁷⁵ I disagree.

56. Dr. Backman’s argument disregards the fact that a POSA would have recognized, based on the disclosure of Lenhard and the knowledge in the art, that combining FOBT with fecal DNA tests was a general strategy for improving assay

⁷³ Levin (EX1013), pp. 1572-1573.

⁷⁴ Imperiale (EX2008), p. 1288.

⁷⁵ Backman Declaration, ¶¶98-104.

sensitivity that was not limited to any single DNA biomarker, including methylation of HIC1.⁷⁶ Thus, even if a POSA were motivated to use methylated SFRP2 or the DNA markers of Itzkowitz in place of or in addition to HIC1 in the Lenhard assay, they also would be motivated to further improve the sensitivity of the resulting a fecal DNA test by combining it with an FOBT assay, such as the iFOBT test of Vilkin.

57. What is more, the relatively high sensitivities reported in Vilkin and Itzkowitz would motivate a POSA to improve Lenhard's assay by incorporating strategies applied in Itzkowitz and Vilkin to achieve such sensitivity. For example, Itzkowitz's disclosure that improving its stool collection process to incorporate a DNA stabilization buffer contributed to an increase in assay sensitivity from 51.6% to 72.5% would motivate a POSA to apply a similar sample collection strategy to Lenhard's assay.⁷⁷ Likewise, Vilkin's disclosure that gFOBT like the one used in Lenhard is "faulted for its low sensitivity" would motivate a POSA to use Vilkin's more sensitive iFOBT in its place.⁷⁸

⁷⁶ Opening Declaration (EX1002), ¶¶63, 241-243.

⁷⁷ Itzkowitz (EX1006), p. 114.

⁷⁸ Vilkin (EX1005), p. 2519.

58. Moreover, Vilkin teaches that sensitivity and specificity could be adjusted to an optimal level by relying on different thresholds for hemoglobin concentration. Vilkin also shows that even with the lowest threshold (50 ng/ml), to provide the highest sensitivity (79.4%) that the specificity remains acceptably high (89.7%).⁷⁹ Using a threshold of 200 ng/ml led to a specificity of 96.3% while maintaining a sensitivity of 64.7%. Therefore, a POSA would recognize that the iFOBT was a suitable choice for improving overall test sensitivity without substantially decreasing specificity.

59. Dr. Backman also appears to argue that a POSA would not be motivated to improve the combined HIC1 and FOBT test because Lenhard “expressly suggests using multiple methylation markers, not combining methylation marker testing with FOBT.”⁸⁰ In making this argument, Dr. Backman erroneously treats the addition of more methylation markers and their combination with an FOBT as an either/or choice, which it clearly is not. Lenhard does not suggest that additional methylation markers would be added to the disclosed assay in place of the FOBT test. Indeed, a POSA would understand from the disclosure of Lenhard that the logical starting point for further assay improvement would be

⁷⁹ Vilkin (EX1005), Table 2, p. 2523.

⁸⁰ Backman Declaration (EX2022), ¶103.

through *the addition of more biomarkers to the combined test, which has a sensitivity of 65%, and not the addition of more biomarkers to the test for HIC1 alone, which has a sensitivity of only 42%.*

60. Thus, even if a POSA were motivated to improve the HIC1 assay disclosed in Lenhard by adding more DNA markers, it does not mean they would not also be motivated to improve its combined test, or that they would not be motivated to apply any improvements to the HIC1 test to the disclosed combined assay. Notably, at his deposition, Dr. Backman conceded that Lenhard's disclosure Lenhard does not expressly discourage using FOBT in combination with HIC1, nor does it characterize such a combination as unpromising,⁸¹ which is at odds with any suggestion that Lenhard fails to teach combining these approaches.

61. Moreover, by focusing exclusively on Lenhard's final paragraph, Dr. Backman ignores the repeated teaching Lenhard makes elsewhere that the combination of a DNA methylation assay with an FOBT assay results in increased assay sensitivity compared to either assay alone. This improvement in assay sensitivity disclosed in Lenard would be particularly important to a POSA. As acknowledged by Exact, "[s]ensitivity is the most important characteristic for

⁸¹ Backman Dep. Tr. (EX1090), 98:10-99:19, 104:20-23.

screening tests because the primary role of such testing is to rule out diseases such as cancer.”⁸²

2. A POSA Would Accept Some Loss in Specificity in Exchange for Increased Sensitivity

62. Dr. Backman argues that “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.”⁸³ I disagree. A POSA reading Lenhard would appreciate that the combination assay of Lenhard maintained sensitivity for adenomas (no change) while simultaneously markedly increasing sensitivity for detection of CRC subgroups including localized cancers, advanced cancers, rectum and sigmoid colon cancers, cancers from descending colon to cecum, asymptomatic cases, and symptomatic cases.⁸⁴ As discussed above, the primary aim of fecal CRC tests as of the priority date was detection of cancers.

63. Dr. Backman’s argument also disregards the relative importance a POSA would place on increased assay sensitivity versus specificity. As I discussed

⁸² Imperiale (EX2008), p. 1295.

⁸³ Backman Declaration (EX2022), ¶106.

⁸⁴ Lenhard (EX1004), Table 4 and p. 147.

in my Opening Declaration, the fact that the consequence of a false positive test is a low risk, routine procedure like a colonoscopy, as balanced against the risk of patient death associated with false negative diagnoses, favors the development of CRC screening tests with higher sensitivity (*i.e.*, fewer false negatives), even if some tradeoff against specificity (*i.e.*, more false positives) is required.⁸⁵ Exact expressly acknowledges in their publication that reported the results of the Cologuard clinical trial that “[s]ensitivity is the most important characteristic for screening tests because the primary role of such testing is to rule out diseases such as cancer.”⁸⁶ As I note above, the emphasis placed by a POSA on sensitivity and their willingness to sacrifice specificity for improved sensitivity is illustrated, for example, in Exact’s 2007 Itzkowitz publication. In Itzkowitz, Exact describes the development of a “second generation” of their fecal DNA CRC test with improved sensitivity for detection of CRC.⁸⁷ Notably, whereas Exact’s “first generation” test had a specificity of 94%, the specificity of the “second generation” test was only 82%.⁸⁸ Despite this reduction in specificity, Exact considers their second

⁸⁵ Opening Declaration (EX1002), ¶62.

⁸⁶ Imperiale (EX2008), p. 1295.

⁸⁷ Itzkowitz (EX1006), abstract.

⁸⁸ *Id.*

generation test to be “[a]n improved fecal DNA test that... shows much higher sensitivity for CRC.”⁸⁹

64. It is further my opinion that the reduced specificity of the combined DNA methylation and FOBT test disclosed in Lenhard would be acceptable to a POSA. As acknowledged by Dr. Backman, the specificity of the combined HIC1 and FOBT test in Lenhard was 89%.⁹⁰ For comparison, the specificity of the “improved” second generation Itzkowitz assay was only 82%.⁹¹ Indeed, as acknowledged by Dr. Backman, the specificity of Cologuard for CRC is only 86.6%.⁹² Clearly then, the 89% specificity observed in Lenhard would be acceptable to a POSA, particularly given the more than 20 percentage point increase in sensitivity provided by the combined test.

65. A POSA would also have recognized that the slight reduction in specificity exhibited by Lenhard’s combined assay was almost entirely a product of its gFOBT component, which alone exhibited a specificity of 89.9%.⁹³ This would further motivate a POSA to replace Lenhard’s gFOBT with Vilkin’s more specific

⁸⁹ *Id.*

⁹⁰ Backman Declaration (EX2022), ¶106

⁹¹ Itzkowitz (EX1006), abstract.

⁹² Backman Declaration (EX2022), ¶41.

⁹³ Lenhard (EX1004), p. 147.

iFOBT in order to increase the specificity of the combined assay.⁹⁴ Vilkin explains that gFOBT are faulted for “low specificity due to non-specificity for human hemoglobin (Hb),” whereas its iFOBT is “human Hb specific.”⁹⁵

66. Accordingly, it is my opinion that a POSA would consider the reduction in specificity associated with the combination of a DNA methylation test with an FOBT to be an acceptable trade-off in view of the substantial increase in sensitivity that Lenhard observed with the combined test.

3. Vilkin Does Not Require Multiple Samples or Home Refrigeration

67. Dr. Backman opines that “[t]he 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.”⁹⁶ I disagree. A POSA would recognize that, in clinical use, Vilkin’s assay requires neither multiple sample collection nor at-home refrigeration.

68. Contrary to Dr. Backman’s assertions, Vilkin does not require the collection of three daily samples for clinical use of the disclosed iFOBT test. Vilkin explains that “[t]he *decision on the number of fecal samples to be obtained* and optimal fecal Hb threshold chosen for screening an average risk population

⁹⁴ Vilkin (EX1005), p. 2523.

⁹⁵ *Id.*, p. 2519

⁹⁶ Backman Declaration (EX2022), ¶111.

will also *involve an evaluation of cost-benefit.*”⁹⁷ Consistently, the Vilkin authors elected to continue “collecting three *annual* sample fecal tests” in certain **high-risk** populations (as opposed to three consecutive daily samples). Vilkin further recognizes different standards would apply to an “average-risk population.”⁹⁸ Indeed, Vilkin notes that different countries screen with different frequencies, such as “2 annual samples...in Japan *versus* 1 biennial [i.e., every other year] sample...in Italy.”⁹⁹ **None** of the clinical examples discussed in Vilkin tested samples collected on three consecutive days. Clearly, Vilkin does not teach that collection of three daily samples is a requirement for its iFOBT assay. At his deposition, Dr. Backman admitted that Vilkin does **not** require collection of three consecutive daily samples when its assay is used in clinical practice.¹⁰⁰ I further note that none of the claims of the ’781 patent require any particular testing frequency.

69. A POSA would also understand that, in clinical practice, a patient would not be required to refrigerate stool samples at home when using the iFOBT

⁹⁷ Vilkin (EX1005), p. 2524 (emphasis added).

⁹⁸ *Id.*, p. 2524 (emphasis added).

⁹⁹ *Id.*

¹⁰⁰ Backman Dep. Tr. (EX1090), 141:4-142 :19.

of Vilkin. As discussed above, in clinical practice, the Vilkin iFOBT test does not require samples to be collected over three consecutive days, so a patient would be able to ship their stool sample back to the diagnostic laboratory immediately after collection, without refrigeration.¹⁰¹ Vilkin says nothing about the conditions under which the sample was shipped to the laboratory, but to the extent a cold-pack was used during shipment, that would be at worst a minor inconvenience readily accepted by a patient in exchange for a better assay. Indeed, it is my opinion, based on the data presented in Vilkin, that a fecal sample in Vilkin's hemoglobin stabilization buffer would be sufficiently stable to allow for the shipment of a freshly collected fecal sample to the diagnostic laboratory either at room temperature or conveniently packaged with a cold-pack. Upon receipt at the laboratory, the stool sample could then be refrigerated until tested. Notably, the claims of the '781 patent do not preclude sample refrigeration.

70. As I also explain above and in my Opening Declaration, a POSA would be motivated to modify Lenhard's assay to replace the gFOBT with an automated iFOBT like the one disclosed in Vilkin at least because Vilkin expressly teaches numerous advantages of using such an FIT instead of gFOBT, including that iFOBT (1) has a higher sensitivity than gFOBT, (2) eliminates the need for the

¹⁰¹*Id.*

diet restrictions associated with gFOBT, and (3) is quantitative, which allows a physician to choose the optimal fecal Hb threshold level for a patient.¹⁰² Thus, a POSA would recognize Vilkin's iFOBT as a superior alternative to the gFOBT used in Lenhard. Indeed, in his deposition Dr. Backman acknowledged that the quantitative nature and fewer dietary restrictions of iFOBT offered clear advantages over gFOBT, making it a more appealing option for clinical use.¹⁰³

71. I also understand that the motivation to combine teachings of references does not need to be found in the references themselves, but rather can be based on knowledge in the art as of the Priority Date. As I explain in my Opening Declaration, even beyond the express teachings of Vilkin itself, the advantages of iFOBT over gFOBT were well recognized in the art by the Priority Date.¹⁰⁴

4. Increased Complexity or Cost Would Not Have Dissuaded a POSA from Combining Detection of Fecal DNA and FOBT

72. Dr. Backman further opines that a POSA would have been dissuaded to combine multiple classes of markers due to increased complexity and cost.¹⁰⁵ I disagree. A POSA would have willingly accepted the incremental increase in cost

¹⁰² Vilkin (EX1005), pp. 2519, 2524.

¹⁰³ Backman Dep. Tr. (EX1090), 120:9-123:5.

¹⁰⁴ Opening Declaration (EX1002), ¶¶145-147.

¹⁰⁵ Backman Declaration (EX2022), ¶¶112-119.

and complexity associated with the performance of two known tests on a fecal sample instead of only one given the substantial increase in sensitivity provided by such a combination.

73. As an initial point, Dr. Backman's argument regarding increased complexity ignores that modifying the assay disclosed in Lenhard by replacing its gFOBT with a FIT like the one disclosed in Vilkin and incorporating the sample collection and stabilization process disclosed in Itzkowitz, in fact, *simplifies* sample collection in the Lenhard assay.

74. Specifically, the fecal test in Lenhard already includes both detection of DNA methylation and performance of a gFOBT on a single fecal specimen. Incorporation of the Itzkowitz sample collection and stabilization processes into the Lenhard assay facilitates at-home sample collection, making the process more convenient for the patient. Likewise, by the Priority Date, the art recognized that the sample collection process used with iFOBT, like the one in Vilkin, were much more convenient for patients than the corresponding collection process used with gFOBT. For example, Young, a 2007 review article, explains that iFOBT technology "simplifies the testing process, removes the need for diet and drug restrictions, provides for preferred and more acceptable stool-sampling methods such as brushes or probes rather than a wooden spatula, and is achieved while

collecting fewer fecal samples.”¹⁰⁶ Levin, a 2008 publication, confirms this assessment, stating that the sample collection of iFOBT assays like the one in Vilkin “are less demanding of patients than gFOBT, requiring fewer samples or less direct handling of stool.”¹⁰⁷ Accordingly, a POSA would, in fact, be motivated to make at-home collection by a patient more convenient in the Lenhard assay by incorporating the Itzkowitz and Vilkin sample collection processes.

75. What is more, as of the priority date, a POSA would be willing to accept a more complex and expensive fecal CRC diagnostic assay in exchange for improved CRC detection sensitivity. For example, the 2008 publication by Levin acknowledges that the unit cost of newly developed DNA-based tests was “much higher than the other stool tests” but that “[p]atient and provider acceptance of this technique appears to be high.”¹⁰⁸ Levin then suggests that adding additional cost and complexity to the fecal diagnostic test may be acceptable by noting that “[a] question worthy of consideration is whether or not including a sensitive gFOBT or

¹⁰⁶ Young (EX1024), p. 29.

¹⁰⁷ Levin (EX1013), p. 1576.

¹⁰⁸ *Id.*, p. 1578.

FIT at the time of testing would improve sensitivity without adversely affecting specificity.”¹⁰⁹

76. Thus, for the reasons set forth above and in my Opening Declaration, a POSA would be motivated by the express teachings of the references and the knowledge in the art to improve the combined DNA and gFOBT fecal assay disclosed in Lenhard by incorporating the sample collection and preservation processes disclosed in Itzkowitz and by replacing the gFOBT with a FIT like the one disclosed in Vilkin.

77. Dr. Backman further states in his Declaration that 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.¹¹⁰ Dr. Backman further contends that I have not conducted a comparative analysis of DNA stabilization buffer formulations versus blood protein stabilization buffer formulations to determine whether a DNA stabilization buffer could also stabilize blood proteins.¹¹¹

¹⁰⁹ *Id.*

¹¹⁰ Backman Declaration (EX2022), ¶117.

¹¹¹ *Id.*

78. I disagree with Dr. Backman's contention. As I explain in my Opening Declaration, the result of the obvious improvements to the Lenhard assay suggested by the Vilkin and Itzkowitz references would be a method for processing a freshly-collected fecal sample in which a patient defecates directly into a sealable container (as in Itzkowitz), removes a portion of the stool sample and combines it with a buffer known to stabilize blood proteins in a separate sealable container (as in Vilkin), and then adds stabilization buffer to the remaining fecal sample, known to stabilize DNA, before sealing the original sealable container (as in Itzkowitz).¹¹² The fact that the known stabilization buffers used in the references (one for DNA and one for blood proteins) were different requires the obvious step of collecting different portions of a fecal sample into separate containers. The patient would then send both sealed containers to a diagnostic laboratory for analysis of DNA methylation and FOBT, which Lenhard teaches provides improved assay sensitivity compared to either test alone.¹¹³ Dr. Backman's Declaration does not provide any reason why the combined disclosures of Lenhard, Vilkin and Itzkowitz would not result in stabilization of separate portions of fecal samples in their own containers, as set forth above.

¹¹² Opening Declaration (EX1002), ¶159.

¹¹³ *Id.*

79. Moreover, as I explain in my Opening Declaration, by the Priority Date different buffers had been developed to stabilize different types of biomarkers in fecal samples.¹¹⁴ For example, whereas certain buffers were optimized to prevent degradation of DNA,¹¹⁵ others were optimized to stabilize proteins.¹¹⁶ I am not aware of any disclosure before the Priority Date of a buffer optimized to stabilize **both** fecal DNA and fecal blood proteins, and Dr. Backman does not identify any such buffers in his declaration.

80. As I also explain in my Opening Declaration, by the Priority Date, it had long been recognized that, where samples were needed for two or more different tests, the patient could separate the fecal sample into two separated vessels or compartments prior to shipment to a laboratory.¹¹⁷ Indeed, decades before the Priority Date, scientists and clinicians recognized that testing different biomarkers could be facilitated by instructing patients to separate their fecal sample into portions stabilized in separate containers prior to shipment to a

¹¹⁴ *Id.*, ¶¶73-81.

¹¹⁵ Olson (EX1025), p. 183; Shuber (EX1009), 10:10-15; Itzkowitz (EX1006), pp. 111-112.

¹¹⁶ Vilkin (EX1005), pp. 2520-2521; Karl (EX1047), p. 1127; Hirata (EX1071), p. 1573.

¹¹⁷ Opening Declaration (EX1002), ¶¶82-87.

diagnostic laboratory.¹¹⁸ For example, as I noted in my Opening Declaration, a 1985 CDC Lab Manual discloses the separation of a fecal specimen into two portions to separately preserve each specimen in a different preservative.¹¹⁹ This process is illustrated in the CDC Lab Manual in an illustration it adapts from an even earlier 1949 publication, which I reproduced in my Opening Declaration and include below.

¹¹⁸ *Id.*

¹¹⁹ Melvin (EX1026), pp. 7-12.

Figure 2.
Use of PVA-Fixative and Formalin for Submitting Stool Specimens
to be Examined for Parasites

ADAPTED FROM BROOKE AND GOLDMAN, 1949

NOTE: BOTH SOFT AND *FORMED* SPECIMENS SHOULD BE SUBMITTED BY THIS METHOD.
 SPECIMENS MUST BE *FRESH* WHEN PLACED IN VIALS.



- 1** THE KIT CONSISTS OF TWO GLASS VIALS (ONE WITH 5% FORMALIN AND ONE WITH PVA-FIXATIVE) AND TWO APPLICATOR STICKS.



- 2** THE STOOL SHOULD BE PASSED INTO A DRY CONTAINER. URINE SHOULD NOT BE PASSED INTO THE SAME CONTAINER.



- 3** USING APPLICATOR STICKS, PLACE A QUANTITY OF THE STOOL (ABOUT THE DIAMETER OF A QUARTER) INTO THE VIAL CONTAINING FORMALIN, SCREW CAP ON TIGHTLY.



- 4** PLACE A SIMILAR QUANTITY INTO THE VIAL CONTAINING THE PVA-FIXATIVE.



- 5** THOROUGHLY BREAK UP SPECIMEN IN THE PVA-FIXATIVE, USING APPLICATOR STICKS. SCREW CAP ON TIGHTLY AND SHAKE VIGOROUSLY.



- 6** PACK THE TWO VIALS SO AS TO PROTECT AGAINST BREAKAGE, ENCLOSE APPROPRIATE IDENTIFICATION, AND MAIL OR DELIVER TO YOUR PUBLIC HEALTH LABORATORY.

10-10-10-10

81. I also explain in my Opening Declaration that a POSA would have been motivated based on the express teachings of Itzkowitz and the knowledge in the art to incorporate the sample collection and preservation processes disclosed in Itzkowitz into the Lenhard assay to facilitate at-home collection of the sample.¹²⁰ Itzkowitz, for example, explains that “a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction has the potential to significantly increase participation.”¹²¹ By the Priority Date, fecal collection by direct defecation into a sealable container, as done in Itzkowitz, was a standard and well-accepted method of fecal sample collection for decades that allowed for the at-home collection and shipment of a large portion of the stool sample for testing at a diagnostic laboratory.¹²² Itzkowitz expressly suggests that a stabilizing buffer should be used to preserve such fecal samples because adding DNA stabilizing buffer to the stool “was shown to prevent DNA degradation for several days” which improved assay sensitivity.¹²³ As I further discuss in my Opening Declaration, beyond these express teachings of

¹²⁰ Opening Declaration (EX1002), ¶¶148-162.

¹²¹ Itzkowitz (EX1006), p. 115.

¹²² Opening Declaration (EX1002), ¶¶150-151.

¹²³ Itzkowitz (EX1006), pp. 111, 116.

Itzkowitz, by the Priority Date the advantages of using a stabilization buffer that preserves DNA integrity of stool samples were also well recognized in the art.¹²⁴ Accordingly, a POSA would have had extensive motivation to incorporate the fecal sample collection and preservation processes of Itzkowitz into Lenhard's assay to facilitate convenient at-home sample collection.

C. Shuber And Vilkin Render the Challenged Claims Obvious

82. In his Declaration, Dr. Backman makes many of the same arguments with respect to the Shuber and Vilkin combination that he makes with respect to the Lenhard, Vilkin, and Itzkowitz combination. These arguments also fail when applied to the combined teachings of Shuber and Vilkin for effectively the same reasons I discuss above in the context of the Lenhard, Vilkin, Itzkowitz combination, as discussed below.

1. Shuber and Vilkin teach the combination of a nucleic acid-based test with iFOBT

83. Dr. Backman's argument that "[n]either Shuber nor Vilkin discloses or suggests a combined test in which a patient would separate one stool sample such that there is a remaining and a removed portion, both in sealable containers, to be tested for two different classes of markers as required by the claims"¹²⁵ fails

¹²⁴ Opening Declaration (EX1002), ¶¶154-155.

¹²⁵ Backman Declaration (EX2022), ¶126.

because it considers the references individually, rather than in combination, and disregards the knowledge in the art that a POSA would possess.

84. As described in my Opening Declaration, Vilkin discloses a quantitative FIT assay in which a portion of a fecal sample is removed to a separate sealable container containing a hemoglobin stabilization buffer so it can be shipped to a diagnostic laboratory for analysis.¹²⁶ Similarly, Shuber discloses a fecal DNA analysis method in which a fecal sample is directly deposited in a sealable container, where it is combined with a DNA stabilization buffer so it can also be shipped to a diagnostic laboratory for analysis.¹²⁷ A POSA would be motivated to perform both the FIT assay of Vilkin and the fecal DNA assay of Shuber on a fecal sample because, by the Priority Date, the advantages of combining such stool DNA and blood protein assays were well understood in the art.¹²⁸ As is also explained in my Opening Declaration,¹²⁹ when the combined test was performed, a patient would: (1) directly defecate into a sealable container at home (as in Shuber); (2) use a fecal test sampling device to remove a portion of the sample and combine it

¹²⁶ Opening Declaration (EX1002), ¶175.

¹²⁷ *Id.*, ¶239.

¹²⁸ *Id.*, ¶¶240-244.

¹²⁹ *Id.*, ¶245.

with hemoglobin stabilizing buffer (as in Vilkin); (3) add the DNA stabilizing buffer of Shuber to the remaining sample before sealing the container (as in Shuber); and (4) ship the sealed sampling device and sealed container to a diagnostic laboratory for testing (as in Vilkin and Shuber, respectively). A POSA would recognize that separation of the sample by the patient at home is necessary to ensure that the relevant biomarker in each portion (hemoglobin in one, DNA in the other) is stabilized with an appropriate buffer combined with the portion prior to shipment, as taught by Vilkin and Shuber.¹³⁰ A POSA would also recognize that it is more convenient for the patient to use the Vilkin sampling device before the fecal sample is immersed in buffer. Performance of the obvious fecal processing method includes all the steps of the Challenged Claims.¹³¹

85. Accordingly, the analysis I provide in my Opening Declaration does not rely on hindsight, but rather is an objective analysis on how a POSA would have understood and applied the teachings of Shuber and Vilkin in view of the state of the art as of the Priority Date.

¹³⁰ Vilkin (EX1005), p. 2520; Shuber (EX1009), 29:8-19.

¹³¹ Opening Declaration (EX1002), ¶¶247-271.

2. A POSA would have been motivated to combine fecal DNA tests with fecal blood protein tests

86. Dr. Backman asserts that the “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.”¹³² Dr. Backman’s opinion relies on a selective misreading of prior art references that, in fact, clearly suggest combining fecal DNA testing with FOBT. His opinion also disregards the widespread teaching of the art that combining such tests was a known strategy for improving diagnostic performance and, in particular, assay sensitivity. As I set forth in my Opening Declaration, by the Priority Date, combining different biomarker types was a recognized strategy for improving diagnostic assay sensitivity that had been experimentally demonstrated in fecal samples.¹³³ In particular, a POSA would know that fecal DNA tests would detect CRC in samples that would be missed by FOBT tests, and vice-versa.¹³⁴ Thus, combining detection of fecal DNA biomarkers with fecal blood protein biomarkers was a known

¹³² Backman Declaration (EX2022), ¶127.

¹³³ Opening Declaration (EX1002), ¶¶60-65., 240-244.

¹³⁴ *See, e.g.*, Lenhard (EX1004), Kutzner (EX1012).

strategy for increasing assay sensitivity, which Dr. Backman acknowledged at his deposition was instrumental in achieving high diagnostic performance.¹³⁵

87. Dr. Backman’s attempt to explain-away the extensive teachings in the art of the advantages associated with the combined detection of fecal DNA and fecal blood proteins is misleading and unavailing. For example, Dr. Backman acknowledges that Nishikawa concluded that its DNA test “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**,” but attempts to wave-away this explicit teaching because “seven years passed between Nishikawa and the invention of the ’781 patent.”¹³⁶ However, it is indisputable that Nishikawa’s disclosure reflects a recognition in the art that combining fecal DNA tests with FOBT was a recognized strategy for improved CRC screening by the priority date.

88. Dr. Backman’s assertion that “consideration of the full Lenhard disclosure would have discouraged, not motivated, any combination of FOBT with nucleic acid-based testing”¹³⁷ is particularly confounding. Dr. Backman’s opinion

¹³⁵ Backman Dep. Tr. (EX1090), 112:20-24.

¹³⁶ Backman Declaration (EX2022), ¶128.

¹³⁷ *Id.*, ¶129.

is in direct opposition to the data and teachings of Lenhard, which show that the **combination** of the HIC1 test and FOBT, as compared to either test alone, provided greater sensitivity detection of CRC. Indeed, Lenhard explicitly notes that that “[t]he combination of both assays resulted in increased detection rates for CRCs.”¹³⁸ Lenhard therefore further supports that combining detection of fecal DNA biomarkers with fecal blood protein biomarkers was a known strategy for increasing assay sensitivity. Dr. Backman’s interpretation of Kutzner is likewise confounding. Like Lenhard, Kutzner explicitly concludes that “[t]he combined application of FOBT and MD [a fecal DNA test] **resulted in an overall sensitivity, which could not be achieved by any of the methods alone.**”¹³⁹ Indeed, Kutzner states:

This is one of the first studies, which evaluate and directly compare the potential of the two non-invasive methods MD and FOBT in the diagnosis of colorectal carcinomas. ***The combined application of the two methods together led to a significantly higher sensitivity than the application of any of the methods alone.*** Regarding the low cost and the little technical expense of the FOBT, ***we***

¹³⁸ Lenhard (EX1004), p. 147.

¹³⁹ Kutzner (EX1012), abstract.

suggest that MD and FOBT should complement rather than replace each other.¹⁴⁰

89. Dr. Backman attempts to disregard these explicit teachings of Kutzner because Kutzner “poses a question of ‘whether both [MD and gFOBT] methods should be used together in broad diagnostic screening programs.’”¹⁴¹ However, the statement identified by Dr. Backman simply acknowledges the uncontroversial point that clinical trials are required before the proposed combined assay could be put into broad clinical use. This acknowledgement does not take away from Kutzner’s explicit overall recommendation that “***MD and FOBT should complement rather than replace each other.***”¹⁴² Kutzner therefore further supports that combining detection of fecal DNA biomarkers with fecal blood protein biomarkers was a known strategy for increasing assay sensitivity.

90. Dr. Backman also selectively interprets Levin as “pos[ing] a question for potential investigation.”¹⁴³ Levin directly proposes investigating “whether or not including a sensitive gFOBT or FIT at the time of testing would improve

¹⁴⁰ *Id.*, p. 40.

¹⁴¹ Backman Declaration (EX2022), ¶130.

¹⁴² Kutzner (EX1012), p. 40.

¹⁴³ Backman Declaration (EX2022), ¶131.

sensitivity [of DNA-based assays] without adversely affecting specificity.”¹⁴⁴

Thus, Levin recognizes that combining fecal DNA assays with FIT assays was a potential strategy for improving the sensitivity of fecal CRC assays worth trying.

Moreover, Levin supports its suggestion by citing data from Kutzner

demonstrating the potential benefits of such combinations. Specifically, Levin

states: “[i]n a recent retrospective analysis of stool samples from patients with

CRC and donor controls, ***combined results from a standard gFOBT and a panel***

of DNA markers (APC, BAT26, and L-DNA) resulted in a ***combined sensitivity***

for cancer of 93% and specificity of 89% (Kutzner, 2005).”¹⁴⁵ The results from

Kutzner cited by Levin would provide a POSA with a reasonable expectation that

Levin’s proposed combination of fecal DNA test with FOBT would be successful.

91. Dr. Backman further asserts that Kanaoka “would have discouraged, not encouraged, a combination,” and supports this assertion by pointing out that Kanaoka’s “iFOBT test resulted in one additional positive test ... [t]he 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%).”¹⁴⁶

¹⁴⁴ Levin (EX1013), p. 1578.

¹⁴⁵ *Id.*, p. 1578 (emphasis added).

¹⁴⁶ Backman Declaration (EX2022), ¶133.

These data would not rule out further exploration of a multi-marker approach, especially when they show increased CRC detection when the assays are combined.

92. Shuber's prophetic statements that certain panels of biomarkers could detect adenomas with sensitivities of greater than 60%, 74%, 90%, 95% or even 98% would not dissuade a POSA from combining fecal DNA assays with FOBT, as asserted by Exact. EX1009 14:1-16. A POSA would recognize these hypothetical adenoma sensitivities as overly optimistic given the state of the art, which did not demonstrate fecal CRC tests having adenoma sensitivities of 90% or higher, as Shuber proposes.

3. A POSA Would Accept Increased Cost and Complexity

93. Dr. Backman reiterates the same arguments concerning complexity and cost with respect to the Shuber and Vilkin combination that he made with respect to the Lenhard, Vilkin and Itzkowitz combination.¹⁴⁷ As discussed above in section V(B)3, I disagree with Dr. Backman's opinion. Indeed, it is clear from the state of the art that a POSA would have willingly accepted the incremental increase in cost and complexity associated with the performance of two known tests on a

¹⁴⁷ *Id.*, ¶134.

fecal sample instead of only one given the increase in sensitivity the POSA would expect to gain from such a combination.

4. Vilkin Does Not Require Multiple Samples or Home Refrigeration

94. As he did when opining on the Lenhard, Vilkin and Itzkowitz combination, in his opinion on Shuber and Vilkin Dr. Backman once again incorrectly argues that Vilkin requires collection of multiple samples and at-home refrigeration.¹⁴⁸ As discussed above in section V(A)2 and V(B)4, Dr. Backman's opinion is based on a misreading of Vilkin, and POSA would recognize that clinical use of Vilkin's assay requires neither multiple sample collection nor at-home refrigeration. At his deposition, Dr. Backman admitted that Vilkin does **not** require collection of three consecutive daily samples when its assay is used in clinical practice.¹⁴⁹ Such issues would therefore not dissuade a POSA from combining the DNA test of Shuber with the FIT of Vilkin, as Dr. Backman claims.

5. A POSA Would Have Been Motivated to Stabilize Portions of Fecal Samples in Separate Containers

95. Dr. Backman also reiterates the same arguments regarding sample separation with the Shuber and Vilkin combination that he made within the context

¹⁴⁸ *Id.*, ¶136.

¹⁴⁹ Backman Dep. Tr. (EX1090), 141:4-142 :19.

of the Lenhard, Vilkin and Itzkowitz combination.¹⁵⁰ Again, I disagree with Dr. Backman's opinion. As discussed above in section V(B)5, partitioning fecal samples for separate preservation in biomarker-optimized buffers was well-established in the art by the Priority Date, and would therefore have been an obvious strategy for a POSA to implement when combining the fecal DNA test of Shuber with the FIT of Vilkin.

VI. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

96. I have reviewed Dr. Backman's opinions concerning secondary considerations of non-obviousness (sometimes called "objective indicia of non-obviousness") included in the declaration he submitted in this proceeding. I strongly disagree with Dr. Backman's opinion that Exact Sciences' Cologuard Products provide "strong objective evidence that the '781 patent would not have been obvious at the relevant time" and that "Cologuard ... embodies at least claims 1 and 3 of the '781 patent ... [and] met the long-felt need for a sufficiently sensitive and specific CRC screening test."¹⁵¹

97. I understand that to accord substantial weight to secondary considerations, the evidence of secondary considerations must be shown to have a

¹⁵⁰ Backman Declaration (EX2022), ¶136.

¹⁵¹ *Id.*, ¶¶139-140.

“nexus” to the claims. I understand that the patentee bears the burden of showing a nexus exists, and that presuming nexus is only appropriate when the patentee shows that the asserted secondary consideration is tied to a specific product and that the product embodies the claimed features and is coextensive with them. On the other hand, when the product that is the basis of the secondary consideration is not coextensive with the patented invention—for example, if the patented invention is only a component of a product, the patentee is not entitled to a presumption of nexus. Dr. Backman has not demonstrated, and does not attempt to demonstrate, that Cologuard is coextensive with the challenged claims.

98. I understand that if a party is not entitled to a presumption of nexus, it bears the burden of showing that the success of the commercial product is a direct result of the unique characteristics of the claimed invention. Dr. Backman has also not demonstrated that the success of Cologuard is a direct result of any fundamental characteristics of the claims.

A. Cologuard is Not Coextensive with the Claims of the '781 Patent

99. I note that, while Dr. Backman repeatedly asserts that Cologuard embodies the claims of the '781 patent, he never claims that Cologuard is coextensive with them. This is because the purported invention of the challenged method claims is, at most, a minor component of the Cologuard product. It is further my opinion that, to the extent any of the challenged claims possess novel

features, those features have little or nothing to do with Cologuard's purported success.

100. Cologuard is a product for home CRC screening that is marketed by Exact.¹⁵² Cologuard is a combination of many components and processes, including, but not limited to, a multi-component at-home collection kit, numerous reagents and methods required to assess a diverse collection of specified biomarkers during sample testing, and a proprietary algorithm that translates biomarker data into a screening outcome during data analysis.¹⁵³

101. The complex, multi-component nature of Cologuard is demonstrated by the FDA-approved Cologuard Physician Brochure, which explains that “Cologuard uses a multi-target approach” in which “[t]here different categories of biomarkers are targeted and provide an additive association with CRC and pre-

¹⁵² Cologuard Patient Guide (EX2016), p. 1.

¹⁵³ Cologuard Patient Guide (EX2016), p. 8; Imperiale (EX2008), Abstract; Exact Sciences 2023 Form 10-K (EX2040); Cologuard Physician Brochure (EX1081); Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use (EX1082).

malignant colorectal neoplasia.”¹⁵⁴ The Physician Brochure describes these three categories of biomarkers as follows:¹⁵⁵

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

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

¹⁵⁴ Cologuard Physician Brochure (EX1081), p. 4.

¹⁵⁵ *Id.* Internal citations omitted.

including subjects with colorectal cancer and pre-malignant lesions.

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

102. The Physician Guide summarizes the numerous, complex assays run during the Cologuard process as follows:¹⁵⁶

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

¹⁵⁶ *Id.*

Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.

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

103. The complex, multi-component nature of Cologuard is further demonstrated by **85-page long** Cologuard Instructions for Use approved by FDA.¹⁵⁷ Within these lengthy instructions, ***the specimen collection process is summarized in a single sentence***, simply stating that “[s]pecimens for use with Cologuard must be collected with the Cologuard Collection Kit (Exact Sciences, 100026), including a stool sample for DNA testing (Container) and a stool sample for Hemoglobin testing (Tube).”¹⁵⁸ In contrast, the Laboratory Instructions include approximately five pages devoted to reagents and instrumentation used in Cologuard,¹⁵⁹ about 23 pages devoted to performance of the laboratory assays used

¹⁵⁷ Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use (EX1082).

¹⁵⁸ *Id.* p. 15.

¹⁵⁹ *Id.*, pp. 9-14.

in Cologuard,¹⁶⁰ and about seven pages directed to data analysis and interpretation.¹⁶¹ The remainder of the Laboratory Instructions is devoted to procedural notes and precautions, quality control, a troubleshooting guide, and assay performance characteristics.¹⁶²

104. Exact’s own website also demonstrates the critical importance of components of Cologuard not claimed in the ’781 patent. For example, Exact advertises on its website that it uses specific proprietary platforms for each of the marker assays.¹⁶³ Regarding DNA stability, Exact Sciences states that developing “an enhanced DNA stabilizing buffer was a **critical** step in the process of creating a reliable at-home screening kit” (emphasis added).¹⁶⁴ Exact emphasizes the importance of the DNA Cologuard DNA isolation process, stating that their “scientists needed to first solve the essential problem of effectively isolating DNA from stool before achieving the goal of developing a noninvasive colon cancer

¹⁶⁰ *Id.*, pp. 15-39.

¹⁶¹ *Id.*, pp. 39-46.

¹⁶² *Id.*, pp. 47-83.

¹⁶³ Exact Science’s webpage regarding the Cologuard test as obtained from <https://www.exactsciences.com/our-tests/cologuard> on August 15, 2024 (EX1088).

¹⁶⁴ *Id.*

screening test.”¹⁶⁵ Exact also credits its DNA biomarker detection platform, stating that it “developed our proprietary QuARTS technology (Quantitative Allele-specific Real-time Target and Signal Amplification) which efficiently amplifies and quantifies two separate methylated DNA markers (NDRG4 and BMP3) along with seven distinct KRAS gene point mutations.”¹⁶⁶ Regarding hemoglobin stability and detection, Exact Sciences states that it “improved upon the technology for the ELISA-based detection of a protein biomarker (hemoglobin) through an additive in the stabilization buffer.”¹⁶⁷ Regarding its algorithm, Exact’s website states that “[t]his algorithm is the vital workhorse that translates our invisible biology into actionable information.”¹⁶⁸

105. Cologuard identifies on its website 54 Exact patents unrelated to the ’781 patent that cover components of Cologuard and its use.¹⁶⁹ An additional eight patents were identified on Exact’s webpage as covering Cologuard in 2014, which

¹⁶⁵ *Id.*

¹⁶⁶ *Id.*

¹⁶⁷ *Id.*

¹⁶⁸ *Id.*

¹⁶⁹ Printout of Exact Sciences’ “Patents and Trademarks” page from their website, as visited on August 9, 2024 (EX1083).

I understand are now expired.¹⁷⁰ The claims of these many patents are directed to numerous distinct components of Cologuard, including those set forth below:

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

¹⁷⁰ Printout of Exact Sciences' "Patents and Trademarks" page from their website as of December 6, 2014. Downloaded from Wayback Machine on August 9, 2024 (EX1084).

- Patents related to methods of preparing DNA for methylation analysis: *e.g.*, U.S. Pat. Nos. 9,315,853, 10,144,953, 10,704,083.
- **Patents related to methods of testing for methylated DNA:** *e.g.*, U.S. Pat. Nos. 8,916,344, 9,637,792, 10,519,510, 10,590,489, 10,808,286.
- **Patents related to methods of detecting DNA mutations:** *e.g.*, U.S. Pat. Nos. 8,361,720, 8,715,937, 9,024,006, 9,121,071, 9,212,392, 9,290,797, 9,376,721, 10,000,817, 10,106,844, 10,590,489.
- **Patents related to control molecules used with DNA assays:** *e.g.*, U.S. Pat. Nos. 9,212,392, 10,106,844, 10,138,524, 10,253,358, 10,889,867.

106. In sum, the purported invention of the challenged method claims is, at most, a minor component of the Cologuard product. The claims are not co-extensive with the Cologuard Products, and Exact is not entitled to a presumption of a nexus.

B. Dr. Backman Has Not Established That Cologuard’s Purported Success is a Direct Result of The Claims

107. Dr. Backman’s nexus arguments are based on his assertion that “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.”¹⁷¹ However, beyond this conclusory statement, Dr.

¹⁷¹ Backman Declaration (EX2022), ¶141.

Backman never establishes that claims 1 and 3 are “fundamental” to the diagnostic accuracy or patient uptake of Cologuard. I am not aware of any secondary considerations related to Cologuard that can be attributed to the invention of the challenged claims, as opposed to the other Cologuard components listed above.

108. Neither claim 1 nor 3 includes any limitation requiring any level of diagnostic accuracy or patient uptake. Rather, claim 1 is directed to the separation of a fecal sample into two portions, each preserved in its own stabilization buffer. Claim 3 adds that that these fecal portions are then tested for an amount of a nucleic acid and an amount of a blood protein. In my opinion, claims 1 and 3 are not fundamental to either diagnostic accuracy or patient uptake.

109. Moreover, Dr. Backman has provided no evidence that the diagnostic accuracy of Cologuard is a product of the claimed fecal processing methods of claims 1 and 3. For example, Dr. Backman provides no evidence that the complete Cologuard test, including both a DNA component and a FIT component, has better diagnostic accuracy than the DNA component of the test alone.

110. Indeed, there is significant evidence that the diagnostic performance of Cologuard is not attributable to the method of the challenged claims. For example, in its clinical trial publication, Exact acknowledges that Cologuard’s

improved sensitivity for both colorectal cancer and advanced precancerous lesions
“may be attributed to the DNA marker and algorithm components of the test.”¹⁷²

111. Similarly, during prosecution of an unrelated patent (U.S. Pat. No. 9,163,278, “the ’278 patent”), Exact attributed Cologuard’s success, not to the method of the Challenged Claims, but rather to “a particular combination of markers and methods for extracting the marker DNA.”¹⁷³ Exact noted that Cologuard “comprises the system components recited in the instant claims as amended: stool homogenization buffer, PVPP inhibitor adsorbant, spin filter and guanidine thiocyanate, and magnetic target-specific capture particles for capturing NDRG4, BMP3 and KRAS target human DNAs.”¹⁷⁴ Exact then argued that it was these components of Cologuard that addressed the “long-felt need for a way to screen for colorectal cancers based on DNA screening” and “succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.”¹⁷⁵

¹⁷² Imperiale 2014 (EX2008), p. 1295.

¹⁷³ Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of '278 patent (EX1086), p. 9.

¹⁷⁴ *Id.*, p. 7.

¹⁷⁵ *Id.*, p. 9.

112. The '278 patent asserts a priority date of May 12, 2011, more than two years **after** the February 3, 2009 priority date asserted by the '781 Patent.¹⁷⁶ Thus, when Exact argued during prosecution of the '278 patent that the particular combination of markers and methods for extracting the marker DNA from stool claimed by that patent solved the “long-felt need for screen for a way to screen for colorectal cancers based on DNA screening,” it was **admitting that this problem had not been solved by the method claimed in the '781 Patent.**

113. The evidence of record similarly does not demonstrate that Cologuard's patient uptake is a unique product of claims 1 and 3. At-home collection of stool samples and their preservation in buffers before shipping to a diagnostic laboratory was known in the art well before the Priority Date.¹⁷⁷ Dr. Backman admitted in his deposition that the sample collection process used in Cologuard is no more convenient than that of prior art FIT assays.¹⁷⁸ As fecal samples used in diagnostic assays had been conveniently collected at home for decades before the 2009 priority date, at-home sample collection indisputably is not a distinguishing feature of the Challenged Claims or the Cologuard product.

¹⁷⁶ U.S. Patent No. 9,163,278 (EX1085); '781 patent.

¹⁷⁷ See, e.g., Itzkowitz (EX1006); Vilkin (EX1005); Shuber (EX1009).

¹⁷⁸ Backman Dep. Tr. (EX1090), 74:7-75:8.

Accordingly, it is my opinion that the patient uptake of Cologuard is unrelated to the fecal processing method of claims 1 and 3.

114. As noted above, Exact identifies on its website 54 patents unrelated to the '781 patent that cover components of Cologuard and its use, and an additional eight now-expired patents were previously identified on Exact's webpage in 2014. In his Declaration, Dr. Backman does not attempt to assess the role of the more than 60 other patented inventions had on the success of Cologuard. In addition to ignoring the later innovations required to achieve Cologuard's success, he does not consider that the commercial success of Cologuard may have been significantly influenced by the exclusivity provided by patents unrelated to the '781 patent. Similarly, Dr. Backman has not shown that any of the supposed industry praise for Cologuard he identified was attributable to the "unique characteristics" of the Challenged Claims, as opposed to unique characteristics associated with these other, unrelated inventions. Without conducting such an analysis, Dr. Backman cannot satisfy Exact's burden of establishing a nexus between Cologuard and the Challenged Claims.

115. It is also my opinion that the patient uptake of Cologuard is primarily the product of the more than \$3 billion Exact spent in marketing its Cologuard products—which I note amounts to more than \$200 in marketing dollars spent for

each of the 14 million Cologuard tests sold to date.¹⁷⁹ In his declaration, Dr. Backman does not offer an opinion regarding the effect that Exact's extensive marketing efforts have had on Cologuard's success. For example, Dr. Backman does not provide an opinion with respect to how many Cologuard tests would have been sold in the absence of Exact's multibillion-dollar marketing efforts.

116. The important role of Exact's marketing efforts to Cologuard's commercial success is confirmed by a recent article published in Forbes.¹⁸⁰ In this article, Exact's CEO Kevin Conroy explains that, shortly after Cologuard's launch, Exact ran direct-to-consumer (DTC) marketing tests in five cities. As explained by Mr. Conroy, "We ran targeted TV commercials in these five markets and compared them to the five control markets. These markets grew cumulatively 10% per week over the five control markets. After 9 weeks, we were up 100% compared to the control markets."¹⁸¹ Notably, in the above DTC marketing test, the exact same Cologuard product was being sold in both the test market and the control market. The 100% improvement in commercial success observed over nine

¹⁷⁹ Declaration of Peter Wood (EX2023), ¶13

¹⁸⁰ Feiger, Chase, "How This CEO Consumerized Cancer Into a \$13B Enterprise" Forbes, April 8, 2024 (EX1087).

¹⁸¹ *Id.*, p. 6.

weeks in the test markets can therefore only be attributable to the advertising Exact placed in those markets, and is certainly not attributable to the Challenged Claims.

117. Dr. Backman therefore has not demonstrated that the secondary considerations he alleges are associated with Cologuard (e.g., commercial success, industry praise, failure by others, meeting a long-felt need) have any nexus to the methods of the Challenged Claims. The secondary considerations identified by Dr. Backman therefore should be given little or no weight.

C. Dr. Backman Does Not Establish that Geneoscopy Copied Cologuard

118. I understand that establishing “copying by others” as a secondary consideration of non-obviousness requires more than simply showing infringement by a third-party product. Dr. Backman has not met this burden, as the entirety of his copying-by-others analysis argument is based on Exact’s claim that ColoSense practices the claims of the ’781 patent.¹⁸² Dr. Backman therefore has not satisfied Exact’s burden of establishing copying by others as a secondary consideration of nonobviousness.

119. Cologuard’s purported success therefore has little or no nexus with the methods of the claims of the ’781 patent, and the secondary considerations identified by Dr. Backman therefore should be given little or no weight.

¹⁸² Backman Declaration (EX2022), ¶¶177-185.

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

Dated: January 27, 2025

Respectfully submitted,

A handwritten signature in blue ink, appearing to read 'Duncan Whitney', is written over a horizontal line.

Duncan Whitney, Ph.D.