

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

PETITIONER'S REPLY

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In its POR Exact makes the same flawed arguments it made in IPR2024-00459 when it attempted unsuccessfully to defend patentability the '746 patent's parent. Exact again bases its argument on the references' disclosures individually instead of in combination, erroneously disregards the prior art authors' statements expressly suggesting Petitioner's proposed combinations, and asserts secondary considerations based on their Cologuard® product without proving nexus. The Board rejected these same arguments in its Final Written Decision in IPR2024-00459 (EX1087, "FWD"), and Exact offers nothing new in its POR that warrants the Board revisiting its earlier determination. Indeed, the claim scope of the '746 patent is broader than that of its invalidated parent, and the Board's reasons for finding all claims unpatentable in IPR2024-00459 apply equally to the claims challenged in the present IPR.

I. GROUND I: LENHARD, VILKIN AND ITZKOWITZ

As recognized by the Board in this IPR's Institution Decision, the Petition demonstrates that "the combination of Lenhard, Vilkin, and Itzkowitz teaches each limitation" of the Challenged Claims 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 20-21. Exact's rehashed arguments in its POR do not justify any change in the Board's preliminary finding. Indeed, the Board has already held that narrower

claims are rendered obvious by Lenhard, Vilkin, and Itzkowitz in IPR2024-00459. EX1087 34-57. The Challenged Claims are obvious over these references for the same reasons.

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 24-26. As recognized in the FWD, when the references are properly considered together and in accordance with their substantial focus, 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 19-24; EX1087 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 19. A POSA would be motivated to incorporate the sample collection and preservation processes of Itzkowitz based on advantages taught by Itzkowitz. *Id.* 21-23. 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.* 20-21. The straightforward application

of these well-established improvements to Lenhard's combined assay is suggested by the references themselves and results in the fecal processing method that meets every limitation of the Challenged Claims. *Id.* 23-34.

A. At-Home Separation of Samples Was Routine

Exact argues that a POSA would not have been motivated to separate a sample into two containers because “a POSA would have pursued the less complex and more patient-acceptable approach of using a single stabilizing buffer (such as Tris-EDTA) that also preserves blood protein.” POR 24. Exact's argument fails for many reasons.

First, Exact's premise that a POSA would not design assays to include at-home sample separation unless separate buffers were required to stabilize DNA and proteins is incorrect. By the Priority Date, at-home separation was a standard feature of commercial iFOBT, which required patients to separate a small portion of the fecal specimen for shipment to a diagnostic laboratory from the rest of the specimen, which was discarded. EX1004; EX1086 ¶¶66-67; EX1089 135:13-20. Such iFOBT included at-home separation even though they only required one stabilizing buffer. EX1086 ¶¶66-67. This standard workflow would be maintained when iFOBT were used in combination with fecal DNA tests. *Id.*

Moreover, as Exact's expert acknowledges, a POSA would be motivated to use **existing** buffers that had already been proven to stabilize specific biomarker

types, rather than develop a new buffer optimized to stabilize multiple biomarker types. EX1089 68:17-70:2; EX1086 ¶68. There is no dispute that buffers optimized to separately preserve DNA or proteins were well known in the art by the Priority Date; they are disclosed in Itzkowitz and Vilkin, respectively. EX1002 ¶¶74-82; EX1086 ¶68. In contrast, neither Exact nor its expert identifies a then-available buffer that had been demonstrated to preserve both fecal nucleic acid and protein, let alone one that had been optimized for such a purpose. EX1086 ¶¶68-73.

Exact's only support for its contention that a Tris-EDTA based DNA stabilizing buffer would also be suitable to stabilize fecal hemoglobin is a 1991 Japanese patent application that merely includes Tris and EDTA in laundry lists of possible buffer components, but never tests a Tris-EDTA buffer for either blood protein **or** DNA stabilization. EX2049 ¶¶10-11; EX1089 149:4-6, 161:4-8; EX1086 ¶71. Likewise, Exact's contention that RNAlater could be used to stabilize fecal proteins as well as nucleic acids ignores that it was marketed to "stabilize both RNA and protein ***within tissues or cells,***" whereas fecal hemoglobin is extracellular. EX2048, emphasis added; EX1089 161:17-23; EX1086 ¶72. Exact's expert was unaware of any experimental evidence showing that RNAlater preserves hemoglobin in feces. EX1089 161:17-23. Even today, Exact uses

separate DNA and hemoglobin stabilizing buffers in its commercial test, despite the purported advantages of using a single buffer. EX1076.

Finally, partitioning a fecal sample to separately preserve each portion in different stabilizing buffers was a well-established strategy decades before the Priority Date. EX1002 ¶¶74-82; EX1086 ¶74; EX1010 9-13, 56. Exact's hypothetical single buffer, which has not been shown to have existed at the Priority Date, would not have led a POSA to reject implementing this conventional strategy using already available biomarker-optimized buffers. EX1086 ¶¶65-74.

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

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

Exact's argument that Lenhard "does not motivate pursuing a combined test for both nucleic acid and fecal occult blood" is contrary to Lenhard's express disclosure and contradicts the knowledge in the art. POR 28. As acknowledged in the FWD, "Lenhard unquestionably teaches combined blood and nucleic acid, dual-portioned, fecal screening test for CRCs, but it is by no means the only incidence or suggestion of such in the prior art of record." EX1087 47.

Lenhard expressly discloses a combined assay that includes a test for fecal DNA and an FOBT, and reports that the combined assay exhibits increased sensitivity compared to either test alone. EX1004 147. It is indisputable that having

a higher sensitivity for CRC is a desirable feature for a fecal CRC diagnostic assay. EX1002 ¶29; EX1086 ¶¶90. A test with a higher sensitivity will produce fewer false negative results, meaning fewer patients with cancer will go untreated and potentially die. *Id.* 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.” EX1077 1295. Lenhard’s positive statements concerning increased sensitivity and its supporting data “are sufficient to provide a ‘rational underpinning’ to combine the gFOBT and DNA test.” ID 18.

The misleading statistical calculations made by Exact’s expert (and found nowhere in Lenhard) do not indicate that “the real sensitivity of the combined results could be lower than that of HIC1 alone,” as Exact contends. POR 11 EX1086 ¶¶22-24, 33-36. As admitted by Exact’s expert, when two tests that each detect incidents of cancer missed by the other are combined, as in Lenhard, “***the sensitivity would be and can only be higher***” than either test alone. EX1089 90:2-11, emphasis added; EX1086 ¶¶22-24. Consistently, the authors of Lenhard conclude “[t]he combination of both assays resulted in increased detection rates for CRCs.” EX1004 147.

Exact’s argument citing Lenard’s statement concerning the possible “[c]ombination of HIC1 with a few additional sensitive and specific methylation

markers” is unavailing, even if the combination would further improve Lenhard’s test. POR 29. 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 19, 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. EX1086 ¶¶46, 86-88. Indeed, a POSA would understand that a logical starting point for further improvement of Lenhard’s assay would be this combined assay with its considerably higher sensitivity compared to the 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 disparage Lenhard’s combined assay. POR 30. Rather, the relatively high sensitivities reported in Vilkin and Itzkowitz would motivate a POSA to incorporate strategies used in these references to further improve the sensitivity of Lenhard’s assay. EX1086 ¶¶82-84. *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 incorporating a DNA stabilization buffer contributed to an increase in sensitivity would motivate a POSA to apply a similar strategy to Lenhard’s assay. EX1086 ¶¶82-84; 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. EX1086 ¶¶82-85; EX1005 2519.

The fact that Lenhard’s combined assay did not increase sensitivity for advanced adenomas does not negate Lenhard’s express motivation to combine tests. POR 29. 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. EX1086 ¶¶26-29, 79-81. As of the Priority Date, cancer detection was of primary importance in fecal CRC assays. *Id*; EX1013 1752-1753. Indeed, in Itzkowitz, Exact assesses performance of different versions of its fecal DNA assay based solely on their ability to detect CRC. EX1006. A POSA would not discredit the improved sensitivity for CRC provided by Lenhard’s combined assay because it maintained only equal sensitivity for adenomas. EX1086 ¶¶26-29, 79-81.

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

Exact’s argument that a POSA would not have been motivated to combine classes of markers because of the slightly lower specificity of Lenhard’s combined

assay ignores the importance a POSA places on sensitivity and the POSA's corresponding willingness to sacrifice some specificity to improve sensitivity. POR 32; EX1086 ¶¶30-32, 89-93. Indeed, whereas Lenhard repeatedly extols the improved sensitivity of the combined test, Lenhard never mentions its reduced specificity.

A POSA's willingness to accept reduced specificity for improved sensitivity is illustrated, for example, in Itzkowitz, which describes the development of a "second generation" of Exact's fecal DNA test. EX1006 111; EX1086 ¶90. Whereas Exact's "first generation" test had a specificity of **94%**, the specificity of its "second generation" test was only **82%**. *Id.* Despite its reduced 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." EX1077 1295.

The specificity exhibited by Lenhard's combined test would be acceptable to a POSA. EX1086 ¶91. 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. The specificity for CRC of Exact's ultimate, FDA-approved

Cologuard product, at only 86.6%, is no higher than that of Lenhard's combined test. EX1077 1287.

A POSA also would have recognized that the slight reduction in specificity exhibited by Lenhard's combined assay was almost entirely a product of its gFOBT component. EX1004 147; EX1086 ¶¶92. 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. EX1086 ¶¶92.

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

Exact misreads Vilkin as "require[ing] both home-refrigeration and testing of three separately-collected samples," which Exact contends "would have dissuaded combining the iFOBT of Vilkin with any other form of test." POR 34. Here, Exact focuses on minor details specific to the particular sample collection protocol Vilkin used when testing reproducibility its iFOBT in a research study, while ignoring Vilkin's broader teachings concerning sample collection frequencies used in practice. EX1086 ¶¶47-51, 94-99.

Vilkin explains that different countries use different sample collection frequencies when screening CRC in average risk populations. EX1005 2524. In no country Vilkin identifies were samples collected on three consecutive days. *Id.* Vilkin further explains that "three **annual** fecal tests" would be collected when

testing high-risk populations. *Id.* (emphasis added). Vilkin recognized that a different testing frequency might be appropriate for average-risk populations. *Id.* Exact's expert acknowledged that Vilkin does not require collection of three consecutive daily samples when its assay is used in clinical practice. EX1088 141:4-142:19.

At-home refrigeration of stool samples is only necessary when a patient collects consecutive daily samples. In the absence of multiple-day sample collection, a patient can ship the sample immediately after collection. EX1086 ¶¶97. Because multiple-day collection is not required by Vilkin, in 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 most, a minor inconvenience readily accepted by a patient in exchange for a better assay. *Id.*

Exact relies on a 1999 publication (EX2047), to argue that "iFOBT testing alone routinely required sample collection on two consecutive days." POR 34. Notably, this publication uses a different iFOBT from Vilkin. EX2047 229. In contrast, by the Priority Date, the OC Sensor iFOBT of Vilkin was being used to test single samples without requiring at-home refrigeration. EX1086 ¶¶96-97;

EX1090 83 (“The OC-Sensor test consisted of a single sampling tube... If the test could not be returned immediately, storage in a refrigerator was advised.”).

Moreover, whether Vilkin requires sample refrigeration before shipment to the laboratory is ancillary to the obviousness of the Challenged Claims, which exclude **freezing**, not refrigeration. Vilkin experimentally demonstrates that freezing of fecal samples is not required for sample stability. EX1005.

The evidence is overwhelming that a POSA would recognize the iFOBT of Vilkin as a superior alternative to the gFOBT of Lenhard. Petition 20-21; EX1086 ¶¶98-99. Indeed, Vilkin expressly teaches numerous advantages of iFOBT over gFOBT. EX1005 2519, 2524.

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

Exact’s contention that “[a] POSA seeking to improve CRC screening would not have been motivated to pursue an approach that would increase both cost and complexity” also fails. POR 35. Exact’s argument ignores that modifying the assay disclosed in Lenhard to incorporate the sample collection and stabilization process of Itzkowitz and replace 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 improvements. EX1086 ¶¶100-102.

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 Lenhard's assay facilitates at-home sample collection, making the process more convenient for the patient. EX1086 ¶102. Likewise, the sample collection process used in iFOBT, such as the one in Vilkin, was known to be more convenient for patients than the collection process used with gFOBT, like the one in Lenhard. *Id.* A 2007 review article explains, for example, 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." EX1020 29. A POSA would be motivated to make the Lenhard assay more convenient for patients by incorporating the Itzkowitz and Vilkin sample collection processes.

Regardless, as of the Priority Date, a POSA would have been willing to accept a more complex and expensive CRC diagnostic assay if it meant better detection of CRC. EX1086 ¶¶103-104. Adding a routine, commercially available, and inexpensive iFOBT to a fecal DNA test only marginally increases cost and complexity. EX1020 31 (explaining that iFOBT cost "up to USD 30", whereas fecal DNA tests cost "in excess of USD 400"). Indeed, Levin's 2008 CRC

screening guidelines note 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.

II. GROUND III: SHUBER AND VILKIN

Exact similarly attacks the Ground III references individually rather than in combination to assert that Shuber and Vilkin do not render obvious the Challenged Claims. POR 37-38. Here, again, the Board has considered and rejected Exact’s arguments in the context of narrower claims and held those claims obvious. EX1087 57-69.

As acknowledged in the FWD, a POSA 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 38-40; EX1087 67 (“The ordinary skilled artisan would have good reason to combine the methods of Shuber and Vilkin to achieve a better CRC screening method than either method provided individually.”). When such a combined test was performed, the result would be the method of the challenged claims. Petition 40-41; EX1087 67-68.

A. 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 38-40. Exact's attempt to explain-away these extensive teachings is unavailing.

Exact acknowledges Nishikawa's conclusion 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 40 (emphasis added). Exact attempts to wave-away this explicit teaching because "seven years passed between Nishikawa and the invention of the '746 patent." *Id.* 40-41. 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. EX1086 ¶111.

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 41) 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 baffling, 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. EX1086 ¶¶112-113.

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. EX1013 1578; EX1086 ¶114. 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%.” *Id. 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. EX1008 14:1-16; POR 43. A POSA would recognize these hypothetical adenoma sensitivities as unsupported by any data and overly optimistic given the state of the art. EX1086 ¶116.

B. Vilkin Does Not Require Multiple Samples or Refrigeration

Exact once again misreads Vilkin to argue that a POSA would be dissuaded from combining Vilkin with a fecal DNA assay. POR 44. 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 dissuade a POSA from combining its iFOBT with a DNA test of Shuber to arrive at the method set forth in the Challenged Claims. EX1086 ¶118.

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

Exact again argues that a POSA would not have been motivated to choose a path that would increase cost and complexity. POR 44-45. Exact's argument fails because, (1) as explained in section II(A), 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. EX1086 ¶117.

III. GROUND VI: INBAR SHUBER AND VILKIN

Exact argues that a POSA would not have been motivated to use the Inbar system to collect samples for performance of the assays disclosed in Shuber and Vilkin because “nucleic acids and blood protein do not require different preservation media.” POR 46. As explained in section I(A), neither Exact nor its expert identifies a then-available buffer that had been demonstrated to preserve both fecal DNA and fecal blood proteins, yet alone one optimized to preserve both types of biomarkers. A POSA therefore would be motivated to use the Inbar system to separately preserve portions of a fecal sample in existing buffers that had been proven to separately preserve DNA or blood proteins. EX1002 ¶¶74-82; EX1086 119.

IV. GROUNDS II, IV and VII

With respect to claims 12 and 13, which relate to RNA analysis, Exact argues that “[p]etitioner shows neither motivation to add Kanaoka to the various combinations nor reasonable expectation of success in doing so.” POR 47. Here, again, the Board has already considered the validity of narrower claims and concluded “that claims 12 and 13 are unpatentable as obvious over this same prior

art combination adding Kanaoka's disclosed technique of using RNA as a CRC biomarker." EX1087 57, 69. In particular, the Board noted that "COX-2 RNA would have been attractive to the ordinary skilled artisan because Kanaoka discloses its process works (high sensitivity and specificity) and also that COX-2 was effectively combined with iFOBT in a complementary way (each detects certain CRC that the other does not)." EX1087 56.¹

A. A POSA Would Be Motivated to Test for RNA

Exact once again considers the references individually rather than in combination to argue that, because Kanaoka describes stabilizing RNA in a fecal sample by freezing, a POSA "would not have been motivated to incorporate the COX-2 RNA testing of Kanaoka in a method of processing a freshly collected fecal sample that excludes freezing." POR 47-48. When considered collectively, however, the cited references teach that use of a nucleic acid stabilizing buffer to preserve fecal samples was a known alternative to freezing them that facilitated convenient at-home sample collection. EX1086 ¶¶120-122; EX1006; EX1008. As acknowledged by Exact's expert, buffers for stabilizing RNA were known in the art and, indeed, were commercially available. EX1089 42:6-11; EX2048; EX1024.

¹ Cologuard does not detect RNA biomarkers and Exact does not assert secondary considerations for claims 12 and 13.

B. A POSA Would Have Had a Reasonable Expectation of Successfully Using an RNA Stabilizing Buffer

Exact argues that “[a] POSA would not have had a reasonable expectation of combining Kanaoka in a home-collection process that excludes freezing” because “Kanaoka stabilizes RNA in the fecal sample by immediate freezing.” POR 49.

To begin, Exact ignores that obviousness merely requires that the expectation of success be reasonable, not absolute. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). In any case, Nechvetal’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” demonstrates that by the Priority Date a POSA would have reasonably expected to be successful using a buffer to stabilize fecal RNA. EX1024 131; EX1086 ¶¶123-124. Indeed, Nechvetal states that the RNeasy buffer was “chosen for [its] likely suitability for preserving RNA.” EX1024 125. RNeasy is specifically advertised as an alternative to the liquid nitrogen-based freezing strategy used in Kanaoka. EX2048 (“No need to freeze sample in liquid nitrogen.”). Tellingly, Exact’s expert acknowledged that the ’746 patent itself does not disclose any buffers for stabilizing RNA, so a POSA would use prior art buffers to practice claims 12 and 13. EX1089 37:22-38:1, 40:8-42:11. Exact’s expert also acknowledged that he did

not provide any experimental evidence contradicting Nechvetal's assertion regarding its RNA stabilizing buffer. EX1089 166:24-167:14.

C. A POSA Would Have Used Separate Optimized Buffers to Preserve Fecal RNA and Blood Protein

Exact further argues that if a POSA used RNeasy "there would have been no reason to separate the sample to use different buffers for RNA and blood protein." POR 51. As explained in section I(A), Exact's argument ignores that at-home fecal separation was standard in iFOBT, even when no second stabilizing buffer was required. Moreover, Exact's contention that RNeasy could be used to stabilize fecal proteins overlooks that it is marketed to "stabilize both RNA and protein *within tissues or cells*," whereas fecal hemoglobin is extracellular. EX2048, emphasis added; EX1089 161:21-23; EX1086 ¶125. Exact's expert testified that he was not aware of any experimental evidence showing that RNeasy preserves hemoglobin in feces. EX1089 161:17-20.

V. 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 Board has already held that Exact failed to demonstrate nexus between Cologuard and narrower claims in IPR2024-00459. EX1087 23-34. Exact's asserted secondary considerations should be accorded 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.* “[T]o meet the coextensiveness requirement, what we do require is that the patentee demonstrate that the ***product is essentially the claimed invention.***” *Id.*, at 1374, emphasis added. Exact does not show that Cologuard is coextensive and as a result, Exact is not entitled to a presumption of nexus. Indeed, the POR fails to cite, let alone apply, *Fox Factory*.

Cologuard clearly is not coextensive with the claimed method. EX1086 ¶¶129-132. Cologuard has a multitude of features, many of which Exact admits are critical to the success of their product. EX1002 ¶¶335-347; EX1086 ¶¶130-131; EX1077 1295; EX1079. This is confirmed by Exact's prosecution of dozens of patents covering Cologuard that are unrelated to the '746 patent. EX1002 ¶345; EX1026. Indeed, Exact argued to the Patent Office that Cologuard's ability to satisfy long felt need and succeed where others had failed was attributable to Cologuard features claimed in a later, unrelated patent (Pat. No. 9,163,278).

EX1002 ¶346; EX1029 9. *See Fox Factory*, at 1366 (“A patent claim is not coextensive with a product that includes a ‘critical’ unclaimed feature that is claimed by a different patent and that materially impacts the product’s functionality.”).

B. Cologuard’s Purported Secondary Considerations Are 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 a purported secondary consideration is “a direct result of unique characteristics of the claimed invention.” *Fox Factory, Inc.*, 944 F.3d at 1373-74. Exact has failed to meet its burden. EX1086 ¶¶133-144.

Exact argues that the “Cologuard 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 ’746 patent is essential to both.” POR 57. Exact’s only support for this contention is a citation to a single paragraph in its expert’s declaration that merely parrots 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). None of the Challenged

Claims contains any limitation requiring any level of diagnostic accuracy or uptake.

Exact offers no evidence that Cologuard's diagnostic accuracy is a product of the claimed fecal processing method, as opposed to Cologuard's many other components covered by the dozens of unrelated patents referenced 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. EX1086 ¶135. Indeed, in its Cologuard clinical trial publication Exact stated that Cologuard's diagnostic accuracy ***“may be attributed to the DNA marker and algorithm components of the test.”*** EX1077 1295 (emphasis added). Exact itself attributes the diagnostic accuracy of Cologuard to features unrelated to the Challenged Claims.

As explained in the Petition, during its prosecution of an unrelated patent, Exact 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.” Petition 68-69, quoting EX1029 9. See EX1087 29-30. In the POR, Exact misleadingly argues that these statements only “address the long-felt need for a method of ‘isolat[ing] DNA from stool samples’ and the success of Cologuard's methods for extracting marker DNA to satisfy that

need.” POR 55-56. On the contrary, Exact’s arguments to the Office identified the long-felt need as “***a way to screen for colorectal cancers based on DNA stool testing.***” EX1029 9 (emphasis added). It then stated that the pending claims of its unrelated patent “addressed this long-felt need and succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.” *Id.*

Exact’s POR also disregards that the success of Cologuard may have been significantly influenced by the exclusivity provided by the dozens of unrelated patents it identifies as covering Cologuard. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (“Because market entry by 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 claimed sample processing method, as opposed to these unrelated inventions.

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. EX2019 ¶13. The significance of Exact’s marketing efforts is confirmed by an article published in *Forbes* in which Exact’s CEO describes targeted direct-to-consumer TV commercials in five markets and compares sales in those markets to sales in five

control markets. EX1091 6. In markets where Cologuard was highly advertised, sales grew significantly faster than in control markets, and after 9 weeks they were up 100% compared to control. *Id.* Exact's own market study thus confirms that the product's improved commercial success cannot be attributed to the claimed sample collection method.

Finally, Exact's assertion of "copying" as a secondary consideration of nonobviousness fails. Establishing "copying by others" requires more than simply evidence of infringement by a third-party product. *In re Celorio Garrido*, 646 F. App'x 942, 944 (Fed. Cir. 2016). Exact offers no evidence that Geneoscopy undertook copying efforts 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 they cannot overcome Geneoscopy's strong *prima facie* showing that the claims are obvious.

Dated: August 22, 2025

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, this Petitioner’s Reply contains 5,558 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 August 22, 2025 via the delivery method indicated to the attorneys of record for the Patent Owner as follows:

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