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

PATENT OWNER'S SUR-REPLY

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Petitioner's Reply does not cure Petitioner's errors and failures of proof.

Petitioner refers to the Final Written Decision in IPR2024-00459 (EX1087, "FWD") and incorrectly asserts that Exact Sciences offers "nothing new in its POR." Yet the POR provides evidence that the very same buffer Petitioner contends was "optimized" for preserving DNA in stool could also have been used to stabilize hemoglobin in stool, thus negating any purported motivation to require user separation of a stool sample. *See* Reply at 1, 4; POR at 22-23. The POR also describes in more detail why dependent claims 12 and 13 are not obvious. *See* POR at 47-51.

Petitioner makes contradictory arguments in response to this evidence. In arguing that a POSA would be motivated to require user separation of the fecal sample, Petitioner relies on a lack of data demonstrating that a single buffer would preserve both fecal nucleic acid and protein. Reply at 4. However, when arguing that there was reasonable expectation of successfully combining the specific frozen-sample COX-RNA test of Kanaoka into the non-frozen, stabilizing buffer method of claims 12 and 13, Petitioner relies entirely on speculation about "likely suitability," without data. Reply at 20. Petitioner cannot have it both ways.

Petitioner also fails to give adequate, if any, weight to the undesirability of user interaction with the stool sample. Ultimately, "[t]he best test is the one that gets done." EX2023 at 1; *see also* EX2057 at 42:11-19. Petitioner's expert focused on

diagnostic results without considering whether requiring the user to separate the sample would reduce user adherence because of aversion. EX2057 at 45:12-18; *see also id* at 23:18-24:6; 40:19-42:11; 55:6-12. To the extent Petitioner addresses the disadvantages of the asserted combinations, Petitioner considers each disadvantage individually rather than weighing all of the disadvantages together against Petitioner's sole purported motivation – the potential (based on limited data) for some increase in sensitivity for CRC.

The prior art considered as a whole weighs heavily against motivation to arrive at the claimed invention. Non-obviousness is further confirmed by objective indicia.

I. PETITIONER FAILS TO SHOW MOTIVATION TO REQUIRE THE SPECIFIC ELEMENTS OF THE CLAIMED INVENTION

A. A POSA Would Have Avoided At-Home Sample Separation

Petitioner does not argue, and could not credibly argue, that at-home user interaction with stool is desirable. Reply at 3-4; EX1086 ¶¶44-49. The fact that at-home separation was *feasible* is not motivation to require that undesirable step. *See Winner Intern. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 (Fed. Cir. 2000) ("Trade-offs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter.").

A POSA in 2009 would have been motivated to minimize at-home interaction with the stool sample. *See,* EX2044 ¶128; EX1005 at 2524. Petitioner contends that a POSA would have been motivated to use "**existing** buffers" that had already been proven to stabilize specific biomarkers. Olson and Shuber describe an "optimized," existing "DNA-stabilizing buffer" containing Tris, EDTA, and NaC1. EX1086 ¶86. The POSA would have understood that a buffer using these common components would also prevent denaturation or degradation of blood protein in stool. EX2044 ¶121; *see also* EX2049 at [Abstract][09]-[011], EX1041 at 5:35-36.

For example, the Tsuji Japanese Patent Application from 1991 ("Tsuji") concerned "preventing denaturation of human hemoglobin present in a test liquid containing feces when left unattended." EX2049 at [Abstract]; EX2044 ¶123. Tsuji discloses liquids for dissolving feces containing human hemoglobin, including Tris-HCl buffer. EX2049 at [0010]; EX2044 ¶123. Tsuji describes adding EDTA to the buffer solution "to suppress the denaturation of human hemoglobin." EX2049 at [0010]; EX2044 ¶123. Tsuji further states that it "is preferable to add salt to the buffer solution at a concentration close to that of physiological salt." EX2049 at [0010]. Tsuji therefore teaches that buffers of Tris, EDTA, and NaCl, as taught in Olson and Shuber, would also prevent denaturation of human hemoglobin in feces. EX2049; EX2044 ¶123. Further, the 1993 Grow patent titled "Fecal Sample Immunoassay Method Testing for Hemoglobin," states "[a]ny conventional

buffering agents can be used to prepare the test buffer solution…" EX1041 at 5:35-36.

Petitioner's expert asserts only that he is "unaware" of a buffer "that had been tested" for stabilizing both analytes. EX1086 ¶70. He does not contend that the same buffer would not have worked. *Id.* ¶¶68-71; EX2057 at 14:16-20. He also offers no evidence showing the components of the Vilkin "Hb stabilizing buffer" that Petitioner argues differed from the Olson/Shuber buffers. Reply at 3-4; EX1002 ¶¶74-75; EX1086 ¶68; EX1005.

Petitioner notes that Exact Sciences' Cologuard product still "uses separate DNA and hemoglobin stabilizing buffers in its commercial test." Reply at 4-5. To the extent current product designs are indicative of whether a single buffer could have been used in 2009, Petitioner recently announced a single-container, single-buffer redesign of its Colosense product. EX2057 at 30:4-31:18. Despite awareness of Petitioner's redesign and Petitioner's messaging which discussed eliminating "the most burdensome aspects" "the most confusing and undesirable step" of at-home sample collection "to drive higher [patient] adherence," Dr. Whitney ignored it in his declaration. EX2057 at 30:4-31:18; 33:8-12; 34:6-14; 38:16-42:19; EX1086.

A POSA in 2009 would have been motivated to pursue the more user-friendly sample collection of Itzkowitz with a single buffer, such as the Olson Tris/EDTA/NaCl buffer, with the understanding that the same buffer would also

prevent denaturation or degradation of blood protein. *See* EX2044 ¶¶119-128; *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004)(prior art as a whole must suggest the desirability of the combination). The fact that commercially available buffers such as RNAlater were sold to stabilize both nucleic acid and proteins further supports that the POSA would have been motivated to use a single buffer to avoid requiring undesirable at-home sample separation. EX2044 ¶¶124, 193.

B. A POSA Would Have Been Discouraged from Combining Lenhard, Vilkin, and Itzkowitz

In assessing whether a POSA would have been motivated to combine references, "benefits, *both lost and gained*, should be weighed against one another." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Even where evidence "may not rise to the level of teaching away," it may still demonstrate lack of motivation to combine where "the same reference suggests a reason to combine, but also suggests reasons that a skilled artisan would be discouraged from pursuing such a combination." *Arctic Cat, Inc. v. Bombadier Recreational Products, Inc.,* 876 F.3d 1350, 1363 (Fed. Cir. 2017).

A POSA seeking to improve CRC screening tests would have considered that "[a]n ideal screening test must be non-invasive, acceptable to patients, simple, have high sensitivity and specificity, inexpensive, cost-effective, easy to implement across a large population and should be effective in reducing morbidity and mortality

from CRC in the screened population." EX1023 at 146. Petitioner's references emphasize the importance of, *inter alia*, early detection through detection of advanced adenomas, specificity, simplicity, cost, and patient acceptance. *See, e.g.,* EX1004-EX1006, EX1013.

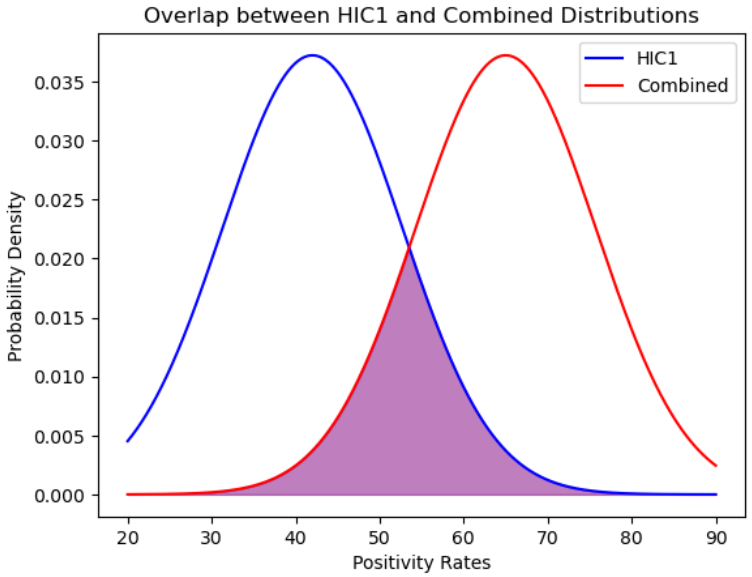
Petitioner relies on the potential for increased sensitivity for CRC. Reply at 5. A POSA would have assessed Lenhard's reported data, including the reported confidence intervals and whether any differences were statistically significant. EX2044 ¶¶64-69. As shown in Table 4 of Lenhard, and as illustrated by Dr. Backman, the confidence intervals for "All cancers" for HIC1 and the "Combined" data in Lenhard substantially overlap.

Table 4. Positivity Rates of the Fecal DNA Assay, FOBT, and Combination of the Tests

	HIC1		FOBT		Combined	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
All cancers	11/26 (42)	23%–63%	9/26 (35)	17%–56%	17/26 (65)	44%–83%
Localized cancers	4/6 (67)	22%–96%	2/6 (33)	4%–77%	6/6 (100)	12%–188%[a]
Advanced cancers	5/20 (25)	9%–49%	7/20 (35)	15%–59%	11/20 (55)	32%–77%
Rectum and sigmoid colon	5/13 (39)	14%–68%	5/13 (39)	14%–68%	9/13 (69)	39%–91%
From descending colon to cecum	6/13 (46)	19%–75%	4/13 (31)	14%–68%	8/13 (62)	39%–91%
Asymptomatic cases	4/10 (40)	12%–74%	3/10 (30)	7%–65%	6/10 (60)	26%–88%
Symptomatic cases	7/16 (44)	20%–70%	6/16 (38)	15%–65%	11/16 (69)	41%–89%
Adenomas	4/13 (31)	9%–61%	1/13 (8)	.2%–36%	4/13 (31)	9%–61%

[a]Estimated by normal approximation of Poisson distribution.

EX1004 (Table 4); EX2044 ¶¶64-66.



EX2044 ¶66. A POSA would have understood from the broad, overlapping confidence intervals that the combined test might not be any more sensitive for CRC than HIC1 alone. EX2044 ¶¶65-69; EX1089 at 90:2-93:21.

Petitioner's arguments concerning Lenhard give the POSA—here a person with a high level of training and skill—little credit. A POSA would consider that the test population in Lenhard is not representative of the screening population. EX2044 ¶¶63-64. The POSA would know that Lenhard's test group—where roughly one third were diagnosed with CRC—was far different from the roughly one percent prevalence in the average risk population. EX2057 at 72:10-19; 71:3-9; EX1004. Although Dr. Whitney calculated "test accuracy" based on the limited data in Lenhard, he admitted that his calculation is not representative of the clinical population for CRC screening tests, and that his opinion concerning "test accuracy"

was "not intended to extend that to another population that has a very different prevalence in this case." EX1086 ¶40; EX2057 at 67:5-72:13; 75:91-6; 80:3-83:23; 85:24-86:10. A POSA would discount any alleged increase in "test accuracy" accordingly.

Petitioner's argument concerning potential improved sensitivity for CRC is based on limited, not statistically significant data. EX2044 ¶¶64-66. Unlike Petitioner, a POSA would have weighed the limited data against other important characteristics of CRC screening tests: (1) the combined results of gFOBT and HIC1 testing in Lenhard showed no increased sensitivity for advanced adenomas, (2) the combined results of gFOBT and HIC1 testing in Lenhard were less specific than the HIC1 test alone, (3) patient acceptance is important for the success of a screening test, and (4) testing for two classes of markers increases cost and complexity as compared to testing for a single class of markers. EX2044 ¶¶41-42, 70-79, 129-159. When the single factor of speculative potential for increased sensitivity of CRC is weighed against the many disadvantages, a POSA would have been dissuaded from pursuing the claimed invention. *Id*.

1. Lack of Improvement for Detection of Advanced Adenomas Weighed Against Combination

Lenhard establishes that a POSA seeking to develop an improved CRC screening test would have considered sensitivity for advanced adenomas, stating,

inter alia, that "a stool-based screening assay also should detect relevant premalignant lesions (ie, adenoma)." EX1004 at 147.

In trying to minimize the importance of detecting advanced adenomas, Petitioner cites an excerpt that distinguishes between two categories of then-existing screening tests. Reply at 8; EX1013 at 1572-1573. Levin highlights that non-invasive screening tests (versus invasive tests like colonoscopy) had limited ability to detect advanced adenomas thus limited ability to prevent disease. EX1013 at 1572-1573. Levin also states that "[i]t is the strong opinion of this expert panel that *colon cancer prevention* should be the primary goal of CRC screening." EX1013 at 1573. A POSA seeking to improve a non-invasive test would consider and try to address limitations of those tests—including improving detection of advanced adenomas. EX2044 ¶¶32, 79, 131.

2. Reduced Specificity Weighed Against Combination

Lenhard also shows the importance of specificity—repeatedly emphasizing the need for both high sensitivity and specificity. *See* Ex. 1004 at 142, 143, 147, 148; *see also* EX2044 ¶72. Reduced specificity would have weighed against a potential combination of nucleic acid testing and FOBT.

Petitioner's arguments do not consider the references as a whole. Reply at 8-10. For example, contrary to Petitioner's suggestion (Reply at 9), the improvements to the second-generation test discussed in Itzkowitz were not limited to sensitivity,

but also related to ease of use and cost due to use of ***fewer*** markers. Petitioner replaces an important part of the Itzkowitz "Conclusions" with an ellipsis. *Id.* Itzkowitz concludes that "[a]n improved fecal DNA test that ***incorporates only two markers*** shows much higher sensitivity for CRC." *Compare* Reply at 9 *with* EX1006 at 111 (emphasis added). Itzkowitz also states "[t]he new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening." EX1006 at 111; *see also* EX1006 at 117. A POSA would consider all of these aspects in the context of benefits gained and lost.

Petitioner also relies on a quote from Imperiale 2014. Reply at 9, citing EX1077 at 1295.[1] However, unlike Petitioner's arguments, the quoted sentence is not limited to sensitivity for CRC. EX1077 at 1295. In fact, the next sentence discusses sensitivity "for the detection of advanced precancerous lesions." *Id.* As demonstrated by Imperiale 2014, a critical aspect of Cologuard is its sensitivity for detecting advanced adenomas. *See generally* EX1077; *see also* EX1088 at 75:18-79:19; EX2044 ¶¶45, 197. Imperiale 2014 also makes clear that sensitivity is not the only important characteristic, stating "[a]though high sensitivity is the most important attribute of cancer-screening tests, ***specificity is also important***, since it

[1] In addition to failing to support Petitioner's specificity argument, the 2014 statement is not prior art. EX1077.

affects the number of persons who have positive test results…." EX1077 at 1295 (emphasis added).

Petitioner's argument that reduced specificity in Lenhard "would be acceptable to a POSA" incorrectly considers specificity in a vacuum. Reply at 9. As Itzkowitz shows, a POSA would consider multiple factors: simplicity, cost, and whether there was a significant increase in sensitivity. EX1006; EX2044 ¶¶89, 91. Cologuard is not prior art. However, even if it were proper to consider Cologuard, a significant advantage from the Cologuard combination is improved detection of advanced adenomas. EX1077; *see also* EX1088 at 75:18-79:19; EX2044 ¶¶45, 197.

Petitioner also argues that the reduced specificity in Lenhard would have provided additional motivation to "replace Lenhard's gFOBT with Vilkin's more specific iFOBT and thereby increase the specificity of the combined assay." Reply at 10. However, in a later publication concerning the same iFOBT of Vilkin, specificity "for advanced adenomas and cancers was significantly lower compared with the G-FOBT." EX1090[2] at 87.

[2] As discussed below, Exhibit 1090 is new evidence that should not be considered. *See* 77 Fed. Reg. 48,767 ¶I. To the extent that Exhibit 1090 is considered, it undermines Petitioner's arguments.

3. Vilkin's Multiple Samples and Refrigeration Weighed Against Combination

Petitioner argues that Exact Sciences focuses on "minor details" of Vilkin. Reply at 10. The specific testing methodology that resulted in Vilkin's reported test performance is not a "minor" detail. Vilkin tested "three consecutive daily samples," and reported that "[t]he best results were obtained when all three tests were performed and utilized for analysis." EX1005 at 2520, 2522. A POSA, considering Vilkin, would understand that the reported performance of the iFOBT of Vilkin was based on three tests over three consecutive days. EX1005 at 2520; EX 2044 ¶87.

Petitioner tries to undercut Exact Sciences' reliance on a 1999 publication. Reply at 11. That publication, which is cited in Vilkin, taught that collection over two consecutive days "is the most desirable in immunochemical occult blood testing as a means of screening for colorectal cancer." EX2047 at 231; EX2044 ¶149. Faced with this evidence, Petitioner improperly seeks to introduce new evidence that it contends shows that the Vilkin test was being used "to test single samples without requiring at-home refrigeration." Reply at 11. This new evidence should be excluded. *See* 77 Fed. Reg. 48,767 ¶I. Even if it is considered, it does not change that Vilkin's reported performance was based on testing three samples that were collected over three consecutive days and kept in the user's refrigerator, and that the prior art taught collection over two consecutive days. EX1005; EX2044 ¶¶82-83,

149; EX2047 at 231. Even Petitioner's improperly cited new reference advised storing the Vilkin device in the refrigerator if the test "could not be returned immediately." EX1090 at 83.

Petitioner also argues that the claims do not exclude refrigeration. Reply at 11-12. That does not address whether there was a motivation to combine the iFOBT of Vilkin, which described at-home refrigeration of the samples – something that users were reluctant to do, as Vilkin itself reported. EX1005 at 2524.

In weighing disadvantages against potential benefits, a POSA would have considered that Vilkin taught multiple samples per patient and required refrigeration of those samples to arrive at the reported results. These facts would have also weighed against the combination.

4. Added Complexity Both for the User and the Testing Laboratory Weighed Against Combination

Lenhard describes laboratory collection and testing a sample using two separate tests. EX1004. Lenhard does not suggest the claimed at-home collection method, let alone sample separation at home into two separate containers for eventual testing for two different classes of markers. EX1004; EX2044 ¶¶58-50. A POSA considering whether to combine two classes of markers in a test that requires at-home separation of the stool sample would consider, among other factors, added complexity for the user and potential for patient acceptance – particularly as

compared to the more user-friendly collection device of Itzkowitz. EX2044 ¶¶90, 127-128, 152-155; EX1006 at 112, 116. A POSA would also have considered the additional operational and logistical complexity at the laboratory where testing for different classes of markers requires separate equipment, analysis, and workflows. EX2044 ¶155.

The balance of advantages and disadvantages taken together weighs heavily against motivation to combine. On one side, a POSA would have weighed Lenhard's limited data concerning potential for some increased sensitivity for CRC. On the other side, the POSA would have weighed (1) limitations of the data, (2) that the Lenhard combination did not improve sensitivity for advanced adenomas, (3) that the combination would reduce specificity, (4) concerns about patient compliance and ease of use, and (5) increased complexity of testing for more than one class of marker. EX2044 ¶¶129-159. With the disadvantages of a potential combination far outweighing the single, speculative benefit, a POSA seeking to improve non-invasive CRC screening would have been dissuaded from combining Lenhard, Vilkin, and Itzkowitz.

C. A POSA Would Have Been Discouraged from Combining Shuber and Vilkin

Petitioner argues that a POSA would have been motivated to combine Shuber and Vilkin "because combining such assays was an art-recognized strategy for

improving assay sensitivity." Reply at 14. Petitioner refers to the Petition at pages 38-40, where Petitioner addresses the same four references, and relies on essentially the same quotes from those references. Reply at 15-16. Exact Sciences previously addressed Petitioner's select quotations. POR at 40-43.

Nishikawa, Lenhard, and Kutzner do not describe at-home collection or separation of a stool sample. *See generally* EX1011, EX1004, EX1012. Levin is a 2008 joint guideline that discusses various CRC screening options and merely poses an open question of "whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity." EX1013 at 1578.

Petitioner's argument that Nishikawa, Lenhard, Kutzner, and Levin establish an "art-recognized strategy for improving assay sensitivity" (Reply at 14) is belied by both the lack of data and the relative timing. Nishikawa was published in 2002. EX1011. Lenhard and Kutzner were published in 2005. EX1004, EX1012. Levin makes clear that whether this approach "would improve sensitivity without adversely affecting specificity" was an open question several years later, in 2008. EX1013 at 1578. So notwithstanding the purported "art-recognized strategy," Petitioner identifies no one who pursued that strategy for an at-home test before the patented invention.

Like its Lenhard combination, Petitioner's argument concerning motivation to combine Shuber with Vilkin rests on a supposed strategy to improve assay sensitivity. Reply at 15-17. Petitioner's declarant testified that his opinion "is that there have been sufficient evidence provided in prior art ***to suggest*** that combinations of biomarkers ***could*** lead to increased detectability of cancers, and therefore, would provide for ***some probability*** of success in being able to demonstrate that." EX2020 at 152:7-17. Petitioner does not argue that a POSA would have had a reasonable expectation that combining iFOBT and nucleic acid testing would result in an ***improved assay*** when early detection, specificity, ease of use, patient acceptability, cost, and complexity are all also considered.

As discussed above, Petitioner incorrectly minimizes the disadvantages of Vilkin. Petitioner has not shown that a POSA would have been motivated by the prior art at the time to select only specific aspects of Vilkin to combine with select aspects of Shuber to arrive at the claimed invention. *See Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 886-87 (Fed. Cir. 2024).

Finally, Petitioner's argument concerning a POSA's purported willingness to accept higher cost and complexity "for better CRC detection" are unsupported and fail to properly balance the limited, speculative, potential gain against known disadvantages for the same reasons discussed above concerning the proposed Lenhard, Vilkin, and Itzkowitz combination.

D. A POSA Would Have Been Discouraged from Combining Shuber, Vilkin, and Inbar

Petitioner's proposed combination of Shuber, Vilkin, and Inbar fails to render the claims obvious for the same reasons that the Shuber and Vilkin combination fails.

Petitioner also has not shown that a POSA would have been motivated "to use the Inbar system to separately preserve portions of the fecal sample in existing buffers," (Reply at 18) particularly where Petitioner has no evidence concerning the components of the Vilkin buffer, where the Shuber buffer could also have been used to also preserve hemoglobin, and where the "Inbar system" was not a convenient direct-defecation device. *See* EX1002 ¶¶139-142; EX1009.

II. A POSA WOULD NOT HAVE BEEN MOTIVATED TO ADD KANAOKA TO ANY COMBINATION, AND WOULD HAVE HAD NO REASONABLE EXPECTATION OF SUCCESS IN DOING SO

In its attempt to rebut Exact Sciences' argument that a POSA would not have been motivated to require at-home user to separate the stool sample into two containers, Petitioner asserts that there is insufficient data demonstrating the effectiveness of known buffers for preserving both analytes. Reply at 3-4. At the same time, Petitioner relies entirely on two partially-quoted statements from Nechvatal to argue that a POSA would have had a reasonable expectation of combining the frozen-sample COX-2 RNA test of Kanaoka in the claimed method

of processing a freshly collected fecal sample without freezing. Reply at 20. Nechvatal reports no data concerning preservation of RNA in stool. *See generally* EX1024; EX2044 ¶¶188, 191. Nechvatal primarily tests bacterial DNA and contains only limited data concerning preservation of human DNA in stool. EX2044 ¶¶188-190; EX1024 at 130; Fig. 5. Petitioner offers no evidence that Nechvatal's limited data concerning preservation of human DNA would provide a reasonable expectation of combining the COX-2 RNA of Kanaoka in the method of claim 12 which requires sufficient preservation to be able to measure "an amount of RNA expressed from the human gene." *See* POR at 36, Reply at 20. The limited DNA-related data, and the lack of any RNA-related data, in Nechvatal does not support a reasonable expectation of success in incorporating the COX-2 RNA of Kanaoka in to arrive at the methods of claims 12 and 13. EX2044 ¶¶188-190. *See also Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd*., 923 F.3d 1051, 1061 (Fed. Cir. 2019) (no reasonable expectation of success for cancer treatment without supporting data); *Eli Lilly and Co. v. Teva Pharma. Intn'l GmbH*, 8 F.4th 1331, 1348 (Fed. Cir. 2021) (it is "at all times" Petitioner's burden to show reasonable expectation of success).

In related litigation, Petitioner's expert, Dr. Whitney, opined that "[u]se of RNA as a biomarker is challenging because RNA is much less stable than DNA." EX2053 18:4-19; EX2052 ¶32. He further opined that "[d]ifferent stabilization buffers are required for DNA and RNA." EX2053 19:15-20:8; EX2052 ¶¶51-55. He

also opined that "RNA stabilization buffers need to be specifically formulated to address the unique challenges posed by RNA fragility and susceptibility to degradation by RNAses, and thus differ in composition from DNA stabilizing buffers." EX2053 22:5-20; EX2052 ¶55. In addition, Dr. Whitney's opinions concerning the use of two buffers (discussed above) contradict his opinion that Nechvatal is sufficient to support a reasonable expectation that the COX-2 RNA of Kanaoka could have been preserved in a buffer without freezing. *See, e.g.,* EX1086 ¶68; EX1002 ¶223; *see also* EX2057 at 15:21-16:10; 17:14-19 (testifying that it was "imperative" that there be some data concerning a buffer's ability to stabilize the analyte of interest); *see also* 18:12-19:18.

Petitioner tries to switch the burden to Exact Sciences, asserting that Dr. Backman "did not provide any experimental evidence contradicting Nechvetal's [sic] assertion regarding its RNA stabilizing buffer." Reply at 20-21. However, it is Petitioner's burden to show a reasonable expectation of success. The speculative statements from Nechvatal and the contradictory opinions from Petitioner's expert do not meet that burden. *See Interactive Comm's Intn'l, Inc. v. BlackHawk Network Inc.*, IPR2024-00465 Paper 39 (Director PTAB Decision, Oct. 1, 2025) (reversing final written decision and terminating proceeding where Board finding rested on contradictory expert testimony); *Finesse Wireless LLC v. AT&T Mobility LLC*, No. 2024-1039, 2025 WL 2713518, at *4 (Fed. Cir. Sept. 24, 2025) ("When the party

with the burden of proof, . . .rests its case on an expert's self-contradictory testimony, we may conclude the evidence is insufficient to satisfy that standard.")(citation omitted).

III. OBJECTIVE INDICIA SEPARATELY DEFEAT OBVIOUSNESS

"The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler*, Co., 829 F.3d 1317, 1328 (Fed. Cir. 2016).

A. Clear Nexus Exists Between the Invention of at Least Claim 3 and Cologuard

Nexus is presumed "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.'" *Quanergy Sys. Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022)(citations omitted). "The coextensive requirement does not require a patentee to prove perfect correspondence between the product and a patent claim." *Id.* (citation omitted). "Rather, it requires the patentee to demonstrate that 'the product is essentially the claimed invention.'" *Id.* at 1418. Whether the presumption applies "turns on the nature of the claims and the specific facts." *Teva Pharms. Intn'l GmbH v. Eli Lilly and Company*, 8 F.4th 1349, 1362 (Fed. Cir. 2021). Here Cologuard is essentially the invention of at least claim 3 of the '746 patent. EX2044 ¶¶99-213. As Dr. Backman explained, use of

Cologuard includes, *inter alia*, convenient at-home collection; at-home separation of the sample into two separate containers, each containing a buffer; extracting nucleic acid from one portion of the sample; testing the extracted nucleic acid; and testing the second portion of the sample for blood protein. *Id.*

Petitioner does not dispute that every limitation of claim 3 is found in the method of using Cologuard. *See* Reply at 22. Accordingly, there is unrebutted evidence that the commercial product is the invention disclosed and claimed in the patent, and nexus should be presumed. *Polaris Indus., Inc. v. Artic Cat Inc.,* 882 F.3d 1056, 1073 (Fed. Cir. 2018).

The '746 patent claims, and is coextensive with, the overall Cologuard workflow. Petitioner incorrectly contends that Exact Sciences is not entitled to the presumption of nexus because Cologuard "has a multitude of features" and Exact Sciences has identified numerous patents that cover some aspect of Cologuard. Reply at 22-23. Relying on Petitioner's characterizations, the other patents each concern only a component of Cologuard, and Petitioner's expert offered no opinion as to whether any of them were responsible for uptake or accuracy of Cologuard. POR at 67-68; EX1002 ¶344; EX1086 ¶139; EX2051 at 58:16-59:12; 61:18-62:3. Merely identifying the existence of other patents that relate to a limited aspect of a multi-component product cannot defeat nexus. *See Quanergy Sys.,* 24 F.4th at 1418

(purported unclaimed features insufficient to defeat nexus without evidentiary support).

B. Cologuard's Commercial Success Supports Non-Obviousness

Where the commercial product is "the invention disclosed and claimed in the patent," there is a presumption that commercial success is due to the claimed invention. *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 734, 747 (Fed. Cir. 2016). The presumption applies "even when the product has additional, unclaimed features." *Id*.; *see also Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991). Even absent the presumption, Exact Sciences has demonstrated the desirable characteristics of a non-invasive CRC screening test. EX2044 ¶¶41-45; EX1023 at 146. The commercial success of Cologuard is based on Cologuard meeting those characteristics due to diagnostic accuracy and patient uptake that are directly connected to the patented invention.[3] EX2044 ¶¶41-45; 197-221.

[3] The FWD in IPR2024-00459 concerning the parent patent noted that "steps of collecting two portions of a fecal sample at home, and combining a respective buffer stabilizer/preservative with each of the two portions … and then processing those fecal samples by testing for blood and nucleic acids" are "nearly the most basic steps for using the Cologuard kit" and "these steps do illustrate a certain ease of use and consumer-friendliness that may be a contributing factor in Cologuard's success." EX1087 at 25.

Petitioner argues that Exact Sciences has not shown that Cologuard's combination results in better diagnostic accuracy than the DNA component alone. Reply at 24. It defies logic to suggest that Exact Sciences would have developed the nucleic acid/blood protein combination of Cologuard if earlier attempts to develop a nucleic-acid-only test had produced satisfactory results. Moreover, Petitioner's exhibits show that Cologuard outperformed Exact Sciences' earlier, nucleic-acid-only screening tests. *See, e.g.,* EX1006, EX1042, EX1043; EX1077.

Petitioner also incorrectly contends that Exact Sciences "attributes the diagnostic accuracy of Cologuard to features unrelated to the Challenged Claims," citing a partial quotation from Imperiale 2014 out of context. Reply at 24. Imperiale 2014 "compared a noninvasive, multitarget stool DNA test [Cologuard] with a fecal immunochemical test (FIT)." EX1077 at 1287. Imperiale 2014 observes that the sensitivity of the Cologuard test[4] for "the detection of both colorectal cancer (92.3%) and advanced precancerous lesions (42.4%) exceeded that of FIT by an absolute difference of nearly 20 percentage points." EX1077 at 1295. Imperiale 2014 also states that "[t]his difference may be attributed to the DNA marker and algorithm components of the test, since the test performance of the hemoglobin immunoassay component of the DNA test was nearly identical to that of FIT." *Id.*; *see also* EX2044

[4] Imperiale 2014 refers to the multi-target Cologuard test as the "DNA test." *See* EX1077; EX1088 at 70:23-71:14.

¶¶197-198. Stated differently, Cologuard's improved sensitivity was due to the combination test—an embodiment of the fundamental workflow of the challenged claims. EX2044 ¶198.

Petitioner also tries to defeat the nexus by pointing to other Exact Sciences patents, including statements during prosecution of U.S. Patent No. 9,163,278, titled "isolation of nucleic acids." EX1029. Petitioner again mischaracterizes these statements as admitting that "Cologuard has a multitude of features, many of which … are critical to the success of [Cologuard]." Reply at 22. These statements address the long-felt need for a method of "isolating DNA from stool samples" and the success of Cologuard's methods for extracting marker DNA to satisfy that need, rather than any blanket attribution of Cologuard's commercial success to another invention. EX1029 at 8.

Petitioner further argues that "the commercial success of Cologuard ***may have been*** significantly influenced" by the exclusivity periods of other patents listed on Exact Sciences website. Reply at 25 (emphasis added). Petitioner offers no evidence concerning the claims of those patents or how those claimed inventions purportedly blocked market entry by any potential competitors to Cologuard. *Id.* This is insufficient to defeat nexus. "[A] patent challenger cannot successfully rebut the presumption with argument alone—it must present evidence." *WBIP,* 829 F.3d at 1329.

Relying primarily on a 2024 article, petitioner argues that Cologuard's commercial success is the result of Exact Sciences' marketing efforts. Reply at 25-26, citing EX1091. However, that article does not attribute success solely, or even substantially, to marketing, but states that Exact Sciences has "not relied solely - or even primarily - on" direct to consumer marketing to achieve its success. EX1091 at 7. The article attributes success to "innovation, discipline, and grit," including the effort to educate "100 million patients and 300,000 doctors." *Id.* Petitioner's expert agreed there "must be evidence that provides some convincing aspect of utility of a test in order for people to prescribe it." EX2051 at 143:3-14. Accordingly, while advertising was necessary to educate, advertising would not result in prescriptions. Here, similar to in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), "the products have to work, and there is no evidence that that is not the case or that the success was not due to the merits" of the claimed invention. *Id.* at 1382. Even where marketing has played a role in commercial success, as in *Hybritech*, the continued, increasing success of Cologuard would not be as great or as prolonged if not for the merits of the test. *See id.* at 1383. These screening tests that require a prescription from a physician are not "the kind of merchandise that can be sold by advertising hyperbole." *Id.* at 1383-84.

C. Failure by Others, Long-Felt Unmet Need, and Industry Praise Also Support Non-Obviousness

In addition to commercial success, the unrebutted evidence of failure by others, long-felt but unmet need, and praise strongly supports non-obviousness.

Petitioner does not dispute that others tried and failed, that there was a long-felt unmet need that Cologuard met, and that Cologuard has received industry praise. These objective indicia of non-obviousness provide a practical check to avoid improper reliance on hindsight when considering whether an invention would have been obvious to a POSA. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012).

Had Petitioner's proposed combinations been obvious, the unmet need would not have continued for four years after Lenhard, Vilkin, and Shuber. Petitioner's own declarant is a named inventor on Shuber (EX1009), yet Dr. Whitney—who worked on CRC screening at Exact Sciences from 2000 to 2005—did not pursue what he now contends was obvious. EX1002, EX1086, EX2020 at 24:4-10.

IV. CONCLUSION

For the foregoing reasons, the Board should confirm the patentability of all challenged claims.

Date: October 3, 2025 */s/ James M. Glass*

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CERTIFICATE OF LENGTH (37 C.F.R. §§ 42.24)

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 5,497 words and thus complies with the applicable word limit.

Date: October 3, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on October 3, 2025 the foregoing Sur-Reply from Patent Owner was served via email on the following counsel of record for the Petitioner:

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