

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

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

SECOND DECLARATION OF DUNCAN WHITNEY, Ph.D.

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I. INTRODUCTION

1. As set forth in the declaration I submitted on August 20, 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. 11,970,746 (EX1001; the “’746 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 ’746 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 ’746 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 ’746 patent. I have now been asked to respond to the opinions concerning validity of the claims of the ’746 patent set forth in the May 30, 2025 declaration of Dr. Vadim Backman (EX2044, 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

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

4. I previously prepared two declarations as evidence in IPR proceeding No. IPR2024-00459, which concerned U.S. Patent No. 11,634,781 (“the ’781 patent”). I understand the ’781 patent is the parent of the ’746 patent.

5. The claims of the ’781 patent are very similar to, and in fact, broader than, the corresponding claims of the ’746 patent. In the declarations I prepared for IPR2024-00459, I opined that the claims of the ’781 patent are invalid as obvious over many of the same combinations of references that serve as the basis for my opinions in the present IPR, including (a) Lenhard, Vilkin and Itzkowitz; (b) Lenhard, Vilkin, Itzkowitz and Kanaoka; (c) Shuber and Vilkin; and (d) Shuber, Vilkin and Kanaoka.

6. I have reviewed the Final Written Decision (“FWD”) issued by the Board in IPR2024-00459.¹ In the FWD, the Board held all of the claims of the ’781 patent obvious and therefore unpatentable for essentially the reasons I set forth in the declarations I submitted in that IPR. Inasmuch as the claims of the ’781 patent are broader than the corresponding claims of the ’746 patent, the reasons the

¹ EX1087.

Board found the claims of the '781 patent to be obvious are equally applicable to the corresponding claims of the '746 patent.

II. OVERVIEW OF OPINIONS

7. In my Opening Declaration, I opined that the claims of the '746 patent are invalid as obvious over prior art. After reading the Backman Declaration, my opinions regarding the obviousness of the claims of the '746 patent are unchanged.

8. Nothing in the Backman Declaration has altered my opinion that the claims of the '746 patents are not inventive. The claims of the '746 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. Dr. Backman also does not contend that the combined performance of the two assays yields unexpected results.

9. 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 combination fecal CRC diagnostic assay in

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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 for detection of a blood protein biomarker with the superior automated iFOBT assay of Vilkin and by incorporating the fecal collection and DNA stabilization process of Itzkowitz to facilitate at-home sample collection of a fecal sample, and, in doing so, would arrive at the methods of the claims of the '746 patent.

10. 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, and clearly demonstrates the additive and complementary detection sensitivity of the two types of tests. As I explain in my Opening Declaration, a POSA would recognize that incorporation of the iFOBT of Vilkin and the sample collection 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.

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11. Dr. Backman also has not changed my opinion that the Challenged Claims are obvious in view of Shuber (EX1008) 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 result in a more complicated test. Dr. Backman's arguments ignore the importance a POSA places on improved test sensitivity. Exact acknowledges in their publication of the Cologuard clinical trial, for example, 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."² At his deposition, Dr. Backman acknowledged that in "screening tests, different characteristics can be sacrificed in order to improve some others," and he noted that there "are many examples" where "in order to improve diagnostic performance, you would sacrifice some other attributes, for example, how easy it is to implement or its cost."³ A POSA would have been willing to sacrifice some assay specificity, cost and complexity if the result was a test with markedly better sensitivity.

² Imperiale (EX1077), p. 1295.

³ Backman Dep. Tr. (EX1089), 59:15-17, 60:10-15.

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12. 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 '746 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 and separately preserve them so that different assays could be performed on each portion.

13. Dr. Backman has also not provided convincing arguments to rebut my opinion that the Challenged Claims are obvious in view of Inbar, Shuber, and Vilkin. Here, Dr. Backman argues that a POSA would be dissuaded from merging Inbar's split-specimen format with the individual preservation schemes disclosed in Shuber (DNA) and Vilkin (hemoglobin). Dr. Backman's arguments ignore the teaching of Inbar, which is to divide a single stool collection into separate, preservative-filled tubes, each optimized to stabilize a particular type of biomarker. Nothing in the cited art suggests any technical impediment to that straightforward aliquoting step. To the contrary, Shuber discloses that stool nucleic acid can be stabilized with an optimized Tris/EDTA-based buffer, while Vilkin confirms that

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FIT-style immunoassays operate reliably in their own hemoglobin stabilizing buffer.

14. Dr. Backman argument that a POSA would not be motivated to use Inbar's sample collection system to separately preserve samples for a fecal DNA and a FIT test because a single buffer could be used to stabilize both biomarkers is based on an incorrect assessment of the state of the art as of the Priority Date. Dr. Backman does not identify any buffer known to exist in 2009 that had been optimized to stabilize both fecal DNA and hemoglobin, and I am aware of none. Notably, Dr. Backman does not provide any examples of buffers that had even been demonstrated to stabilize both fecal nucleic acids and blood proteins simultaneously, let alone one that has been optimized to stabilize both. Even today, Exact still uses separate buffers to separately stabilize DNA and hemoglobin in their Cologuard products.

15. In contrast, by the Priority Date, buffers optimized to stabilize hemoglobin for use in FIT assays and buffers optimized to stabilize nucleic acids for use in fecal-DNA assays had already been developed, and they are repeatedly described in the prior art. It would have been far more straightforward for a POSA to use these existing separate buffers in conjunction with an existing fecal sample collection and preservation system like that of Inbar than to try to develop a single buffer optimized to preserve both fecal DNA and hemoglobin. A POSA would

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therefore have found it eminently obvious, and well within ordinary skill, to adopt Inbar's dual-container approach—placing one aliquot in Shuber's nucleic-acid stabilizing buffer and the other in Vilkin's hemoglobin stabilizing buffer—thereby achieving the dual-analyte processing method with a reasonable expectation of success.

16. Finally, the secondary considerations identified by Dr. Backman should be accorded no weight because there is no nexus between the Cologuard product and the methods claimed in the '746 patent. Dr. Backman does not demonstrate that the Cologuard test is coextensive with the Challenged Claims, which I understand is required for a presumption of nexus. As I explained in my Opening Declaration, the sample processing methods of the Challenged Claims are, at best, a minor component of the Cologuard assay. Indeed, as I explain below and in my Opening Declaration, the Cologuard product has many features not covered by the '746 patent's claims, some of which Exact has acknowledged are critical to the functioning of their Cologuard product. Tellingly, Dr. Backman does not address in his Declaration the dozens of other patents that I identify in my Opening Declaration and that Exact admits also cover its Cologuard product. Nor does he address Exact's statements to the patent office regarding the critical importance of key elements of its Cologuard product that are covered by the later-invented claims of at least one of these other patents.

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17. Dr. Backman has also not demonstrated that any purported secondary consideration is a direct result of any unique characteristics of the Challenged Claims, which I understand is required to establish nexus where no presumption of nexus has been proven. Instead, Dr. Backman makes the conclusory and unsupported assertion that "... Cologuard practices at least Claim 3 of the '746 patent, and the invention claimed in Claim 3 is fundamental to the diagnostic accuracy and patient uptake of Cologuard."⁴ Dr. Backman does not demonstrate that the diagnostic accuracy and patient uptake of Cologuard are attributable to the claimed method, as opposed to the result of other Cologuard components covered by the more than 60 unrelated patents Exact identifies on its website or the result of the more than \$3 billion that Exact admits it spent marketing Cologuard. Indeed, as I discussed in my Opening Declaration, Exact admits in its publications and advertisements that features of Cologuard that are unclaimed by the '746 patent are critical to Cologuard's success, and it has argued as much to the patent office.⁵ Dr. Backman's conclusory assertions do not satisfy Exact's burden of demonstrating nexus, and his opinion on alleged secondary considerations deserves no weight.

⁴ Backman Declaration (EX2044), ¶199.

⁵ Opening Declaration (EX1002), ¶¶343-347.

III. THE PERSON OF ORDINARY SKILL IN THE ART

18. I provided my opinions concerning the definition of a POSA in my Opening Declaration.⁶ 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

19. I provided my understanding of the legal standards of obviousness in my Opening Declaration.⁷ 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

20. 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.⁸

⁶ Opening Declaration (EX1082), ¶¶9-13.

⁷ *Id.*, ¶¶89-96.

⁸ Backman Declaration (EX2044), ¶¶58-118.

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21. What is more, throughout his Declaration, Dr. Backman consistently attacks prior art references individually, rather than considering their collective teachings in combination, as I understand is required in an obviousness analysis.

1. Lenhard

22. In his Declaration, Dr. Backman contends that a POSA reading Lenhard, would “not have expected improved performance from a test combining nucleic acid testing and FOBT.”⁹ Dr. Backman’s analysis ignores the express and repeated teachings in Lenhard that combining the DNA methylation marker test with FOBT **increased** CRC assay sensitivity, which Exact acknowledges is the most important characteristic for screening tests.¹⁰

23. 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.”¹¹ 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.¹² Indeed, Lenhard twice notes that “[t]he combination of HIC1 methylation analysis with FOBT allowed for

⁹ Backman Declaration (EX2044), ¶74.

¹⁰ Imperiale (EX1077), at p. 1295

¹¹ Lenhard (EX1004), p. 147 (emphasis added).

¹² *Id.*, pp. 143, 147.

the detection of two thirds of CRCs.”¹³ 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.¹⁴

24. Dr. Backman’s analysis fixates on peripheral aspects of Lenhard’s study not even mentioned in Lenhard itself, such as minor differences in specificity and Dr. Backman’s own p-value and AUC calculations, while disregarding Lenhard’s central and repeated teaching that combining HIC1 detection with FOBT results in a fecal assay that better detects CRC. In particular, Lenhard demonstrates that its HIC1 test detects incidents of cancer that are missed by its FOBT test and vice-versa. Under such circumstances, a POSA would recognize, as the Lenhard authors explicitly recognized, that a combined assay would necessarily have a higher sensitivity than each test individually. Indeed, at his deposition Dr. Backman agreed that “if the HIC1 test detects cancers that are missed by the FOBT and the FOBT test also detects cancers that are missed by the HIC1” “the

¹³ *Id.*

¹⁴ *Id.*, Table 4, and p. 147.

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sensitivity would be and can only be higher.”¹⁵ Dr. Backman also ignores that this central teaching of Lenhard aligns with the state of the art as of the Priority Date.¹⁶

25. 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).¹⁷ Dr. Backman offers no evidence that inclusion of late-stage cases would alter Lenhard’s core results; nor is there any basis to believe that Lenhard’s principal findings would differ in a cohort lacking late-stage cancers, given that both fecal DNA biomarkers and FOBT have been evaluated in broad screening populations that likewise can include late-stage disease. In my opinion, this does not discredit Lenhard’s findings, particularly because Lenhard also includes early-stage cancers. Also, a POSA would be motivated in developing a fecal screening 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

¹⁵ Backman Dep. Tr. (EX1089) 90:2-11, 91:8-14.

¹⁶ Nishikawa (EX1011) p. 112; Kutzner (EX1012), abstract, p. 40; Levin (EX1013), p. 1578.

¹⁷ Backman Declaration (EX2044), ¶63

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combine a DNA methylation marker test with a blood protein-based test because “[t]he combination of both assays resulted in increased detection rates for CRCs.”¹⁸

26. Dr. Backman states that Lenhard discloses that “the specific combination HIC1 and gFOBT showed ‘no increase in the sensitivity for adenoma’.”¹⁹ 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.²⁰

27. 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 only potential indicators of future cancer; as Dr. Backman acknowledges in his declaration, only about 10% of adenomas progress to invasive cancer.²¹ I strongly

¹⁸ Lenhard (EX1004), p. 147.

¹⁹ Backman Declaration (EX2044), ¶71.

²⁰ Lenhard (EX1004), Table 4.

²¹ Backman Declaration (EX2044), ¶32.

disagree with Dr. Backman's opinion that detection of adenomas would be more important to a POSA than detection of cancer.

28. 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 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 (i.e., 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.***²²

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

²² Levin (EX1013), pp. 1572-1573, emphasis added.

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30. 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 numerically higher, the specificity is considerably lower.”²³ I note, however, that as of the Priority Date the most 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.”²⁴ Thus, while specificity would be considered, a POSA would be willing to sacrifice some specificity in exchange for increases in sensitivity. Nowhere does Dr. Backman contend that a specificity of 89% in order to achieve greater sensitivity would be unacceptable to a POSA. In my opinion, the slight reduction in specificity in Lenhard to 89% clearly 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

²³ Backman Declaration (EX2044), ¶73.

²⁴ Opening Declaration (EX1002), ¶29.

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least as good as Cologuard's 86.6% specificity,²⁵ which Dr. Backman describes as "excellent."²⁶ As Dr. Backman admitted in his deposition, he does not identify any place in the art stating that a specificity of 89% for a fecal colorectal cancer test would be unacceptable.²⁷

31. Furthermore, a minor decrease in specificity would principally result in more subjects being referred for follow-up colonoscopy, which is long recognized as the gold standard for CRC screening and has been shown to be safe and effective across large studies and routine clinical practice. Thus, the trade-off is not symmetric from a clinical standpoint: missed cancers may be fatal, whereas false positives generally lead only to additional colonoscopy. In short, Lenhard teaches that the combined testing increases CRC detection while introducing only a modest number of additional false positives.

32. A POSA's willingness to sacrifice some specificity for improved sensitivity is illustrated, for example, in Exact's own Itzkowitz publication in 2007, where it describes development of a "second generation" of its fecal DNA CRC

²⁵ Imperiale (EX1077), Table 1.

²⁶ Backman Declaration (EX2044), ¶45.

²⁷ Backman Dep. Tr. (EX1089), 112:18-22.

test with improved sensitivity for CRC.²⁸ Notably, whereas Exact’s “first generation” test had a specificity of 94%, the specificity of the “second generation” test decreased to 82%.²⁹ In comparison, as noted above, the specificity of the combined test in Lenhard is 89%.³⁰ 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.

33. In his declaration, Dr. Backman relies on nominal p-values—most prominently a $p = 0.13$ for “all cancers”—to conclude that “a POSA would not consider a claim of increased sensitivity for all CRCs for the combination of HIC1 and gFOBT.”³¹ Dr. Backman’s assertion relies on a p-value he computed by treating the HIC1 and gFOBT sensitivities as if they came from two unrelated patient groups. This is not a proper statistical analysis and a POSA would not rely on it to assess whether Lenhard’s combined assay exhibits a higher sensitivity than the HIC1 and FOBT tests individually that make it up. Notably, no such statistical

²⁸ Itzkowitz (EX1006), abstract.

²⁹ *Id.*

³⁰ Backman Declaration (EX2044), ¶73.

³¹ Backman Declaration (EX2044), ¶¶67-68.

comparison is found in Lenhard itself. A POSA would readily observe that Lenhard's data demonstrate that the fecal HIC1 test and the FOBT each detect cancers that the other test missed. In view of this, a POSA would recognize that the CRC sensitivity of the combined test must be higher than that of each individual test alone, as Dr. Backman admitted himself at his deposition.³²

34. The flaw in Dr. Backman's statistical analysis is exhibited by the fact that, based on this analysis, Dr. Backman arrived at the objectively incorrect conclusion that "it is possible that the real sensitivity of HIC1 with gFOBT could be lower than HIC1 alone."³³ As discussed above, and as Dr. Backman later admitted in his deposition, Lenhard's combined test **necessarily** had a higher sensitivity than either test alone because each individual test detected incidents of CRC that the other test missed.³⁴ This is consistent with the express teaching of Lenhard itself that "[t]he combination of both assays resulted in increased detection rates for CRCs."³⁵

³² Backman Dep. Tr. (EX1089) 90:2-11, 91:8-14.

³³ Backman Declaration (EX2044), ¶66.

³⁴ Backman Dep. Tr. (EX1089) 90:2-11, 91:8-14.

³⁵ Lenhard (EX1004), p. 147 (emphasis added).

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35. In short, the absence of a reported p-value in Lenhard's comparison of the combined test with each test individually is not evidence against the desirability of combining HIC1 with gFOBT; it simply reflects that a POSA would not rely on Dr. Backman's flawed statistical analysis when making such an assessment. In considering Lenhard's results, scientists and clinicians would look first at effect size and biological plausibility, not at significance thresholds. In Lenhard, the effect is substantial: the combined assay exhibited a 21-percentage point increase in CRC sensitivity while sacrificing only a modest increment of specificity, and this is the teaching of the Lenhard reference.

36. Lenhard reveals a biologically sensible combination that improves cancer detection and motivates, rather than dissuades, continued development. FOBT interrogates the phenotypic consequence of mucosal bleeding, whereas stool-DNA assays target tumor-derived genomic alterations. Because bleeding and tumor DNA shedding are only partially overlapping phenomena, combining them captures cancers that either modality alone may miss, as exhibited by Lenhard's results. A POSA, by the priority date, would have recognized this and would have been motivated to pursue the combined assay. In my opinion, Dr. Backman's p-value calculations carry little or no weight for a POSA evaluating Lenhard and do not undermine the study's stated conclusion that the combined assay improves detection of CRC.

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37. In his declaration, Dr. Backman also provides calculated values for “expected area under the receiver operating characteristic (ROC) curve (AUC)” for the combined HIC1 with gFOBT of Lenhard. It is not clear how Dr. Backman calculates these values. Furthermore, any calculation of an AUC from a single pair of sensitivity and specificity values, which was all the Lenhard study provided, 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 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 and perhaps misleading.

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38. 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, as discussed above, 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.³⁶ 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 4.³⁷

39. 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

³⁶ Itzkowitz (EX1006).

³⁷ Vilkin (EX1005), Figure 4.

CRC detection).³⁸ 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.³⁹ When this method is used to approximate AUC values from the Lenhard data, ***the result is a 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.

40. A more straightforward mathematical method that does not require making estimates and 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.

³⁸ Backman Declaration (EX2044), ¶73.

³⁹ 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>.

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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 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 provides further motivation to use the combined test.

41. 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. As discussed above, 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, as does Dr. Backman, 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.

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42. 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.⁴⁰ 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%.⁴¹ At his deposition Dr. Backman admitted that combining two methylation markers such as HIC1 and SFRP2 would not increase sensitivity without negatively affecting specificity, and he could not identify any citation or example where combining methylation markers increases sensitivity without decreasing specificity.⁴²

43. As discussed above, 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 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

⁴⁰ Backman Declaration (EX2044), ¶77.

⁴¹ Lenhard (EX1004), p. 143.

⁴² Backman Dep. Tr. (EX1089), 125:12-18; 132:6-24; 133:1-14.

other is due to 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 confirm that they are.⁴³

44. 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.

45. 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 HIC1.⁴⁴ Thus,

⁴³ Lenhard (EX1004), Table 1.

⁴⁴ Opening Declaration (EX1002), ¶¶64, 233-235.

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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.

46. 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.”⁴⁵ Lenhard does not say or 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 applicable to tests that included additional DNA biomarkers in combination with HIC1.⁴⁶

⁴⁵ Backman Declaration (EX2044), ¶78.

⁴⁶ Opening Declaration (EX1002), ¶¶64, 233-235.

2. Vilkin

47. In his Declaration, Dr. Backman mischaracterizes Vilkin as “requiring” three consecutive daily samples and “requiring” storage of those samples in a patient’s refrigerator.⁴⁷ 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 as well as individual 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.”⁴⁸

48. 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.**”⁴⁹ At his deposition in the IPR proceeding IPR2024-00459 (“the ’459 IPR”), which concerned the validity of the ’746 patent’s parent, Dr. Backman admitted that Vilkin does **not** require collection of

⁴⁷ Backman Declaration (EX2044), ¶¶82, 87.

⁴⁸ Vilkin (EX1005), p. 2519

⁴⁹ *Id.* p. 2524 (emphasis added).

three consecutive daily samples when its assay is used in clinical practice.⁵⁰

Indeed, by the Priority Date, it was recognized in the art that collection of only a single sample was sufficient for many iFOBT tests, including the OC-Sensor test used in Vilkin. For example, Van Rossum, a 2008 research article, explains that “[t]he OC-Sensor test consisted of **a single sampling tube** and written instructions. The sampling tube, filled with stabilizing buffer, had an integrated fecal probe.”⁵¹

49. 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.”⁵² As noted by Dr. Backman, Vilkin discusses 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.”⁵³ ⁵⁴ **None** of the countries discussed in Vilkin tested samples collected on three consecutive days.

⁵⁰ Backman Dep. Tr. of IPR2024-00459 (EX1088), 141:4-142 :19.

⁵¹ Van Rossum (EX1090), p. 83.

⁵² Vilkin (EX1005), p. 2524.

⁵³ *Id.*

⁵⁴ Backman Declaration (EX2044), ¶85.

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50. 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 patient using the Vilkin iFOBT device in clinical practice can ship the stool sample back to the diagnostic laboratory immediately after collection, without refrigeration.⁵⁵ For example, in Van Rossum “[p]articipants were instructed to return the test as soon as possible” and only “[i]f the test could not be returned immediately, storage in a refrigerator was advised.”⁵⁶ Indeed, it is my opinion that the data presented in Vilkin indicate 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.

⁵⁵ Vilkin (EX1005), p. 2520.

⁵⁶ Van Rossum (EX1090), p. 83.

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51. 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).⁵⁷ 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 Dr. Backman's assertion that refrigeration alone is an example of storage that would prevent decay.⁵⁸ To put Dr. Backman's assertions in the context of the patent, the claims of the '746 patent notably do not require, or exclude, refrigeration; the claims only exclude freezing. At no point were samples frozen in the Vilkin study.

⁵⁷ Vilkin (EX1005), Abstract

⁵⁸ Backman Declaration (EX2044), ¶83.

3. Itzkowitz

52. 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.”⁵⁹ 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.

53. As noted by Dr. Backman, Itzkowitz discusses “the need for ‘availability of 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.”⁶⁰ In his declaration, Dr. Backman notes a passing reference in Itzkowitz to a study regarding patient preference in CRC testing that was reported in a publication by Schroy *et al* (EX2036), but he does not discuss the underlying reference in detail.⁶¹

54. In the Schroy study, patients were surveyed who had experienced three types of testing: DNA testing, gFOBT, and colonoscopy—but not iFOBT. In particular, Schroy asked patients to (1) submit a stool sample in a “plastic bucket-

⁵⁹ *Id.*, ¶95.

⁶⁰ *Id.*, ¶90.

⁶¹ *Id.*

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.⁶² Thus, Schroy’s survey was based on a particular protocol for a gFOBT test that was especially 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 importantly no test was selected by a majority of the patients. Schroy also shows that ***a substantial fraction of patients still preferred the six-smear gFOBT test (32%), and some preferred colonoscopy (preferred by 15%).***⁶³

55. 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***

⁶² Schroy (EX2036), pp. 208-209

⁶³ *Id.*, Abstract.

*most patients rated both tests comparably with respect to most prep- and test-related features is not unexpected.*⁶⁴

56. 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 relating to the '459 IPR, even under the testing procedures applied in Schroy, there were significant numbers of patients who preferred each.⁶⁵

4. Kanaoka

57. Dr. Backman asserts that since Kanaoka's data show that sensitivity and specificity for colon cancer of COX-2 RNA alone are 90% and 100%, respectively", and then states, "[a]lthough the sensitivity of the combined test is slightly higher, the specificity is considerably lower."⁶⁶ As with Lenhard, Dr. Backman again calculates "expected" AUC estimates for the individual RNA test and the combined test together with what he presents as an associated p-value without stating how these values are calculated and then, based on these "expected" AUC calculations, opines that "a POSA would conclude that the COX-

⁶⁴ *Id.*, pp 211-212 (emphasis added).

⁶⁵ Backman Dep. Tr. of IPR2024-00459 (EX1088), 160:16-162:2.

⁶⁶ Backman Declaration (EX2044), ¶102.

2 should **not** be combined with FOBT.⁶⁷ Notably, none of these estimates are found in the reference itself.

58. 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.⁶⁸ 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.⁶⁹ Dr. Backman further asserts that “the Kanaoka patent application does not conclude that COX-2 should be combined with FOBT.”⁷⁰ 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

⁶⁷ *Id.*

⁶⁸ 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.

⁶⁹ Opening Declaration (EX1002), ¶¶131, 133.

⁷⁰ Backman Declaration (EX2044), ¶104.

“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.⁷¹ Far from indicating “no synergy” and “drop in performance with a combination of COX-2 RNA and FOBT tests” as Dr. Backman contends,⁷² these complementary findings demonstrate to the potential for a combined testing approach to improve overall detection rates by reducing false negative results.

59. Dr. Backman also asserts that “Kanaoka does not describe any method of preserving RNA in the fecal samples other than freezing.”⁷³ I disagree with Dr. Backman’s assertion. Although Example 1 of Kanaoka, as Dr. Backman notes,⁷⁴ describes that “feces were separated into 5 ml tubes about 1 g each, were frozen using liquid nitrogen, and were stored at –80° C”, Kanaoka also states that “[h]ere, said collected biological sample is *preferably* frozen.”⁷⁵ Kanaoka’s use of the

⁷¹ Opening Declaration (EX1002), ¶133.

⁷² Backman Declaration (EX2044), ¶105.

⁷³ *Id.*, ¶99.

⁷⁴ *Id.*

⁷⁵ Kanaoka (EX1007), ¶[0018], emphasis added.

word “preferably” signals that freezing is recommended for convenience and ***not required***.

60. A POSA reading Kanaoka by the Priority Date would understand that the key objective is to keep endogenous RNases from degrading the target transcript. One way to achieve that is to aliquot the sample on ice and snap-freeze it, as Kanaoka illustrates. As of the Priority Date, a known alternative to freezing a sample using liquid nitrogen would be to stabilize the fecal RNA with a buffer, such as the then-commercially available RNAlater buffer.⁷⁶ Indeed, Kanaoka describes “a means to homogenize the collected biological sample in the presence of an RNase inhibitor, to prepare a suspension thereof”.⁷⁷ A POSA would recognize that Kanaoka also contemplated strategies other than snap freezing for preserving a fecal sample.

⁷⁶ Ambion TechNotes (EX2048) (“No need to freeze sample in liquid nitrogen.”); Backman Dep. Tr. (EX1089) 42:6-11 (“There were buffers that would preserve RNA [in 2009].”).

⁷⁷ Kanaoka (EX1007) ¶[0028]

5. Shuber

61. Dr. Bachman asserts that “Shuber does not specifically mention home collection by a patient.”⁷⁸ 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 solution or to which a stabilization solution may be added.”⁷⁹ The sample can be “freshly isolated.”⁸⁰ In some instances, samples were “shipped to EXACT Sciences,” indicating at least that samples were collected at a site remote from a testing facility.⁸¹ 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.”⁸² 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

⁷⁸ Backman Declaration (EX2044), ¶110.

⁷⁹ *Id.*

⁸⁰ Shuber (EX1008), 9:1-3.

⁸¹ *Id.*, 14:27-28.

⁸² *Id.*, 10:12-15.

medical center. In addition, nothing in Shuber is inconsistent with 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.

6. Inbar

62. In his Declaration, Dr. Bachman contends that “[n]othing in Inbar specifies the location of the toilet at which the sample is collected before being transported to the laboratory for testing,” and that “Inbar neither describes nor suggests that the sample collection ‘would’ occur at a subject’s home”.⁸³ As I explain in my Opening Declaration, a POSA reading Inbar would understand that the user would load stool onto a sampling probe, seal the probe in a respective container filled with preservation medium, and then ship the sealed container to a laboratory.⁸⁴ That workflow could apply equally to a bathroom in a clinic and a bathroom in a private residence—the critical point overlooked by Dr. Backman is that the analytical lab is elsewhere and transit time could degrade the sample. It is further my opinion that by disclosing sealed containers, tailored preservation media, and shipment, Inbar expressly addresses the challenges of off-site collection

⁸³ Backman Declaration (EX2044), ¶113.

⁸⁴ Opening Declaration (EX1002), ¶139.

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without needing to stipulate whether the toilet is in a home or a medical facility; it therefore encompasses both scenarios. Nothing in Inbar 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.⁸⁵

63. Dr. Backman asserts that Inbar “does not otherwise discuss testing for, or preservation of, blood in stool samples,” and “does not disclose a ‘solution that prevents denaturation or degradation of blood protein’ in a fecal sample.”⁸⁶ To the contrary, the background of Inbar specifically discusses the importance of “detection of microorganism being bacteria or parasites, ***detection of cryptic blood***, preparation of a biochemical profile, etc.” as “an essential component of modern medicine, health care and environmental management.”⁸⁷ Inbar further discusses that “if the entity is a chemical substance, the medium... ensure[s] that the substance is preserved in a manner to avoid its deterioration.”⁸⁸ A POSA reading

⁸⁵ See, e.g., Vilkin (EX005); Itzkowitz (EX1006); Melvin (EX010), p. 56; Olson (EX1022).

⁸⁶ Backman Declaration (EX2044), ¶¶114-115.

⁸⁷ Inbar (EX1009), 1: 7-12, emphasis added

⁸⁸ *Id.*, 4:4-8.

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Inbar would understand that detection of cryptic blood in the stool would typically involve detection of hemoglobin, and that hemoglobin would therefore be a “chemical substance” that would be preserved using a buffer in Inbar’s system. Therefore, a POSA would immediately recognize how to apply Inbar’s instructions to prevent hemoglobin degradation during shipment.

64. Dr. Backman misreads Inbar to assert that “Inbar teaches separating the sample only when the analytes to be assayed require the different media for preservation.”⁸⁹ Dr. Backman’s interpretation of Inbar’s stool separation approach is too narrow. Inbar involves a sample collection system “compris[ing] two attached containers,” where the containers “hold respective media...which *may both be the same, but are typically different.*”⁹⁰ A POSA reading Inbar would understand dual-container sampling is recommended whenever more than one assay is planned—whether or not the preservatives must differ.⁹¹ Thus, a POSA reading Inbar would not draw a general conclusion that stool should be divided only when the intended assays require different preservatives.

⁸⁹ Backman Declaration (EX2044), ¶116.

⁹⁰ Inbar (EX1009), 8:1-25, emphasis added.

⁹¹ *Id.*, 2:12-30.

B. As of the Priority Date, at Home Sample Separation was Routine

65. I have reviewed Dr. Backman's opinions concerning home sample separation and the use of different stabilization buffers. I disagree with Dr. Backman's assertion 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."⁹²

66. 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).⁹³ 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

⁹² Backman Declaration (EX2044), ¶119.

⁹³ Opening Declaration (EX1002), ¶165.

containers to a diagnostic laboratory for analysis of DNA methylation and FOBT, which Lenhard and other contemporaneous references teach provides improved assay sensitivity compared to either test alone.⁹⁴ Thus as I explain in my Opening Declaration, the straightforward performance of known DNA and FIT tests according to their established protocols would naturally result in at-home fecal separation.

67. Dr. Backman's assumption that a requirement for separate buffers to stabilize nucleic acids and proteins would be a prerequisite for a POSA designing an assay that requires at-home sample separation is incorrect. For example, by the Priority Date at-home sample separation was a standard feature of FIT tests like the one disclosed in Vilkin, which required a patient to separate a small portion of the fecal portion that was to be shipped to the diagnostic laboratory for testing from the rest of the specimen, which was discarded.⁹⁵ This at-home fecal sample separation step occurs with FIT tests even though only one stabilizing buffer is required for such assays. Indeed, at his deposition, Dr. Backman acknowledged that the fecal sample in Vilkin—which only describes iFOBT testing—requires at

⁹⁴ *Id.*

⁹⁵ *See, e.g.,* Vilkin (EX1005); Young (EX1021); Guittet (EX1021).

home collection and subsequent separation of the fecal sample by the patient.⁹⁶

Separation of a small portion of a fecal sample for shipment and automated testing was a standard step of the workflows of commercial FIT assays as of the Priority Date that would be expected to be maintained in combined assays in which the remaining portion was tested for nucleic acid instead of being discarded.

68. Furthermore, I disagree with Dr. Backman's assertion that a POSA in 2009 would not use separate buffers to stabilize fecal DNA and fecal blood proteins when performing a combined assay that tests for both biomarker types. Dr. Backman's analysis disregards that stabilizing buffers used in diagnostic tests are optimized for the type of biomarker being tested for, as Dr. Backman later acknowledged in his deposition.⁹⁷ Indeed, using such an optimized buffer is critical to the reliability of at-home fecal diagnostic tests. As I explained in my Opening Declaration,⁹⁸ at Exact, my team and I put significant work into optimizing a DNA-stabilizing buffer.⁹⁹ A POSA would understand that a buffer optimized for one biomarker type (*e.g.* DNA) is unlikely to be optimized for another biomarker

⁹⁶ Backman Dep. Tr. (EX1089), 135:13-20.

⁹⁷ Backman Dep. Tr. 65:23-66:14.

⁹⁸ Opening Declaration (EX1002), ¶78.

⁹⁹ Olson (EX1022).

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type (*e.g.* protein). Indeed, at his deposition, Dr. Backman acknowledged that the development of a diagnostic test would require a POSA to optimize buffers and that a POSA would preferably rely on a buffer already proven to preserve the analyte of choice.¹⁰⁰ 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.¹⁰¹ For example, whereas certain buffers were optimized to prevent degradation of DNA,¹⁰² others were optimized to stabilize proteins.¹⁰³ 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 my belief is that there was none. Notably, Dr. Backman does not identify any examples of such optimized buffers in his declaration.

69. In his Declaration, Dr. Backman, contends that by the Priority Date a POSA “would have expected that a Tris/EDTA buffer, such as those described in Olson and Shuber, would prevent denaturation or degradation of blood protein in

¹⁰⁰ Backman Dep. Tr. (EX1089), 65:23-66:14, 68:17-69:15, 69:22-70:2.

¹⁰¹ Opening Declaration (EX1002), ¶¶74-82.

¹⁰² Olson (EX1022), p. 183; Shuber (EX1008), 10:10-15; Itzkowitz (EX1006), pp. 111-112.

¹⁰³ Vilkin (EX1005), pp. 2520-2521; Karl (EX1045), p. 1127; Hirata (EX1070), p. 1573.

stool.”¹⁰⁴ It is telling that the only support Dr. Backman cites for this contention is Tsuji (EX2049), a 1991 Japanese patent application that only lists Tris and EDTA in separate laundry lists of potential buffer ingredients¹⁰⁵ and that Dr. Backman admitted at his deposition does not actually test the ability of a Tris/EDTA buffer for the preservation of fecal blood proteins.¹⁰⁶ Dr. Backman does not provide a single reference demonstrating that any Tris/EDTA buffers stabilized fecal hemoglobin, let alone the specific Tris/EDTA buffers disclosed in Olson and Shuber.

70. I disagree with Dr. Backman’s contentions. As I explained above, I am unaware of any buffer known as of the Priority Date, that had been tested for stabilization of both fecal nucleic acids and fecal blood proteins, let alone one that had been optimized for stabilization of both biomarker types. Tellingly, Dr. Backman does not identify any buffer that had been tested for stabilization of both fecal DNA and fecal hemoglobin and, at his deposition, Dr. Backman admitted that

¹⁰⁴ Backman Declaration (EX2044), ¶¶119, 122.

¹⁰⁵ Tsuji (EX2049), ¶¶10, 11.

¹⁰⁶ *Id.*, ¶¶122-123; Backman Dep. Tr. (EX1089), 140:17-142:13, 147:8-16, 149:4-6; 161 4:8.

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he could not identify a buffer that has been experimentally shown to stabilize both biomarker types.¹⁰⁷

71. Dr. Backman's attempt to rely on the 1991 Japanese application by Tsuji to demonstrate that TRIS/EDTA-based buffers similar to those used in Itzkowitz and Shuber also stabilize fecal blood proteins is also unavailing. As Dr. Backman acknowledged at his deposition, Tsuji only lists TRIS/EDTA in a laundry list of possible buffer components and did not test any TRIS/EDTA based buffers for stabilization of fecal blood proteins.¹⁰⁸ At his deposition, Dr. Backman further admitted that he did not independently search for or identify any reference showing Tris-EDTA would preserve fecal hemoglobin, despite Tsuji not being peer-reviewed and despite Dr. Backman's not being familiar with the Tsuji inventors or their reputations.¹⁰⁹

72. Dr. Backman also mentions RNAlater as a commercial product that can stabilize both RNA and proteins.¹¹⁰ However, RNAlater is designed to

¹⁰⁷ Backman Dep. Tr. (EX1089), 140:17-142:13, 147:8-16, 149:4-6.

¹⁰⁸ *Id.*, 147:8-16, 148:6-23, 149:4-6.

¹⁰⁹ *Id.*, 155:17-23; 158:14-24; 159:1-16.

¹¹⁰ Backman Declaration (EX2044), ¶124.

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“stabilize both RNA and protein *within tissues or cells*.”¹¹¹ Notably, whereas cells shed into feces contain RNA that can be used as a biomarker,¹¹² Dr. Backman acknowledges that fecal hemoglobin is extracellular (i.e., not found within cells).¹¹³ Dr. Backman was aware of no evidence that RNA later would effectively stabilize hemoglobin in feces.¹¹⁴

73. At his deposition, Dr. Backman acknowledged that developing a diagnostic test requires buffer optimization and that “a person of skill in the art would preferably use a buffer that had been proven to work for the preservation of their analyte of choice.”¹¹⁵ For example, Dr. Backman agreed that “a person of skill in the art who was testing for DNA would use a buffer that had been proven to stabilize fecal DNA” and “if one of skill in the art were testing hemoglobin in a stool sample in their assay, that person would preferably use a buffer that had been proven to stabilize blood proteins.”¹¹⁶ Dr. Backman provides no evidence that any

¹¹¹ Ambion TechNotes (EX2048).

¹¹² Nechvatal (EX1024), pp. 124-125.

¹¹³ Backman Dep. Tr. (EX1089) 161:17-23.

¹¹⁴ *Id.*

¹¹⁵ Backman Dep. Tr. (EX1089), 68:17-21.

¹¹⁶ *Id.*, 68:22-69:4, 69:22-70:2.

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buffer optimized or proven to stabilize both fecal DNA and hemoglobin was known in the art as of the Priority Date. On the other hand, buffers optimized to separately preserve DNA or proteins were well known in the art by the Priority Date and are disclosed in Itzkowitz and Vilkin, respectively. EX1005; EX1006. Thus, a POSA would have been motivated to separate and test a stool sample into two aliquots, each immersed in a buffer optimized for the type of biomarker to be tested, rather than attempt to develop a new buffer that can optimally stabilize both biomarker types. Indeed, it is telling that, even today, Exact uses separate DNA and hemoglobin stabilizing buffers in its Cologuard test, despite the purported advantages of using a single buffer.¹¹⁷

74. 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.¹¹⁸ 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

¹¹⁷ Cologuard Patient Guide (EX1076), p. 8.

¹¹⁸ Opening Declaration (EX1002), ¶¶83-88.

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diagnostic laboratory.¹¹⁹ 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.¹²⁰ 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.

¹¹⁹ *Id.*

¹²⁰ Melvin (EX1010), 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.

10-10-10-10



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

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

75. 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.

76. I disagree with Dr. Backman's assertion that "the references on which Geneoscopy relies, either alone or in combination, would have discouraged the combination of FOBT and nucleic acid-based tests."¹²¹ 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.¹²² Thus, Lenhard alone, the primary reference in this obviousness combination, already discloses an assay combining a FOBT with DNA-based testing. As set forth in my Opening

¹²¹ Backman Declaration (EX2044), ¶161.

¹²² Opening Declaration (EX1002), ¶145.

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Declaration, a POSA would be motivated to 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.¹²³

77. 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.”¹²⁴ 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).¹²⁵ 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

¹²³ *Id.*, ¶¶149-164.

¹²⁴ Backman Declaration (EX2044), ¶159.

¹²⁵ Opening Declaration (EX1002), ¶165.

alone.¹²⁶ When the resulting obvious fecal processing methods are performed the assay meets each and every limitation of the Challenged Claims.¹²⁷

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

78. I disagree with Dr. Backman's assertion that "[a] POSA would not have been motivated to combine Lenhard with the iFOBT of Vilkin and the DNA-based testing of Itzkowitz."¹²⁸ 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 strategy for improving test performance.¹²⁹

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

¹²⁶ *Id.*

¹²⁷ *Id.*, ¶¶154-168.

¹²⁸ Backman Declaration (EX2044), ¶131.

¹²⁹ Opening Declaration (EX1002), ¶¶64, 233-236.

improvement in the critical detection of advanced adenomas”¹³⁰ 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.

80. 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.¹³¹ 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 (i.e., gFOBT, FIT, and sDNA), which are tests that primarily***

¹³⁰ Backman Declaration (EX2044), ¶131.

¹³¹ Itzkowitz (EX1006); Backman Dep. Tr. of IPR2024-00459 (EX1088), 73:15-21.

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.*¹³²

81. 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.”¹³³

82. 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 and also because both Vilkin and Itzkowitz report sensitivities higher than reported in Lenhard for the HIC1 and gFOBT combination.¹³⁴ I disagree.

83. 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 recognized strategy for improving

¹³² Levin (EX1013), pp. 1572-1573.

¹³³ Imperiale (EX1077), p. 1288.

¹³⁴ Backman Declaration (EX2044), ¶¶133-138.

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assay sensitivity that was not limited to any single DNA biomarker, including methylation of HIC1.¹³⁵ Furthermore, FOBT assays were known to offer relatively high specificity and to detect cancers via a mechanism complementary to fecal DNA biomarkers; accordingly, it would have been obvious to add an FOBT to any single DNA marker or panel of DNA markers. 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.

84. 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.¹³⁶ Likewise, Vilkin's disclosure that gFOBT like the one used in

¹³⁵ Opening Declaration (EX1002), ¶¶64, 233-235.

¹³⁶ Itzkowitz (EX1006), p. 114.

Lenhard is “faulted for its low sensitivity” would motivate a POSA to use Vilkin’s more sensitive iFOBT in its place.¹³⁷

85. Moreover, Vilkin teaches that sensitivity and specificity could be adjusted to an optimal level by relying on different thresholds for hemoglobin concentration. Vilkin 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%).¹³⁸ 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.

86. 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.”¹³⁹ 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 say

¹³⁷ Vilkin (EX1005), p. 2519.

¹³⁸ Vilkin (EX1005), Table 2, p. 2523.

¹³⁹ Backman Declaration (EX2044), ¶137.

or 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 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%***.

87. 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 in the '459 IPR, Dr. Backman conceded that Lenhard does not expressly discourage using FOBT in combination with HIC1, nor does it characterize such a combination as unpromising,¹⁴⁰ which is at odds with any suggestion that Lenhard fails to teach combining these approaches.

88. 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

¹⁴⁰ Backman Dep. Tr. of IPR2024-00459 (EX1088), 98:10-99:19, 104:20-23.

sensitivity disclosed in Lenhard would be particularly important to a POSA. As acknowledged by Exact, “[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.”¹⁴¹

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

89. 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.”¹⁴² I disagree. A POSA reading Lenhard would appreciate that the combined 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.¹⁴³ As discussed above, the primary aim of fecal CRC tests as of the priority date was detection of cancers.

¹⁴¹ Imperiale (EX1077), p. 1295.

¹⁴² Backman Declaration (EX2044), ¶145.

¹⁴³ Lenhard (EX1004), Table 4 and p. 147.

90. Dr. Backman's argument also disregards the relative importance a POSA would place on increased assay sensitivity versus specificity. Tellingly, whereas Lenhard repeatedly extolls the combined assay's increased sensitivity, it never even mentions its slightly decreased specificity. As I discussed 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.¹⁴⁴ Exact expressly acknowledges in their publication reporting 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."¹⁴⁵ 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

¹⁴⁴ Opening Declaration (EX1002), ¶63.

¹⁴⁵ Imperiale (EX1077), p. 1295.

sensitivity for detection of CRC.¹⁴⁶ Notably, whereas Exact's "first generation" test had a specificity of 94%, the specificity of the "second generation" test was only 82%.¹⁴⁷ Despite this reduction in specificity, Exact considers their second generation test to be "[a]n improved fecal DNA test that... shows much higher sensitivity for CRC."¹⁴⁸

91. 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%.¹⁴⁹ For comparison, the specificity of the "improved" second generation Itzkowitz assay was only 82%.¹⁵⁰ Indeed, as acknowledged by Dr. Backman, the specificity of Cologuard for CRC is only 86.6%.¹⁵¹ 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. As Dr. Backman admitted in

¹⁴⁶ Itzkowitz (EX1006), abstract.

¹⁴⁷ *Id.*

¹⁴⁸ *Id.*

¹⁴⁹ Backman Declaration (EX2044), ¶145.

¹⁵⁰ Itzkowitz (EX1006), Abstract.

¹⁵¹ Backman Declaration (EX2044), ¶45.

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his deposition, he does not identify any place in the art that states a specificity of 89% for a fecal colorectal cancer test would be unacceptable, nor does he offer any opinion that such specificity would have been unacceptable to a POSA.¹⁵²

92. 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%.¹⁵³ This would further motivate a POSA to replace Lenhard's gFOBT with Vilkin's more specific iFOBT in order to increase the specificity of the combined assay.¹⁵⁴ Vilkin explains that gFOBT are faulted for "low specificity due to nonspecificity for human hemoglobin (Hb)," whereas its iFOBT is "human Hb specific."¹⁵⁵

93. 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.

¹⁵² Backman Dep. Tr. (EX1089), 112:18-22.

¹⁵³ Lenhard (EX1004), p. 147.

¹⁵⁴ Vilkin (EX1005), p. 2523.

¹⁵⁵ *Id.*, p. 2519.

3. Vilkin Does Not Require Multiple Samples or Home Refrigeration

94. 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.”¹⁵⁶ I disagree. A POSA would recognize that, in clinical use, Vilkin’s assay requires neither multiple sample collection nor at-home refrigeration.

95. 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 will also *involve an evaluation of cost-benefit*.”¹⁵⁷ 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.”¹⁵⁸ 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]

¹⁵⁶ Backman Declaration (EX2044), ¶151.

¹⁵⁷ Vilkin (EX1005), p. 2524 (emphasis added).

¹⁵⁸ *Id.*, p. 2524 (emphasis added).

sample...in Italy.”¹⁵⁹ **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 in the ’459 IPR, Dr. Backman admitted that Vilkin does **not** require collection of three consecutive daily samples when its assay is used in clinical practice.¹⁶⁰ I further note that none of the claims of the ’746 patent require any particular testing frequency.

96. Indeed, by the Priority Date, it was recognized in the art that collection of only a single sample was sufficient for many iFOBT tests, including the OC-Sensor test used in Vilkin. For example, Van Rossum, a 2008 research article, explains that “[t]he OC-Sensor test consisted of a single sampling tube and written instructions. The sampling tube, filled with stabilizing buffer, had an integrated fecal probe.”¹⁶¹

97. A POSA would also understand that, in clinical practice, a patient would not be required to refrigerate (let alone freeze) stool samples at home when using the iFOBT of Vilkin. As discussed above, in clinical practice, the Vilkin

¹⁵⁹ *Id.*

¹⁶⁰ Backman Dep. Tr. of IPR2024-00459 (EX1088), 141:4-142 :19.

¹⁶¹ Van Rossum (EX1090), p. 83.

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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.¹⁶² For example, in Van Rossum “[p]articipants were instructed to return the test as soon as possible” and only “[i]f the test could not be returned immediately, storage in a refrigerator was advised.”¹⁶³ 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 ’746 patent do not preclude sample refrigeration.

98. 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

¹⁶² Vilkin (EX1005), p. 2524.

¹⁶³ Van Rossum (EX1090), p. 83.

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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 diet restrictions associated with gFOBT, and (3) is quantitative, which allows a physician to choose the optimal fecal Hb threshold level for a patient.¹⁶⁴ Notably, iFOBT also delivers higher specificity by avoiding false positives from non-human hemoglobin and other dietary interferents that affect gFOBT, reinforcing the motivation to replace the gFOBT in Lenhard. In addition, iFOBT collection typically requires fewer samples than gFOBT, improving convenience and compliance which serves as an additional practical advantage motivating this substitution. Thus, a POSA would recognize Vilkin's iFOBT as a superior alternative to the gFOBT used in Lenhard. Indeed, in his deposition in the '459 IPR, 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.¹⁶⁵

99. 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

¹⁶⁴ Vilkin (EX1005), pp. 2519, 2524.

¹⁶⁵ Backman Dep. Tr. of IPR2024-00459 (EX1088), 120:9-123:5.

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.¹⁶⁶

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

100. Dr. Backman further opines that a POSA would have been dissuaded to combine multiple classes of markers due to increased complexity and cost.¹⁶⁷ I disagree.

101. 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.

102. 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

¹⁶⁶ Opening Declaration (EX1002), ¶¶149-153.

¹⁶⁷ Backman Declaration (EX2044), ¶¶152-159.

the sample collection process used with iFOBT, like the one in Vilkin, was 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.”¹⁶⁸ 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.”¹⁶⁹ 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.

103. 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. Certainly, the authors of Kutzner were aware of the marginal (at most) added cost and complexity associated with combining a fecal DNA test with an FOBT, but still recommendation that “***MD and FOBT***

¹⁶⁸ Young (EX1020), p. 29.

¹⁶⁹ Levin (EX1013), p. 1576.

should complement rather than replace each other.¹⁷⁰ As another 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.”¹⁷¹ 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 FIT at the time of testing would improve sensitivity without adversely affecting specificity.”¹⁷² Dr. Backman admitted at his deposition that “there are many examples” in which “in order to improved diagnostic performance you would sacrifice some other attributes, for example, how easy it is to implement or its cost.”¹⁷³

104. In fact, it is unlikely that adding a FIT test with a fecal DNA test would increase the overall cost of an assay more than adding additional fecal DNA markers. At the time of the priority date, iFOBT tests were much less expensive than fecal DNA tests. Young explains that FIT tests cost “up to USD 30”, whereas

¹⁷⁰ Kutzner (EX1012), p. 40.

¹⁷¹ Levin (EX1013), p. 1578.

¹⁷² *Id.*

¹⁷³ Backman Dep. Tr. (EX1089) 60:10-15.

fecal DNA tests cost “in excess of USD 400.”¹⁷⁴ It is typically more expensive to develop and then implement entirely new DNA biomarkers into an assay than to incorporate an existing DNA biomarker with an off-the-shelf FIT.

105. 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.

D. Shuber And Vilkin Render the Challenged Claims Obvious

106. 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 shown below.

¹⁷⁴ Young (EX1020), p. 31.

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

107. 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 there is a first portion and a second portion, both in sealable containers, to be tested for two different classes of markers as required by the claims"¹⁷⁵ fails because it considers the references individually, rather than in combination, and disregards the knowledge in the art that a POSA would possess.

108. 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.¹⁷⁶ 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.¹⁷⁷ 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

¹⁷⁵ Backman Declaration (EX2044), ¶166.

¹⁷⁶ Opening Declaration (EX1002), ¶181.

¹⁷⁷ *Id.*, ¶231.

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and blood protein assays were well understood in the art.¹⁷⁸ As is also explained in my Opening Declaration,¹⁷⁹ when the combined test was performed, a patient would: (1) directly defecate into a sealable container at home (as in Shuber); (2) use a fecal test sampling device to remove a portion of the sample and combine it with hemoglobin stabilizing buffer (as in Vilkin); (3) add the DNA stabilizing buffer of Shuber to the remaining sample before sealing the container (as in Shuber); and (4) ship the sealed sampling device and sealed container to a diagnostic laboratory for testing (as in Vilkin and Shuber, respectively). A POSA would recognize that separation 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.¹⁸⁰ At his deposition, Dr. Backman also acknowledged that the fecal sample in Vilkin requires at home separation by the patient prior to shipping one of the portions to a diagnostic laboratory for testing.¹⁸¹ A POSA would also recognize that it is more convenient for the patient

¹⁷⁸ *Id.*, ¶¶232-236.

¹⁷⁹ *Id.*, ¶237.

¹⁸⁰ Vilkin (EX1005), p. 2520; Shuber (EX1008), 29:8-19.

¹⁸¹ Backman Dep. Tr. (EX1089), 135:13-20.

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.¹⁸²

109. 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.

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

110. 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.”¹⁸³ 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

¹⁸² Opening Declaration (EX1002), ¶¶239-262.

¹⁸³ Backman Declaration (EX2044), ¶167.

sensitivity that had been experimentally demonstrated in fecal samples.¹⁸⁴ 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.¹⁸⁵ Thus, combining detection of fecal DNA biomarkers with fecal blood protein biomarkers was a known strategy for increasing assay sensitivity.

111. 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 '746 patent."¹⁸⁶ However, it is indisputable that Nishikawa's disclosure reflects a longstanding recognition in the art that combining fecal DNA tests with FOBT was a recognized strategy for improved CRC screening by the priority date.

¹⁸⁴ Opening Declaration (EX1002), ¶¶62-66, 232-236.

¹⁸⁵ See, e.g., Lenhard (EX1004), Kutzner (EX1012).

¹⁸⁶ Backman Declaration (EX2044), ¶168, emphasis added.

112. 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"¹⁸⁷ is particularly confounding. Dr. Backman's opinion 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."¹⁸⁸ 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 baffling. 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.**"¹⁸⁹ 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.

¹⁸⁷ *Id.*, ¶169.

¹⁸⁸ Lenhard (EX1004), p. 147.

¹⁸⁹ Kutzner (EX1012), Abstract.

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 suggest that MD and FOBT should complement rather than replace each other.***¹⁹⁰

113. Dr. Backman attempts to disregard these explicit teachings of Kutzner because Kutzner “poses the question of ‘whether both [MD and gFOBT] methods should be used together in broad diagnostic screening programs.’”¹⁹¹ 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.***”¹⁹² Kutzner therefore further supports that combining detection of fecal DNA biomarkers with fecal blood protein biomarkers was a known strategy for increasing assay sensitivity.

¹⁹⁰ *Id.*, p. 40.

¹⁹¹ Backman Declaration (EX2044), ¶170.

¹⁹² Kutzner (EX1012), p. 40.

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114. Dr. Backman also selectively interprets Levin as “pos[ing] a question for potential investigation.”¹⁹³ Levin directly proposes investigating “whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity [of DNA-based assays] without adversely affecting specificity.”¹⁹⁴ 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).”¹⁹⁵ 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.

115. Dr. Backman further asserts that Kanaoka “would have discouraged, not encouraged, a combination,” and supports this assertion by pointing out that

¹⁹³ Backman Declaration (EX2044), ¶171.

¹⁹⁴ Levin (EX1013), p. 1578.

¹⁹⁵ *Id.*, p. 1578 (emphasis added).

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%)."¹⁹⁶ These data would not discourage further exploration of a multi-marker approach, especially when they show increased CRC detection when the assays are combined.

116. 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.¹⁹⁷ 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 to Achieve Greater Sensitivity

117. Dr. Backman reiterates the same arguments concerning complexity and cost with respect to the Shuber and Vilkin combination that he made with

¹⁹⁶ Backman Declaration (EX2044), ¶173.

¹⁹⁷ Shuber (EX1008), 14:1-16.

respect to the Lenhard, Vilkin and Itzkowitz combination.¹⁹⁸ As discussed above in section V(C)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 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

118. 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.¹⁹⁹ As discussed above in section V(A)2 and V(C)4, Dr. Backman's opinion is based on a misreading of Vilkin, and a POSA would recognize that clinical use of Vilkin's assay requires neither multiple sample collection nor at-home refrigeration. At his deposition in the '459 IPR, Dr. Backman admitted that Vilkin does **not** require collection of three consecutive daily samples when its assay is used in clinical practice.²⁰⁰ Such issues would therefore not dissuade a

¹⁹⁸ Backman Declaration (EX2044), ¶175.

¹⁹⁹ *Id.*, ¶177.

²⁰⁰ Backman Dep. Tr. of IPR2024-00459 (EX1088), 141:4-142 :19.

POSA from combining the DNA test of Shuber with the FIT of Vilkin, as Dr. Backman claims.

E. Inbar, Shuber, And Vilkin Render the Challenged Claims Obvious

119. Dr. Backman reiterates the same arguments regarding sample separation with the Inbar, Shuber and Vilkin combination that he made within the context of the Lenhard, Vilkin and Itzkowitz combination.²⁰¹ Again, I disagree with Dr. Backman's opinion. As discussed above in sections V(A6), and V(B), 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 the stool separation approach of Inbar when combining the fecal DNA test of Shuber with the FIT of Vilkin.

F. Kanaoka, in combination with the Lenhard, Vilkin and Itzkowitz, Shuber and Vilkin, or Inbar Shuber and Vilkin Renders Dependent Claims 12 and 13 Obvious

120. Dr. Backman once again considers the references individually rather than in combination to argue that "a POSA in 2009 would not have been motivated to incorporate the COX-2 RNA testing of Kanaoka – which requires freezing – in a method of processing a freshly collected fecal sample that excludes freezing."²⁰²

²⁰¹ Backman Declaration (EX2044), ¶¶177-178.

²⁰² *Id.*, ¶181.

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121. I disagree. As explained in my Opening Declaration, when the cited references are considered collectively in the context of the state of the art as of the Priority Date, a POSA would be motivated to modify the fecal processing method rendered obvious by Lenhard, Vilkin, and Itzkowitz, Shuber and Vilkin, and/or Inbar, Shuber and Vilkin to incorporate the COX-2 RNA detection process disclosed in Kanaoka.²⁰³ In particular, COX-2 RNA would have been attractive to a POSA because Kanaoka discloses its it is a high sensitive and specific biomarker and also that COX-2 was effectively combined with iFOBT in a complementary way, with each test detecting incidents of CRC that the other one missed.²⁰⁴ As Dr. Backman acknowledged in his deposition “when one test misses one cancer and another misses the other, the sensitivity [of the combined test] would be and can only be higher.”²⁰⁵

122. The fact that Kanaoka included examples in which it froze fecal samples using liquid nitrogen would not have discouraged such a combination. In particular, both Itzkowitz and Shuber teach that use of a nucleic acid stabilizing buffer to preserve fecal samples was a known alternative to freezing that facilitated

²⁰³ Opening Declaration, ¶¶221-222, 273-274, 330.

²⁰⁴ *Id.*

²⁰⁵ Backman Dep. Tr. (EX1089) 90:2-11.

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convenient at-home sample collection.²⁰⁶ As Dr. Backman acknowledged in his deposition, as of the Priority Date, similar buffers suitable for RNA stabilization were known in the art.²⁰⁷ As I explained in my Opening Declaration, by the Priority Date it had been reported in a publication by Nechvatal et al. that “preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible.”²⁰⁸ Indeed, as acknowledged by Dr. Backman, buffers for stabilizing RNA, such as the RNeasy buffer used in Nechvatal, were known in the art and commercially available.²⁰⁹ Indeed, the commercial RNeasy buffer was explicitly marketed as an alternative to using liquid nitrogen to freeze samples, with its marketing materials explicitly extolling that there was “[n]o need to freeze sample in liquid nitrogen.”²¹⁰

123. Dr. Backman’s argument that “[a] POSA in 2009 also would not have had any expectation that they could successfully incorporate the RNA analysis of Kanaoka into an at-home collection methodology that expressly excludes

²⁰⁶ Itzkowitz (EX1006); Shuber (EX1008).

²⁰⁷ Backman Dep. Tr. (EX1089) 42:6-11.

²⁰⁸ Nechvatal (EX1024) p. 131.

²⁰⁹ Backman Dep. Tr. 42:6-11; Ambion TechNotes (EX2048).

²¹⁰ Ambion TechNotes (EX2048).

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freezing”²¹¹ also ignores that, by the Priority Date, use of RNA stabilizing buffers such as RNAlater were a known commercially available alternative to sample freezing readily available in the art.²¹² Indeed, Nechvatal’s statement that “preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible” is an express teaching that a POSA would have reasonably expected to be successful in using a buffer to stabilize fecal RNA by the Priority Date.²¹³ Dr. Backman further acknowledged at his deposition that he is aware of no data that would indicate that Nechvatal’s statements are inaccurate, and he offers no contrary data showing that fecal RNA cannot be preserved at room temperature in a medium suitable for DNA and RNA analysis.²¹⁴ Dr Backman also acknowledged at his deposition that RNAlater—which is used by Nechvatal—was a commercially available reagent for preserving RNA without freezing.²¹⁵

²¹¹ Backman Declaration (EX2044), ¶185.

²¹² Backman Dep. Tr. (EX1089) 42:6-11; Ambion TechNotes (EX2048).

²¹³ Nechvatal (EX1024), p. 131.

²¹⁴ *Id.*, 166: 24-167:14.

²¹⁵ *Id.*, 161: 9-16.

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124. I also note that the '746 patent does not disclose any buffers to preserve RNA and, at his deposition, Dr. Backman admitted that in order to practice claim 12 of the '746 patent, a POSA would use buffers already known in the art.²¹⁶

125. Dr. Backman also offers the unsubstantiated opinion that “a POSA relying on Nechvatal would have had no reason to separate the sample into two containers with buffers in each container,” alleging that RNAlater could be used to preserve both fecal RNA and hemoglobin.²¹⁷ As explained in section V(B), Dr. Backman’s argument once again ignores that at-home fecal separation was a standard part of the workflow used with FIT assays, even when no second stabilizing buffer was required. Dr. Backman’s statement ignores that RNAlater is designed to “stabilize both RNA and protein ***within tissues or cells.***”²¹⁸ Notably, whereas fecal RNA is primarily present within cells shed into feces,²¹⁹ Dr. Backman acknowledges that fecal hemoglobin is extracellular (i.e., not found

²¹⁶ Backman Dep. Tr. (EX1089), 41:6-42:11.

²¹⁷ Backman Declaration (EX2044), ¶193.

²¹⁸ Ambion TechNotes (EX2048).

²¹⁹ Nechvatal (EX1024), pp. 124-125.

within cells).²²⁰ Dr. Backman provides no evidence that RNAlater would effectively stabilize extracellular fecal proteins, like hemoglobin. Indeed, at his deposition Dr. Backman acknowledged that was aware of no evidence that RNAlater would effectively stabilize hemoglobin in feces.²²¹ Dr. Backman acknowledged that developing a diagnostic test requires buffer optimization and that “a person of skill in the art would preferably use a buffer that had been proven to work for the preservation of their analyte of choice.”²²² A POSA would therefore be motivated to separately stabilize a portion of a fecal sample in a buffer optimized for RNA stabilization, like RNAlater, and a portion of the fecal sample in a buffer optimized to stabilize hemoglobin, like Vilkin’s hemoglobin stabilizing buffer, to optimally preserve the RNA and hemoglobin biomarkers respectively.

VI. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

126. 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

²²⁰ Backman Dep. Tr. (EX1089) 161:17-23.

²²¹ *Id.*

²²² Backman Dep. Tr. (EX1089), 68:17-21.

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Products provide “strong objective evidence that the ’746 patent would not have been obvious at the relevant time.”²²³

127. As I explain in my Opening declaration, I understand that to accord substantial weight to secondary considerations, the evidence of secondary considerations must be shown to have a “nexus” to the claims. I understand that the patentee bears the burden of showing a nexus exists, and that presuming nexus is only appropriate when the patentee shows that the asserted secondary consideration is tied to a specific product and that the product embodies the claimed features and is coextensive with them. On the other hand, I also understand, when a 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 that the Cologuard screening assay is coextensive with the challenged claims.

128. 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

²²³ Backman Declaration (EX2044), ¶¶195.

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 '746 Patent

129. I note that, while Dr. Backman repeatedly asserts that Cologuard embodies the claims of the '746 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.

130. As explained in my Opening Declaration, 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.²²⁴ Indeed, Exact's own website demonstrates the critical importance of components of Cologuard not claimed in the '746 patent.²²⁵ As also

²²⁴ Opening Declaration (EX1002) ¶¶335-342.

²²⁵ *Id.* ¶343.

explained in my Opening Declaration, Cologuard identifies on its website dozens of patents unrelated to the '746 patent that cover critical components of Cologuard and its use.²²⁶ As Explained in my Opening Declaration, the claims of these many patents are directed to numerous distinct components of Cologuard.²²⁷

131. Dr. Backman does not even attempt to explain how the claims of the '746 patent could be coextensive with the Cologuard product when Cologuard possesses so many critical features unclaimed by the '746 patent but covered by other Exact patents.

132. 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 Any Secondary Consideration is a Direct Result of The Challenged Claims

133. Dr. Backman's nexus arguments are based on his assertion that "Cologuard practices at least Claim 3 of the '746 patent, and the invention claimed in Claim 3 is fundamental to the diagnostic accuracy and patient uptake of

²²⁶ *Id.* ¶344.

²²⁷ *Id.*

Cologuard.”²²⁸ However, beyond this conclusory statement, Dr. Backman never establishes that sample processing method of Claim 3 is “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 and in my Opening Declaration.

134. Claim 3 does not include any limitation requiring any level of diagnostic accuracy or patient uptake. Rather, Claim 3 is directed to obtaining a pair of portions of a fecal sample separated into two portions and adds that these fecal portions are then tested for an amount of a nucleic acid and an amount of a blood protein. In my opinion, Claim 3 is not fundamental to either diagnostic accuracy or patient uptake. In practice, what determines diagnostic accuracy is the specific selection and optimization of fecal biomarkers and their assay parameters, not the mere act of splitting a specimen and testing for “an amount of a nucleic acid” and “a blood protein.” For example, at his deposition, Dr. Backman admitted that if Cologuard had used only a single DNA marker (out of the ten it employs), sensitivity would have been lower,²²⁹ underscoring that accuracy is driven by

²²⁸ Backman Declaration (EX2044), ¶199.

²²⁹ Backman Dep. Tr. (EX1089), 79:7-16.

marker selection and optimization rather than the generic split-sample processing step recited in Claim 3. Indeed, claim 3 does not even recite a step in which cancer is detected or diagnosed.

135. Dr. Backman has provided no evidence that the diagnostic accuracy of Cologuard is a product of the claimed fecal processing methods of Claim 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. 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.***"²³⁰

136. Similarly, during prosecution of an unrelated patent claiming a later invention (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."

²³⁰ Imperiale 2014 (EX1077), p. 1295.

²³¹ 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.” ²³² 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.”²³³

137. 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 '746 Patent.²³⁴ 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 '746 Patent.***

²³¹ Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of '278 patent (EX1029), p. 9.

²³² *Id.*, p. 7.

²³³ *Id.*, p. 9.

²³⁴ U.S. Patent No. 9,163,278 (EX1028); '746 patent (EX1001).

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138. The evidence of record similarly does not demonstrate that Cologuard's patient uptake is a product of Claim 3 of the '746 patent. 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.²³⁵ Dr. Backman admitted in his deposition in the '459 IPR that the sample collection process used in Cologuard is no more convenient than that of prior art FIT assays.²³⁶ 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. Accordingly, it is my opinion that the patient uptake of Cologuard is unrelated to the fecal processing method of Claim 3.

139. As I noted in my Opening Declaration, Exact identifies on its website 54 patents unrelated to the '746 patent that cover components of Cologuard and its use, and an additional eight now-expired patents were previously identified on Exact's webpage in 2014.²³⁷ 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

²³⁵ See, e.g., Itzkowitz (EX1006); Vilkin (EX1005); Shuber (EX1008).

²³⁶ Backman Dep. Tr. of IPR2024-00459, (EX1088), 74:7-75:8.

²³⁷ Opening Declaration (EX1002), ¶344.

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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 '746 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.

140. 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 at a price of approximately \$500.²³⁸ 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.

²³⁸ Declaration of Peter Wood (EX2019), ¶13.

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141. The important role of Exact's marketing efforts to Cologuard's commercial success is confirmed by a recent article published in Forbes.²³⁹ 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."²⁴⁰ Notably, in the above DTC marketing test, the exact same Cologuard product was being sold in both the test market and the control market. The 100% improvement in commercial success observed over nine weeks in the test markets can therefore only be attributable to the advertising Exact placed in those markets, and is certainly not attributable to the Challenged Claims.

142. Regarding failure of others and long-felt need, Dr. Backman argues that the Cologuard test "has met the long-felt need for a non-invasive CRC screening test with sufficient diagnostic accuracy and patient uptake," but, as discussed above, never establishes that Cologuard's diagnostic accuracy and patient uptake are the product of the claims of the '746 patent as opposed to

²³⁹ Feiger, Chase, "How This CEO Consumerized Cancer Into a \$13B Enterprise" Forbes, April 8, 2024 (EX1091).

²⁴⁰ *Id.*, p. 6.

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Cologuard features covered by the dozens of other patents identified by Exact on its website. Indeed, Dr. Backman does not address in his Declaration that in 2015, during prosecution of one of these unrelated patents, Exact expressly represented to the U.S. Patent Office that it was not the method of the Challenged Claims, but rather to “a particular combination of markers and methods for extracting the marker DNA from stool.” 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.”²⁴¹ The '278 patent had a priority date of May 12, 2011, so that in making this argument to the U.S. Patent Office, as noted above, Exact was ***admitting that this long felt need was not solved by the method claimed in the Asserted Patents in 2009.***

143. Regarding Dr. Backman’s “copying by others” analysis, I understand that establishing “copying by others” as a secondary consideration of non-obviousness requires more than simply showing evidence of 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

²⁴¹ Response to Nonfinal Office Action filed on July 31, 2015 during prosecution of '278 patent (EX1029), p. 9.

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practices the claims of the '746 patent.²⁴² He offers no evidence, as would be required, that in developing ColoSense the Petitioner undertook to replicate the Cologuard product. Dr. Backman has not satisfied Exact's burden of establishing copying by others as a secondary consideration of nonobviousness.

144. Dr. Backman therefore has not demonstrated that the secondary considerations that 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. In my opinion, the secondary considerations identified by Dr. Backman should be given no weight.

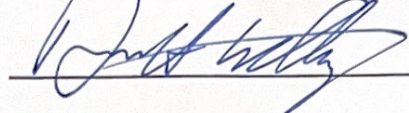
²⁴² Backman Declaration (EX2044), ¶¶238-246.

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

Dated: August 21, 2025

Respectfully submitted,

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

Duncan Whitney, Ph.D.