

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

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

PETITIONER'S REPLY

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Exact reiterates in its POR the same flawed arguments it made in its POPR, focusing again on the references' disclosures individually instead of in combination and erroneously treating their disclosure of alternative embodiments as teaching away from the invention. The Board preliminarily rejected these arguments in the Institution Decision, and Exact offers nothing new post-institution that warrants the Board revisiting its earlier conclusions.

Exact's new arguments alleging secondary considerations based on the success of its Cologuard® product also fail because Exact has not met its burden of proving a nexus between Cologuard and the claimed invention. Tellingly, the word "nexus" appears nowhere Exact's POR. This glaring omission is for good reason—Exact cannot demonstrate that any purported success of Cologuard is attributable to the claimed methods, rather than to other Cologuard components covered by at least 60 unrelated Cologuard patents or the more than \$3 billion Exact spent marketing Cologuard. Exact's asserted secondary considerations should be given no weight and certainly do not overcome Geneoscopy's strong *prima facie* showing that the Challenged Claims are unpatentable as obvious.

I. GROUND I: LENHARD, VILKIN AND ITZKOWITZ

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

As recognized by the Board in the Institution Decision, the Petition demonstrates that “the combination of Lenhard, Itzkowitz, and Vilkin teaches each limitation of the claims for the reasons stated by Petitioner” and “a POSA would have had a reason to modify the assay of Lenhard to combine Vilkin’s iFOBT and Itzkowitz’s collection process and DNA stabilization buffer with a reasonable expectation of success.” ID 14, 17. Exact’s regurgitated POR arguments do not justify any change to this preliminary finding. Lenhard, Vilkin and Itzkowitz render obvious the claimed method of processing a freshly collected fecal sample.

Exact’s argument that the combination of Lenhard, Vilkin and Itzkowitz would not have resulted in the claimed method cherry-picks from each reference individually rather than considering them in combination. POR 22-24. When the references are properly considered together, a POSA would have reason, in view of the additional disclosures in Vilkin and Itzkowitz, to make straightforward improvements to the fecal CRC diagnostic assay of Lenhard to arrive at the claimed method. Petition 20-26; ID 14; EX1080 ¶¶48-50.

Specifically, Lenhard discloses a method for performing a fecal CRC 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 a DNA biomarker. Petition 21. A POSA would be motivated to incorporate the sample collection and preservation processes of Itzkowitz based on advantages taught by Itzkowitz. Petition 23-25. Likewise, a POSA would be motivated to replace the gFOBT used in Lenhard with the automated iFOBT of Vilkin based on numerous advantages of iFOBT set forth in Vilkin. *Id.* 21-23. The straightforward application of these well-established improvements to Lenhard's assay are suggested by reading the references themselves in combination and require neither a roadmap nor hindsight, as alleged by Exact. POR 23.

Exact's assertion that "the combination would not have resulted in the specific at-home collection method of the claims" ignores that the natural result of these obvious improvements is the claimed method. POR 24. When the iFOBT of Vilkin and the stool collection and preservation processes of Itzkowitz are applied to the CRC assay of Lenhard, the result is a method 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). Petition 25-26. The patient then sends both containers to a laboratory

for analysis of DNA methylation and FOBT, which Lenhard teaches provides improved sensitivity compared to either test alone. *Id.* 26. The resulting fecal processing method meets every limitation of the Challenged Claims. *Id.* 26-43.

Exact argues that a POSA would not have been motivated to separate the sample into two containers because “the less complex and patient-acceptable approach would have been to use a nucleic acid stabilizing buffer that also preserves blood protein.” POR 39. Tellingly, neither Exact nor its expert identifies a then-available buffer that preserves both nucleic acids and proteins. EX2022 ¶¶117-119. On the other hand, buffers that separately preserve DNA or proteins were well known in the art by the Priority Date and are disclosed in Itzkowitz and Vilkin, respectively. EX1002 ¶¶73-81; EX1080 ¶¶77-81; EX1005; EX1006.

Moreover, partitioning a fecal sample to separately preserve each portion in different stabilizing buffers was a well-established strategy decades before the Priority Date. EX1002 ¶¶82-84; EX1080 ¶80. Exact’s hypothetical single buffer, which has not been shown even to exist, would not have led a POSA to eschew this conventional strategy using known, biomarker-optimized buffers. EX1080 ¶¶77-81.

B. A POSA Would Be Motivated to Modify Lenhard to Arrive at the Claimed Method

Exact mischaracterizes Geneoscopy's argument by stating that it "begins from the premise that a POSA would have been motivated to combine a nucleic acid test with FOBT." POR 24-25. This is incorrect because, as explained in the Petition, Lenhard *already discloses* an assay that combines a nucleic acid test with a gFOBT. Petition 21. Lenhard's repeated statements regarding the combined assay's superiority for detection of CRC and the lack of any corresponding teaching away simply provides the POSA a reason to further improve this existing disclosed embodiment, for example by replacing its gFOBT with the superior iFOBT of Vilkin and incorporating Itzkowitz's improved stool collection and stabilization buffer. Petition 21-26; EX1080 ¶¶16-33, 51-61.

1. A POSA would be motivated to improve Lenhard's combined assay

Exact's argument that Lenhard "does not provide motivation to develop a combined test for both nucleic acid and fecal occult blood" (POR 26) is unsupported by Lenhard's disclosure and runs counter to the knowledge in the art. POR 26.

Lenhard expressly discloses that combining its DNA assay with its FOBT results in increased sensitivity compared to either assay alone. EX1004 147 ("The combination of both assays resulted in increased detection rates for CRCs"). It is

indisputable that having a higher sensitivity for CRC is a desirable feature for a fecal CRC diagnostic assay. EX1002 ¶28; EX1080 ¶¶23-24, 62-66. A test with a higher sensitivity will produce fewer false negative results, meaning fewer patients with cancer will go untreated. *Id.* Indeed, in a publication reporting its Cologuard clinical trial, Exact admits “[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.” EX2008 1295. As the Board preliminarily held in its Institution Decision, Lenhard’s positive statements concerning increased sensitivity and supporting data “are sufficient to provide a ‘rational underpinning’ to combine the gFOBT and DNA test.” ID 17.

Exact’s argument that “Lenhard discloses that another methylation marker alone, SFRP2, was more sensitive” and suggests “[c]ombination of HIC1 with a few additional sensitive and specific methylation markers” is unavailing. POR 26-27. Under the legal standard, neither disclosure “teaches away” from Lenhard’s combined assay. As the Board noted in the Institution Decision, “the reason to combine need not coincide with the preferred or most desirable combination described in the prior art to provide motivation for the invention.” ID 18, citing *Gen. Elec. Co. v. Raytheon Techs. Corp.*, 983 F.3d 1334, 1351 (Fed. Cir. 2020). Lenhard’s suggested inclusion of additional DNA markers as a strategy to improve

assay performance does not preclude incorporating those markers into its combined DNA/FOBT test. EX1080 ¶¶33, 59-61. Indeed, a POSA would understand that a logical starting point for further assay improvement would be the combined test, with its significantly higher sensitivity compared to either the DNA test or FOBT alone. *Id.*

Similarly, the fact that “Vilkin and Itzkowitz also each disclose tests that were more sensitive than the combined HIC1/gFOBT results reported in Lenhard,” does not teach away from Lenhard’s combined assay. POR 27-29. Rather, the relatively high sensitivities reported in Vilkin and Itzkowitz would motivate a POSA to incorporate strategies used in these references to achieve such sensitivities into Lenhard’s assay. EX1080 ¶¶55-58. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (“if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious”). For example, Itzkowitz’s disclosure that improving its stool collection process to incorporate a DNA stabilization buffer contributed to an increase in assay sensitivity would motivate a POSA to apply a similar sample collection strategy to Lenhard’s assay. EX1080 ¶57; EX1006 114. Likewise, Vilkin’s disclosure faulting

gFOBT like the one used in Lenhard for low sensitivity would motivate a POSA to use Vilkin's more sensitive iFOBT in its place. EX1080 ¶57; EX1005 2519.

The fact that Lenhard's combined assay did not also increase sensitivity for advanced adenomas does not constitute a teaching away. POR 27. A POSA would have reason to use a test with higher sensitivity for detection of CRCs even if that test did not increase sensitivity for the detection of adenomas. EX1080 ¶¶19-22, 52-54. As of the Priority Date, cancer detection was of primary importance in fecal CRC assays. *Id.* For example, in Itzkowitz, Exact assesses performance of different versions of its fecal DNA assay based solely on their ability to detect CRC, without even measuring their ability to detect adenomas. EX1006. Similarly, Levin explains in its 2008 CRC screening guidelines that fecal tests "primarily are effective at identifying CRC" and that "[s]ome premalignant adenomatous polyps may be detected, providing an opportunity for polypectomy and 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.***" EX1013 1752-1753 (emphasis added). A POSA would not discount the improved sensitivity for CRC of the combined Lenhard assay because it maintained only equal sensitivity for adenomas. EX1080 ¶52.

2. A POSA Would Not Have Been Dissuaded by Reduced Specificity

Exact notes that the specificity of Lenhard's combined assay is lower than the corresponding specificity of the HIC1 assay alone and argues on that basis that a POSA would not have been motivated to combine classes of markers because "Lenhard itself teaches that the specific HIC1/gFOBT combination reduced specificity and that other methylation markers alone achieved greater sensitivity." POR 32. Exact's argument ignores the importance a POSA places on sensitivity and the POSA's corresponding willingness to sacrifice some specificity to improve sensitivity. EX1080 ¶¶62-66.

A POSA's willingness to accept reduced specificity for improved sensitivity is illustrated, for example, in Itzkowitz. In Itzkowitz, Exact describes the development of a "second generation" of their fecal DNA test for CRC. EX1006 111; EX1080 ¶63. Whereas Exact's "first generation" test had a specificity of 94%, the specificity of its "second generation" test was only 82%. *Id.* Despite this reduction in specificity, Exact considered their second-generation test to be "[a]n improved fecal DNA test that... shows ***much higher sensitivity for CRC.***" *Id.* (emphasis added). This is consistent with Exact's later admission 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." EX2008 1295.

The “reduced” specificity exhibited by Lenhard’s combined test would be acceptable to a POSA. EX1080 ¶64. Notably, the combined assay’s specificity of 89% is higher than that of Exact’s “improved” second generation DNA assay, which was only 82%. EX1006 111. Indeed, the specificity of Exact’s ultimate, FDA-approved Cologuard test for CRC, at only 86.6%, is no higher than that of Lenhard’s combined test. EX2022 ¶41. Even the “other methylation marker” Exact suggests using in place of the Lenhard’s combined assay, SFRP2, has a specificity of only 77%. POR 26.

A POSA also would have recognized that 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%. EX1004 147; EX1080 ¶65. This would provide a POSA with additional motivation to replace Lenhard’s gFOBT with Vilkin’s more specific iFOBT and thereby increase the specificity of the combined assay. EX1080 ¶65; EX1005 2523.

3. A POSA Would be Motivated to Replace Lenhard’s gFOBT with Vilkin’s iFOBT

Exact relies on a misreading of Vilkin as “require[ing] both testing of three separately-collected daily samples and refrigeration of those samples in the test subject’s home refrigerator over multiple days” to assert “these requirements would have dissuaded combination of the iFOBT of Vilkin with any other form of

test.” POR 32-34. Here, Exact relies on the sample collection protocol Vilkin used when testing reproducibility its iFOBT in a research study, which Vilkin makes clear is not representative of sample collection frequencies used in practice.

EX1080 ¶¶34-37, 67-69.

Vilkin explains different countries use different sample collection frequencies when screening for CRC in average risk populations. EX1005 2524. In none of the countries Vilkin mentions were samples collected on three consecutive days. *Id.* Vilkin further explains that they elected to continue “collecting three **annual** fecal tests” when testing high-risk populations. *Id.* (emphasis added). Vilkin recognized that a different testing frequency might be appropriate for average-risk populations, stating 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.**” *Id.* (emphasis added). At his deposition, Exact’s expert acknowledged that Vilkin does not require collection of three consecutive daily samples when its assay is used in clinical practice. EX1090 141:4-142:19.

Whether Vilkin requires sample refrigeration before sending to the laboratory is ancillary to the obviousness of the Challenged Claims, which exclude

freezing, not refrigeration. Vilkin experimentally demonstrates that freezing of the fecal samples is not required for sample stability. EX1005; EX1080 ¶¶37-38].

Moreover, a POSA would also understand that, in clinical practice, a patient would not need to refrigerate stool samples for multiple days when using Vilkin's iFOBT. EX1080 ¶69. At-home refrigeration of the stool samples is only necessary when a patient collects three daily samples—in the absence of multiple-day sample collection, a patient can ship the sample immediately after collection. *Id.* Because collection of three consecutive daily samples is not required, in clinical practice a patient can immediately ship a sample to the laboratory without refrigeration. *Id.* 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. *Id.*

The evidence is overwhelming that a POSA would recognize the iFOBT of Vilkin as a superior alternative to the gFOBT of Lenhard. Petition 21-23; EX1080 ¶¶70-71. Vilkin expressly teaches numerous advantages that its iFOBT has over gFOBT, including that it (1) has a higher sensitivity, (2) eliminates the need for diet restrictions, and (3) is quantitative, which allows a physician to choose the optimal fecal Hb threshold level. EX1005 2519, 2524. In his deposition, Exact's

expert acknowledged that Vilkin teaches advantages of its iFOBT over gFOBT.

EX1090 120:9-124:12

Exact argues that Petitioner's assertion of known advantages of iFOBT over gFOBT is contradicted by disclosure in Levin reporting that "it appears there are no clear patterns of superior performance in overall test performance between a high-sensitivity guaiac-based test (Hemoccult SENSА) and a variety of [iFOBT]." POR 36, quoting EX1013 1576. Exact's argument is based on a selective and misleading reading of Levin.

First, Lenhard does not use the particular high-sensitivity gFOBT that Levin reports can match the performance of certain iFOBT. EX1004 145. Rather, Lenhard's gFOBT has a demonstrably lower sensitivity (35%) than the iFOBT of Vilkin (65%-79%, depending on the Hb threshold applied). EX1004 146; EX1005 2523. Accordingly, Levin's disclosure would not affect a POSA's motivation to replace the gFOBT of Lenhard with the iFOBT of Vilkin.

Second, Exact's argument disregards the numerous other advantages of iFOBT over gFOBT that Levin identifies. For example, Levin states that iFOBT "has several technological advantages when compared with gFOBT" including that it (1) "is more specific for human blood than guaiac-based tests;" (2) "is not subject to false-negative results in the presence of high-dose vitamin C

supplements;” (3) is “more specific for lower gastrointestinal bleeding, thus improving their specificity for CRC;” and (4) that “the sample collection for some variants of [iFOBT] are less demanding of patients than gFOBT, requiring fewer samples or less direct handling of stool.” 1013 1576. Thus, contrary to Dr. Exact’s assertion, Levin supports that a POSA would be motivated to use an iFOBT in place of a gFOBT.

4. A POSA Would Not Have Been Dissuaded by Cost and Complexity

Exact’s contention that “a POSA would have had no motivation to make the combination” because it “would result in a test with increased cost and complexity” also fails. POR 34-35. Most importantly, Exact’s argument ignores that modifying the assay disclosed in Lenhard to incorporate the sample collection and stabilization process of Itzkowitz and replacing its gFOBT with an iFOBT of Vilkin does not increase the complexity of Lenhard’s assay, but rather simplifies it, providing further motivation to make the proposed combination. EX1080 ¶¶72-74.

Lenhard already discloses an assay in which both a DNA test and a gFOBT are performed on a single fecal specimen. EX1004. Incorporation of Itzkowitz’s sample collection and stabilization processes into the Lenhard assay facilitates at-home sample collection, making the process more convenient for the patient. EX1080 ¶¶72-74. Likewise, the sample collection process used in iFOBT, like the

one in Vilkin, was known to be more convenient for patients than the corresponding collection process used with gFOBT, like the one in Lenhard. *Id.* For example, 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.” EX1024 29. Similarly, Levin states that the sample collection methods used with iFOBT “are less demanding of patients than gFOBT, requiring fewer samples or less direct handling of stool.” EX1013 1576. A POSA would therefore be motivated to make the Lenhard assay more convenient for patients by incorporating the Itzkowitz and Vilkin sample collection processes. EX1080 ¶74.

In any case, as of the priority date, a POSA would be willing to accept a more complex and expensive CRC diagnostic assay if it meant better detection of CRC. EX1080 ¶75. For example, Levin’s 2008 CRC screening guidelines notes that the unit cost of 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.” EX1013 1578.

In support of its argument, Exact notes a passage in Itzkowitz referring to an Exact-sponsored study looking at patient preference in CRC testing. POR 35. Far

from supporting Exact's position, this study confirms that a POSA would be willing to accept increased assay complexity for a better test. In the study, patients were asked whether they preferred a fecal DNA test, which only required collection of a single sample and no stool manipulation, a gFOBT test, which required three consecutive days of sample collection and extensive fecal manipulation, or colonoscopy. EX2048 208-209; EX1080 ¶40-43. While 45% of the respondents reported a preference for the fecal DNA test, 32% preferred the gFOBT test despite its more complicated sample collection process, and 15% preferred colonoscopy. EX2048 208. The study concluded that "the finding that most patients rated both tests comparably with respect to most prep- and test-related features is not unexpected." *Id.* 211-212.

II. GROUND IV: SHUBER AND VILKIN

A. Shuber and Vilkin Render the Challenged Claims Obvious

Exact similarly attacks the Ground IV references individually rather than in combination to assert that Geneoscopy's arguments are "based on impermissible hindsight knowledge of the claims" and that "the proposed combination of Shuber with Vilkin fails to teach or suggest all of the claimed elements as arranged in the claims." POR 41-42.

On the contrary, as is clear from in the Petition, Applicant's arguments are based on the teachings of the prior art references and knowledge in the art as of the Priority Date. A POSA as of that date would have been motivated to combine a DNA-based fecal diagnostic test, such as those disclosed in Shuber, with a blood protein-based test, such as the iFOBT disclosed in Vilkin, because combining such assays was an art-recognized strategy for improving assay sensitivity. Petition 48-50. When such a combined test was performed, the natural result would be a method in which a patient: (1) directly defecates into a sealable container (as in Shuber); (2) uses a fecal test sampling device to remove a portion of the sample and combine it with hemoglobin stabilizing buffer (as in Vilkin); (3) adds the DNA stabilizing buffer of Shuber to the remaining sample (as in Shuber); and (4) ships the sealed sampling device and sealed container to a diagnostic laboratory for testing (as in Vilkin and Shuber, respectively). Petition 50. 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, as taught by Vilkin and Shuber. *Id.* As explained in section I(A), partitioning a fecal sample to separately preserve each portion in different stabilizing buffers was a well-established strategy decades before the Priority Date. Accordingly, when considered together in the context of

the knowledge in the art, the combination of Shuber and Vilkin renders obvious a method that includes all the claimed elements as arranged. EX1080 ¶¶83-85, 95.

B. A POSA Would Be Motivated to Combine DNA Tests with FOBT

By the Priority Date the advantages associated with the combined detection of fecal DNA and blood proteins were well recognized in the art. Petition 48-50. Exact's attempt to explain-away these extensive teachings is unavailing.

For example, Exact 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.**” POR 43 (emphasis added). Exact attempts to wave-away this explicit teaching because “seven years passed between Nishikawa and the invention of the '781 patent.”¹ *Id.* Regardless of timing, it is indisputable that Nishikawa's disclosure reflects an appreciation in the art well before the Priority Date that combining fecal DNA tests with FOBT was a recognized strategy for improving assay sensitivity. EX1080 ¶87.

¹ Exact misrepresents that they were the source of the claimed invention, which originated at OncoMethylome and was only purchased by Exact eight years later. Petition 9-10.

As explained above in section I(B)1, Exact's position that the Lenhard reference "would have dissuaded a POSA from combining a nucleic acid marker test with FOBT" (POR 44) is in direct opposition to Lenhard's teaching that "[t]he combination of both assays resulted in increased detection rates for CRC." EX1004 147. Exact's interpretation of Kutzner is similarly confounding, given Kutzner's conclusion 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.**" EX1012 33 (emphasis added). Indeed, Kutzner expressly states "**we suggest that MD and FOBT should complement rather than replace each other.**" *Id.* 40 (emphasis added). Kutzner's statement cited by Exact merely acknowledges that clinical trials would be required before such a combined assay could be put into broad clinical use, and it in no way detracts from Kutzner's express suggestions that DNA and FOBT testing be done in combination. EX1080 ¶88-89.

Similarly, Levin's proposal to investigate "whether or not including a sensitive gFOBT or [iFOBT] at the time of testing would improve sensitivity [of DNA-based assays] without adversely affecting specificity" recognizes that combining fecal DNA assays with iFOBT was a strategy for improving sensitivity that was worth trying. EX1080 ¶90. A POSA would have a reasonable expectation

that such a strategy would succeed based on Levin’s disclosure that, in a recent study, “combined results from a standard gFOBT and a panel of DNA markers... resulted in a combined sensitivity for cancer of 93% and specificity of 89%.”

EX1013 1578. *KSR*, 550 U.S. at 421 (“[W]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions... it is likely the product not of innovation, but of ordinary skill and common sense.”).

Shuber’s prophetic statements that certain panels of biomarkers could detect adenomas with sensitivities of greater than 60%, 74%, 90%, 95% or even 98% would not dissuade a POSA from combining fecal DNA assays with FOBT, as asserted by Exact. EX1009 14:1-16; POR 46. A POSA would recognize these hypothetical adenoma sensitivities as unsupported by any data and overly optimistic given the state of the art, and would not believe that “little, if any, improved sensitivity” could be achieved by a combined test, as Exact argues. POR 46; EX1080 ¶92.

C. Vilkin Does Not Require Multiple Samples or Refrigeration

Exact once again relies on a misreading of Vilkin to argue that a POSA would be dissuaded from combining Vilkin with a fecal DNA assay. POR 47. As explained in section I(B)3, Vilkin does not require collection of three daily

samples, nor does it require refrigeration of a sample in a patient's home when it can be sent to a laboratory the same day it is collected. In any case, the Challenged Claims do not require any collection frequency or exclude sample refrigeration. Nothing in Vilkin's disclosure would preclude its iFOBT from being combined with a DNA test of Shuber to arrive at the method set forth in the Challenged Claims. EX1080 ¶94.

D. A POSA Would Not Have Been Dissuaded by Assay Cost and Complexity

Exact argues that "a POSA seeking to improve CRC screening tests would not have been motivated to choose a path that would increase both cost and complexity unless there was a considerable likelihood of sufficient performance gains." POR 47. Exact's argument fails because, (1) as explained in section II(B), the combination of fecal DNA assays and FOBT was a recognized strategy for improving assay sensitivity; and (2) as discussed in section I(B)4, a POSA would be willing to sacrifice assay cost and complexity in exchange for better CRC detection. EX1080 ¶93.

III. GROUNDS II, III, V and VI

The POR response does not separately argue Grounds II, III, V, and VI, but merely states that "[t]hose Grounds also fail for the same reasons as Grounds I and IV fail." POR 49. Exact's flawed arguments regarding Grounds I and IV are

equally unavailing when applied to Grounds II, III, V, and VI for the same reasons set forth above.

IV. SECONDARY CONSIDERATIONS

Exact's purported secondary considerations based on its Cologuard product fail because Exact has not met its burden of proving a nexus between Cologuard and the claimed invention. Indeed, the word "nexus" does not even appear in the POR. Exact's asserted secondary considerations should be given no weight and cannot overcome Geneoscopy's strong *prima facie* case that the Challenged Claims are obvious.

A. Exact is Not Entitled to a Presumption of Nexus

The patentee bears the burden of proving a nexus exists. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). A presumption of nexus is appropriate only "when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them." *Id.* Exact does not show in its POR that Cologuard is coextensive and as a result, Exact is not entitled to a presumption of nexus.

Indeed, Cologuard is clearly not coextensive with the claimed method. EX1080 ¶¶99-106. Cologuard is a complex, multistep CRC test for which the claimed method of dividing a stool sample into two portions in separate buffers is, at most, a minor component. EX1081 p.4; EX1082 pp. 7-46. This is confirmed by

the dozens of patents unrelated to the '781 patent that Exact identifies as covering Cologuard. EX1080 ¶105; EX1083; EX1084. Distinct components of Cologuard claimed by these patents include its: (a) stool collection containers; (b) DNA stabilization buffer; (c) DNA extraction process; (d) DNA biomarkers; (e) DNA preparation process; (f) DNA methylation assay; (g) DNA mutation assay; and (h) controls. EX1080 ¶105.

B. Cologuard's Purported Success is Not a Product of the Claimed Method

Where a party is not entitled to a presumption of nexus, it bears the burden of showing that the success of the product is “a direct result of unique characteristics of the claimed invention.” *Fox Factory, Inc.*, 944 F.3d at 1373-74. Exact has not demonstrated that the purported success of Cologuard is a direct result of any unique characteristic of the Challenged Claims. EX1080 ¶¶107-117. None of the Challenged Claims contains any limitation requiring any level of diagnostic accuracy or uptake.

Exact's arguments are based on its conclusory assertions that the “Cologuard test would not have achieved commercial success if it did not satisfy two critical aspects of screening tests: diagnostic accuracy and uptake” and that “[t]he claimed invention of the '781 patent is essential to both aspects.” POR 56. Exact's only support for these contentions is a citation to a single paragraph in its expert's

declaration that merely mirrors Exact's conclusory statements, with no evidentiary support. *Bosch Auto. Serv. Sols., LLC v. Matal*, 878 F.3d 1027, 1037 (Fed. Cir. 2017) (“[A]n expert declaration that merely repeats, in conclusory fashion, that the success of the product is due to the claimed invention is insufficient to establish a nexus.”) (citation omitted).

Exact provides no evidence that Cologuard's diagnostic accuracy is a product of the claimed fecal processing method, as opposed to the many other components of Cologuard covered by the dozens of unrelated patents discussed above. Exact provides no evidence that the combination of Cologuard's DNA and FIT components results in better diagnostic accuracy than would be achieved by the DNA component alone. EX1080 ¶109. Indeed, Exact proposed in its Cologuard clinical trial publication that its diagnostic accuracy “**may be attributed to the DNA marker and algorithm components of the test.**” EX2008 1295 (emphasis added). Exact itself therefore attributes the diagnostic accuracy of Cologuard to features unrelated to the Challenged Claims.

During its prosecution of an unrelated patent asserting a later priority date than the '781 patent, Exact also attributed Cologuard's success, not to the sample processing method of the Challenged Claims, but rather to a later-invented “combination of markers and methods for extracting the marker DNA.” EX1085;

EX1086 9; EX1080 ¶¶111-112. Exact argued that these components were present in Cologuard and “addressed this long-felt need and succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.” EX1086 6-7, 9.

Exact’s POR also ignores that the commercial success of Cologuard may have been significantly influenced by the exclusivity provided the dozens of unrelated patents it identifies as covering Cologuard on its website. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (“Because market entry from others was precluded... the inference of non-obviousness... is weak”). Similarly, Exact has not shown that any success, industry praise, or solution of a long felt need it attributes to Cologuard was a result of a unique characteristic of the Challenged Claims, as opposed to these unrelated inventions.

There is likewise no evidence that Cologuard’s uptake is a product of the Challenged Claims. 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. EX1005; EX1006; EX1009. Exact’s expert admitted in his deposition that the convenience of the sample collection process of Cologuard is equivalent to that of a FIT test. EX1090 74:7-75:8.

Exact also fails to demonstrate that Cologuard's uptake was not primarily the product of the more than \$3 billion it spent on its marketing. EX2023 ¶13. The significance of Exact's marketing efforts is confirmed by a recent article published in Forbes. EX1087. In this article, Exact's CEO explains that, after Cologuard's launch, Exact ran direct-to-consumer marketing tests in which targeted TV commercials were run in five markets and sales in those markets were compared sales in five control markets. *Id.* 6. In markets where Cologuard was advertised, sales grew significantly faster than in control markets, and after 9 weeks they were up 100% compared to control. *Id.* As the same Cologuard product was being sold in both the test and control markets, the improved commercial success in the test markets cannot be attributed to the challenged sample collection method.

Finally, Exact's assertion of "copying" as a secondary consideration of nonobviousness fails. Establishing "copying by others" requires more than simply showing infringement by a third-party product. *In re Celorio Garrido*, 646 F. App'x 942, 944 (Fed. Cir. 2016). Exact fails to meet this burden, as the entirety of its argument is based on ColoSense allegedly practicing that Challenged Claims. POR 63-65. Exact presents no evidence that Geneoscopy undertook copying efforts in order to replicate Cologuard.

Because Exact has not demonstrated that any secondary consideration has the required nexus to the Challenged Claims, the asserted secondary considerations should be given no weight, and cannot overcome Geneoscopy's strong *prima facie* showing that the claims are obvious.

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Respectfully submitted,

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that the foregoing complies with the type-volume limitations of 37 C.F.R. § 42.24 because, according to the “word count” function of Microsoft Word, the Petition contains 5,581 words, excluding those portions exempted under 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing **PETITIONER'S REPLY** was served on January 27, 2025 via the delivery method indicated to the attorneys of record for the Patent Owner as follows:

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