

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

PATENT OWNER'S SUR-REPLY

TABLE OF CONTENTS

	<u>Page</u>
I. PETITIONER HAS NOT SHOWN MOTIVATION TO COMBINE.....	2
A. Even to Prioritize Sensitivity for CRC Over All Other Desirable Characteristics, There Was No Motivation to Combine	2
B. Properly Considering the Prior Art as a Whole, There Was No Motivation to Arrive at the Claimed Invention.....	3
1. A POSA Would Not Have Been Motivated To Combine Lenhard, Vilkin, and Itzkowitz	4
2. A POSA Would Not Have Been Motivated to Combine Shuber with Vilkin	14
C. Grounds II and V	18
II. OBJECTIVE INDICIA SEPARATELY DEFEAT OBVIOUSNESS.....	18
A. There Is a Clear Nexus Between the Invention and Cologuard.....	19
B. Cologuard’s Commercial Success Supports Non-Obviousness	21
C. Failure by Others, Long-Felt Unmet Need, and Industry Praise Also Support Non-Obviousness	24
III. CONCLUSION.....	25

TABLE OF AUTHORITIES

	<u>Page</u>
<u>Cases</u>	
<i>Apple Inc. v. Samsung Elecs. Co.</i> , 839 F.3d 1034 (Fed. Cir. 2016)	24-25
<i>Arctic Cat, Inc. v. Bombardier Recreational Products, Inc.</i> , 876 F.3d 1350 (Fed. Cir. 2017)	1, 3-4
<i>Cont'l Can Co. v. Monsanto Co.</i> , 948 F.2d 1264 (Fed. Cir. 1991)	21
<i>Crocs, Inc. v. Int'l Trade Comm'n</i> , 598 F.3d 1294 (Fed. Cir. 2010)	18
<i>Custom Accessories, Inc. v. Jeffrey–Allan Indus., Inc.</i> , 807 F.2d 955 (Fed. Cir. 1986)	12
<i>Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	5
<i>Henny Penny Corp. v. Frymaster LLC</i> , 938 F.3d 1324 (Fed. Cir. 2019)	1, 3
<i>Hybritech, Inc. v. Monoclonal Antibodies, Inc.</i> , 802 F.2d 1367 (Fed. Cir. 1986)	23-24
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	4-5, 17
<i>Mintz v. Dietz & Watson, Inc.</i> , 679 F.3d 1372 (Fed. Cir. 2012)	24
<i>Polaris Indus., Inc. v. Artic Cat</i> , 882 F.3d 1056 (Fed. Cir. 2018)	19, 20
<i>PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC</i> , 815 F.3d 734 (Fed. Cir. 2016)	21
<i>Quanergy Sys. Inc. v. Velodyne Lidar USA, Inc.</i> , 24 F.4th 1406 (Fed. Cir. 2022)	19, 22

<i>Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.,</i> 699 F.3d 1340 (Fed. Cir. 2012)	12
<i>Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.,</i> 97 F.4th 882 (Fed. Cir. 2024)	17
<i>WBIP, LLC v. Kohler Co.,</i> 829 F.3d 1317 (Fed. Cir. 2016)	18, 23

Petitioner misstates Exact Sciences' arguments. Unlike Petitioner, Exact Sciences properly considers the prior art in its entirety. *See, e.g., Arctic Cat Inc. v. Bombardier Recreational Prods., Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017). In contrast, Petitioner's reliance on sensitivity for CRC while discounting all other important features violates the "longstanding principle that the prior art must be considered for all its teachings, not selectively." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Petitioner goes even further to argue that certain disclosures in Levin would "not affect a POSA's motivation" (Reply at 13) notwithstanding that a POSA is presumed to have knowledge of all relevant prior art as of the priority date. When the teachings of the prior art are properly considered as a whole, any suggestion for potential increase in CRC sensitivity as compared to certain prior art solutions is far outweighed by knowledge that the proposed combinations would also result in (i) reduced specificity, (ii) increased complexity for the patient, including more patient interaction with the sample as compared to other solutions, (iii) increased test complexity, and (iv) increased cost.

Further, even if Petitioner could meet its burden of showing a motivation to combine, objective indicia defeat obviousness. Petitioner does not dispute that (1) Exact Sciences' Cologuard® product practices the claimed invention, (2) Cologuard is a commercial success, (3) Cologuard satisfied a long-felt but unmet

need for better non-invasive CRC screening, (4) others tried and failed to meet the long-felt need, and (5) Cologuard received industry praise. Petitioner's only challenge to these compelling objective indicia concerns the nexus between the physician-prescribed Cologuard product and the claimed invention. Yet, Exact Sciences explained in detail – and Petitioner did not dispute – how use of Cologuard tracks the collection and processing steps of claims 1 and 3 of the '781 patent, such that nexus is established. POR at 50-55.

I. PETITIONER HAS NOT SHOWN MOTIVATION TO COMBINE

A. Even to Prioritize Sensitivity for CRC Over All Other Desirable Characteristics, There Was No Motivation to Combine

Petitioner's motivation argument rests on the potential for increased sensitivity for CRC. *See, e.g.*, Reply at 5-6. Accepting *arguendo* that Petitioner is correct, there would have been no motivation to combine the iFOBT of Vilkin with anything else. Vilkin discloses **100%** sensitivity for CRC. EX1005 at 7 (Table 3). It is impossible to improve on 100% sensitivity. Accordingly, if, as Petitioner contends, the potential for increased sensitivity for CRC was the most important consideration, there would have been no reason to combine Vilkin. A POSA seeking to maximize sensitivity for CRC would have just used Vilkin.

However, as described in detail in Patent Owner's Response and below, Petitioner's argument is incorrect. A POSA who sought to improve existing, non-invasive CRC screening tests would also have considered other known

requirements for a screening test, such as (1) overall diagnostic performance, including sensitivity for advanced adenomas and specificity; (2) patient acceptability; (3) complexity; and (4) cost.

B. Properly Considering the Prior Art as a Whole, There Was No Motivation to Arrive at the Claimed Invention

The prior art identifies factors that a POSA seeking to improve CRC screening tests would have considered: “[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.” EX1029 at 2. The final factor, reduction in morbidity and mortality, was known to be directly connected to early cancer detection through detection of advanced adenomas. EX1004 at 1; EX2022 ¶¶29-30. Petitioner’s own 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.

In assessing whether a POSA would have been motivated to combine the cited references, one must weigh the potential for benefits gained against benefits lost. *Henny Penny*, 938 F.3d at 1332. 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, 876 F.3d at 1363. Thus, a POSA would have considered all factors, including prior-art guidance as to what was most promising and what was not.

1. A POSA Would Not Have Been Motivated To Combine Lenhard, Vilkin, and Itzkowitz

(a) Petitioner Selects Specific Claim Elements With the Roadmap of the '781 Patent

Petitioner's combination begins with the incorrect assertion that Lenhard discloses “*an assay* that combines a nucleic acid test with a gFOBT.” Reply at 5 (emphasis added). Lenhard discloses a comparison of two separate tests – a commercially available gFOBT and a new HIC1 test. EX1004 at 1, 6. Lenhard's sample collection occurred at a clinic or laboratory setting, not at home. EX1004 at 2; EX2027 at 43:20-44:8. The sample was aliquoted at the laboratory, not separated at home, and there is no mention of stabilizing buffer. EX1004 at 2. Thus, to the extent Petitioner intends “an assay” to mean a combined test, Lenhard did not describe “an assay.” Instead, Lenhard describes the common-place laboratory comparison of a new test with an existing test. *See, e.g.*, EX1006; EX1043. Petitioner's modification of Lenhard's separate tests to incorporate elements of Vilkin and Itzkowitz to arrive at precisely the elements of the claimed invention makes sense only if one starts with the invention and works backward,

which is impermissible hindsight. *See KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)(warning against “distortion caused by hindsight bias”).

Petitioner criticizes Exact Sciences for identifying a fatal flaw in Petitioner's argument: Petitioner offered no evidence that a “stabilizing buffer” could not also stabilize blood protein. POR at 37-39. Petitioner argues that separate buffers “were well known in the art by the priority date and are disclosed in Itzkowitz and Vilkin, respectively.” Reply at 4. But Petitioner never identifies components of those buffers, much less components suitable for one but not the other. Vilkin simply refers to an “Hb stabilizing buffer.” EX1005 at 4. Further, Petitioner's declarant testified that he had no opinion as to whether a single buffer could have been used. EX2027 at 148:14-22; 149:18-150:20.

Because Petitioner has not shown that a POSA would start from the premise that two buffers were necessary, Petitioner has not met its burden to show that a POSA would have chosen at-home separation of the stool sample into two separate containers rather than the more patient-friendly, simpler, and more cost-effective approach of an unseparated stool sample in a single container with a single buffer. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)(burden of proving unpatentability is on the petitioner “and that burden never shifts to the patentee”).

Petitioner also argues that there was a “well-established strategy decades before the Priority Date,” to separately preserve portions of a sample “in different stabilizing buffers.” Reply at 4. This “strategy” applied only when it is necessary to use different buffers to preserve different biomarkers. *See, e.g.*, EX1002 ¶84. Petitioner offers no evidence that a POSA in 2009 would have concluded that different buffers were necessary, even assuming the POSA would have been motivated to develop a method for at-home collection of stool sample to be tested for both nucleic acid and blood protein.

Petitioner's failure to establish motivation for at-home separation of the fecal sample into separate containers, each containing a buffer, defeats its assertion of obviousness.

(b) The References as a Whole Weighed Against the Combination

Petitioner does not dispute that (1) the combined results of gFOBT and HIC1 testing in Lenhard showed no increased sensitivity for advanced adenomas and were less specific than the HIC1 test alone, (2) patient acceptance is important for the success of a screening test, and (3) testing for two classes of markers increases cost and complexity as compared to testing for a single class of markers. Despite all of these factors that would have weighed against the combination, Petitioner incorrectly contends that potential for increased CRC sensitivity would have motivated a POSA in 2009 to combine FOBT with nucleic acid testing, and

that that POSA would have selected specific aspects of Vilkin and Itzkowitz in making that combination.

A POSA Would Have Considered Sensitivity for Advanced Adenomas in Addition to CRC: Petitioner's argument concerning advanced adenomas is belied by Petitioner's cited references. Reply at 8. As Exact Sciences previously discussed (POR at 10-11), Lenhard emphasizes the importance of detecting adenomas, stating, *inter alia*, that "a stool-based screening assay also should detect relevant premalignant lesions (ie, adenoma)." EX1004 at 6. Vilkin reports sensitivity for detection of both CRC and advanced adenomas. EX1005 at 7. It is not credible to suggest that a POSA would not have weighed the effect, if any, on detecting advanced adenomas when the very references on which Petitioner relies report detection of advanced adenomas.

Petitioner selectively quotes from Levin to try to discount the importance of detecting advanced adenomas, citing a portion of a discussion that distinguishes between two categories of then-existing screening tests. Reply at 8; EX1013 at 3-4. Levin highlights that the then-existing non-invasive screening tests had limited ability to detect advanced adenomas thus limited ability to prevent disease. EX1013 at 3-4. 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 4. Accordingly, a POSA seeking to improve diagnostic performance of

a non-invasive test would consider and try to address limitations of those tests, such as their limited effectiveness in the primary goal of cancer prevention.

Petitioner also argues that a “POSA would not discount the improved sensitivity for CRC of the combined Lenhard assay because it maintained only equal sensitivity for adenomas.” Reply at 8. Stated differently, the combined results did not detect any adenomas not detected by HIC1 alone. EX1004 at 3. However, the combination’s performance was worse overall because, while sensitivity for adenomas did not increase, combining results from gFOBT and HIC1 decreased specificity. EX1004 at 4; EX2022 ¶¶61-62, 65.

A POSA Would Not Accept a Reduction in Specificity Unless Outweighed by Advantages Gained: Unable to dispute that the proposed combination would reduce specificity, Petitioner argues that a POSA would be willing to sacrifice specificity for increased sensitivity. Reply at 9-10. The select information on which Petitioner relies does not support its argument. To begin, 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 because of the 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 1 (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 1. Itzkowitz further emphasizes that with only two markers, “assay complexity can be reduced significantly, thereby decreasing cost and facilitating the development of an assay kit that could be managed by local clinical laboratories.” EX1006 at 7. A POSA would consider all of these aspects in the context of benefits gained and lost.

Petitioner also relies on a statement from Imperiale 2014 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.” Reply at 9, citing EX2008 at 9. However, the quoted sentence is not limited to sensitivity for CRC. EX2008 at 9. In fact, the next sentence discusses sensitivity “for the detection of advanced precancerous lesions.” *Id.* As demonstrated by the extensive discussion in Imperiale 2014, a critical aspect of Cologuard is its sensitivity for detecting advanced adenomas. *See generally* EX2008; *see also* EX1090 at 75:18-79:19. Imperiale 2014 also makes clear that sensitivity is not the only important characteristic, stating “[a]lthough high sensitivity is the most important attribute of cancer-screening tests, ***specificity is also important***, since it affects the number of persons who have positive test results....” EX2008 at 9 (emphasis added). Petitioner’s own declarant agrees – “[s]ensitivity ***and specificity*** are important

metrics of diagnostic performance.” EX1002 ¶27 (emphasis added). Further, the quoted statement from 2014 is not prior art. EX2008.

Petitioner's argument that the reduced specificity in Lenhard “would be acceptable to a POSA” improperly looks at the degree of reduced specificity in Itzkowitz and Patent Owner's Cologuard product without balancing other gains and losses. Reply at 10. As Itzkowitz's conclusion shows, a POSA would consider multiple factors: simplicity, cost, and whether there was a significant increase in sensitivity. EX1006; EX2022 ¶¶112-119. 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. EX2008; *see also* EX1090 at 75:18-79:19. Petitioner's conclusion that a POSA would have been willing to sacrifice some specificity for increased sensitivity assumes that all else is equal, an assumption that is contrary to Petitioner's own cited references.

Moreover, the benefit of increased sensitivity from the combination of nucleic acid and gFOBT in Lenhard was minimal. Analysis of the Lenhard data – which Dr. Whitney did not dispute (EX1080) – shows that the combined results were at best marginally better than HIC1 alone for CRC. EX1090 at 102:8-103:13, 115:15-118:2; EX2022 ¶¶61-68. Petitioner has not shown that a POSA would have accepted the reduction in specificity for a marginal increase in sensitivity for CRC

when balancing sensitivity and specificity to determine whether there was an overall improvement in test performance.

Petitioner Discounts Negative Aspects of Combining Vilkin's iFOBT – Multiple Samples and Refrigeration: Petitioner chose to rely on the “iFOBT of Vilkin.” *See* Pet. at 6. Petitioner now accuses Exact Sciences of “misreading” Vilkin, when Exact Sciences relies on statements taken directly from Vilkin. 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 4, 6. Whether a subsequent cost-benefit analysis would result in fewer than three consecutive daily samples does not change that 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 4; EX 2022 ¶69.

Petitioner also argues that the claims do not exclude refrigeration. Reply at 11-12. Once again, Petitioner poses the wrong question. The question is whether there was a motivation to combine the iFOBT of Vilkin when one aspect of Vilkin is that it required at-home refrigeration of the samples – something that users were reluctant to do even according to Vilkin. EX1005 at 8.

Petitioner also contends that Vilkin would not require refrigeration “in clinical practice.” Reply at 12. Petitioner's argument assumes a single sample and not Vilkin's three samples or even the 2-day collection that was “routinely used in

Japan, United States, and Australia.” EX1005 at 8. Petitioner also ignores the unmistakable implication of Vilkin’s statement that double zip-lock bags “answered some of the screenees’ hesitancy about keeping the prepared test transiently in their home refrigerator. This packaging could be further improved.” EX1005 at 8. If there were no expected need for screenees to refrigerate samples at home, there would be no need to improve packaging for refrigeration.

In weighing the disadvantages of this potential combination against the benefits, a POSA would have considered that Vilkin taught multiple samples per patient and required refrigeration.

Petitioner Improperly Views the gFOBT of Lenhard as of 2005 – Not with the Knowledge of a POSA as of the 2009 Invention Date: Petitioner’s argument concerning Levin is another selective reading of the reference. Petitioner compares the sensitivity of the gFOBT used in Lenhard with the iFOBT of Vilkin and argues that “Levin’s disclosure would not affect a POSA’s motivation to replace the gFOBT of Lenhard with the iFOBT of Vilkin.” Reply at 13.

Petitioner’s argument ignores both that (1) obviousness is judged as of the time of the invention, *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012), and (2) a POSA is presumed to be aware of all relevant prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Levin – a 2008 joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology – is closer in time to the invention date than any of Petitioner's combination references. EX1013. Petitioner asserts that Levin noted certain technological advantages of iFOBT (referred to as "FIT") when compared to gFOBT. Reply at 13. However, Levin also reported "it appears that 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 FIT." EX1013 at 7. Levin further noted FIT's "higher costs" compared to gFOBT. *Id.* Most informative is Levin's 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 9 (emphasis added). Levin, having discussed relative merits of gFOBT and iFOBT, undercuts Petitioner's argument that a POSA in February of 2009 would substitute iFOBT for gFOBT. *Id.*

Testing for Multiple Classes of Markers Is More Complex and More Costly Than Testing for a Single Class of Markers: As discussed above, Petitioner incorrectly refers to Lenhard's tests as if they were a single test and then argues that replacing aspects of that "assay" would not increase cost and complexity. Reply at 14-16. Lenhard describes laboratory collection and testing of a sample using two separate tests. EX1004. Lenhard does not suggest a single at-

home collection assay, let alone sample separation at home into two separate containers for eventual testing for two different classes of markers. EX1004; EX2022 ¶¶55-56. A POSA considering whether there was motivation 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. EX2022 ¶¶76, 112-114.

Petitioner does not dispute that testing for two different types of markers would add cost and complexity in number of components and testing. POR at 35-36; EX2022 ¶¶113-116.

The balance of advantages and disadvantages taken together weighs heavily against motivation to combine. A POSA would have understood that the combination would not increase sensitivity for advanced adenomas, would reduce specificity, would jeopardize patient acceptance, and would increase both test complexity and cost. EX2022 ¶¶96-116. With disadvantages outweighing benefits, a POSA seeking to improve non-invasive CRC screening would have been dissuaded from combining Lenhard, Vilkin, and Itzkowitz.

2. A POSA Would Not Have Been Motivated to Combine Shuber with 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 17. Petitioner’s only support for this assertion is the Petition at pages 48-50, where Petitioner addresses the same four references, and relies on essentially the same quotes from those references. Reply at 18-20. Although Exact Sciences previously addressed Petitioner’s select quotes (POR at 43-46), certain of Petitioner’s arguments are also addressed below.

Nishikawa: Contrary to Petitioner’s argument (Reply at 18), Exact Sciences did not rely on timing alone. As previously noted, the single statement from the 2002 Nishikawa reference includes no data or support. POR at 43. Further, the speculative quote that Petitioner cites undercuts Petitioner’s argument. The full sentence from Nishikawa states “[h]owever, the technique is *highly specific*, noninvasive, and cost-effective, and 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 and other methods for detecting genetic abnormalities.” EX1011 at 6 (emphasis added). Viewed in the context of the prior art as of 2009, a POSA would have understood that a combination would not be more specific.

Lenhard: Lenhard is discussed in detail above. Petitioner’s reliance on “increased detection rates for CRC” (Reply at 19), further highlights Petitioner’s incorrect focus on sensitivity for CRC alone.

Kutzner: Kutzner itself says that the “retrospective data *do not allow* any conclusion on the potential of this approach in diagnostic screening.” EX1012 at 8 (emphasis added). Moreover, Petitioner’s assertion that Kutzer draws definitive conclusions about the value of the combination is belied by the 2008 Levin joint guideline discussed below.

Levin: As noted above, Levin is a 2008 joint guideline from panels of experts. This joint guideline notes “[a]nother question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of [sDNA] testing would improve sensitivity without adversely affecting specificity.” EX1013 at 9. Immediately after posing this open question, Levin references the Kutzner retrospective analysis. *Id.* Accordingly, Levin did not interpret Kutzner as providing any predictable indication that a combination of FOBT and DNA testing would improve test performance.

These four cited references taken together do not establish an “art-recognized strategy for improving assay sensitivity” as Petitioner contends. Reply at 17. Moreover, these references support that a POSA would have considered any increases in sensitivity together with adverse effects on specificity. EX1011 at 6, EX1013 at 9.

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 17, 19-20. 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*. 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." EX2027 at 152:7-17. Essentially, Petitioner's declarant suggests that it might be obvious to try Petitioner's combination. But "obvious to try" fails here, where Petitioner has not established that there is a finite number of identified, predictable solutions, with a reasonable expectation of success. *See KSR Int'l*. 550 U.S. at 421.

Petitioner argues that nothing "would preclude [Vilkin's] iFOBT from being combined with a DNA test of Shuber to arrive at" the claimed invention. Reply at 21. That is not the relevant question. The relevant question is whether a POSA would have been motivated by the prior art at the time to select Vilkin, and in particular just 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). Petitioner has shown no motivation for that selection.

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 potential gains against known disadvantages.

C. Grounds II and V

Petitioner incorrectly asserts that Exact Sciences "merely states" that Grounds II and V fail for the same reasons that Grounds I and IV fail. Reply at 21. For Grounds II and V, Exact Sciences also explains that the combined results from COX-2 and iFOBT described in Kanaoka showed an insignificant increase in sensitivity, with a more significant decrease in specificity. POR at 49. Kanaoka provides another example of reduced test performance when results from nucleic acid testing and FOBT were considered together. EX2022 ¶84. Kanaoka would thus further dissuade a POSA from the combination.

II. 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). Indeed, "[s]econdary considerations 'can be the most probative evidence of non-obviousness in the record, and enables the . . . court to avert the trap of hindsight.'" *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010)(citation omitted).

A. There Is a Clear Nexus Between the Invention 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). Here, Cologuard practices at least claim 3, and the claimed invention is not a subcomponent of the entire product. *See* POR at 50-55. Based on a similar comparison of Exact Sciences’ Cologuard product to a related patent, the Board was persuaded, albeit at the earlier institution decision phase of the proceedings in IPR2024-1330, that “Cologuard ‘embodies the claimed features and is coextensive with them,’ such that a presumption of nexus applies.” IPR2024-1330 Paper 10 at 31.

Petitioner has not rebutted the presumption of nexus. To begin, Petitioner did not challenge Exact Sciences’ evidence that every limitation of claim 3 is found in the method of using Cologuard. *See Polaris Indus., Inc. v. Artic Cat Inc.*, 882 F.3d 1056, 1073 (Fed. Cir. 2018). Further, in *Polaris*, as here, the claims at issue covered the entire product, “rather than ‘only a component of a commercially successful [product].’” *Id.*

Petitioner is incorrect that the patented invention is “a minor component” of the complex Cologuard product. Reply at 22. Claim 3 of the ’781 patent includes

the convenient at-home collection method where the stool sample is divided into two containers with the specified buffers in each container; testing the removed portion of the sample for blood protein; extracting nucleic acid from the remaining portion of the sample; and testing the nucleic acid for an amount of human nucleic acid. EX1001 at 45:21-61. As described in detail in Patent Owner's Response, claim 3 perfectly tracks the collection and testing method of Cologuard. POR at 50-55.

Petitioner tries to break the nexus by arguing that “[d]istinct components” of Cologuard are covered by other patents. Reply at 23. This argument turns the traditional nexus analysis on its head. Nexus is presumed where, as here, the product embodies the claimed features and is coextensive with them. *Polaris*, 882 F.3d at 1072. A patentee must show more only “if the patented invention is only a component of a commercially successful machine or process.” *Id.* (citations omitted). That is not the case here. The other Exact Sciences patents to which Petitioner refers are not at issue here, and Petitioner's declarant offered no opinion as to whether, or how, any of those other patents contributed to uptake or accuracy of Cologuard. EX1080 ¶¶115-116; EX2054 at 61:18-62:3. Moreover, by Petitioner's own description, unlike the '781 patent, those patents each concern “[d]istinct components,” and not the entire method. *See* Reply at 23.

B. Cologuard's Commercial Success Supports Non-Obviousness

Where evidence shows that 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 shown that the commercial success of Cologuard is based on diagnostic accuracy and patient uptake, which are directly connected to the patented invention. EX2022 ¶¶140-160.

In its attempt to defeat nexus, Petitioner first incorrectly argues that Exact Sciences “attributes the diagnostic accuracy of Cologuard to features unrelated to the Challenged Claims.” Reply at 24. Petitioner again relies on a partial quotation out of context. *Id.* Imperiale 2014 “compared a noninvasive, multitarget stool DNA test [Cologuard] with a fecal immunochemical test (FIT).” EX2008 at 1. Imperiale 2014 observes that the sensitivity of the Cologuard test¹ 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.” EX2008 at 9.

¹ Imperiale 2014 refers to the multi-target Cologuard test as the “DNA test.” *See* EX2008; EX1090 at 70:23-71:14.

Imperiale 2014 goes on to state 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.* Stated differently, Cologuard’s improved performance over a commercial FIT test was not due to an improved FIT component, but was instead due to the combination. *See id.* To the extent that Petitioner is incorrectly suggesting that Cologuard’s improved performance is due to the DNA-component alone, it is notable that Cologuard outperformed Exact Sciences’ earlier, nucleic-acid only screening tests. *See, e.g.,* EX1006, EX1043, EX1044; EX2008.

Petitioner tries to defeat the nexus between Cologuard’s commercial success and the claimed invention by pointing to other Exact Sciences patents, including statements during prosecution of U.S. Patent No. 9,163,278, titled “isolation of nucleic acids.” EX1085. However, whether improved means of extracting nucleic acids has also contributed to Cologuard’s success does not change either (1) that CRC screening with Cologuard involves more than just the extraction of nucleic acids, and (2) that CRC screening with Cologuard follows every element of at least claim 3 of the ’781 patent, including “extracting nucleic acid from the remaining portion of the fecal sample.” POR at 50-55. Petitioner’s cursory argument is insufficient to rebut the presumption of nexus. *See Quanergy*, 24 F.4th at 1418-1420.

Petitioner also 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 any such patents or how those claimed inventions purportedly blocked entry from 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 further argues that the indisputable commercial success of Cologuard is the result of Exact Sciences’ marketing efforts. Reply at 26, citing EX1087. However that article does not attribute success solely, or even substantially, to marketing. EX1087. The article states that Exact Sciences has “not relied solely - or even primarily - on” direct to consumer marketing to achieve its success. EX1087 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 own declarant agreed there “must be evidence that provides some convincing aspect of utility of a test in order for people to prescribe it.” EX2054 at 143:3-14. Accordingly, while advertising was necessary to educate physicians and potential users of the Cologuard tests, 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 Cologuard's commercial success, the unrebutted evidence of failure by others, long-felt but unmet need, and praise for Cologuard 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 at the relevant time. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). “Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution

been obvious.” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016).

Logically, had Petitioner’s proposed combinations been an obvious solution, the unmet need would not have continued for four years after Lenhard, Vilkin, and Shuber. The logic is particularly compelling here where 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, does not claim that he pursued what he now contends was obvious. EX1002, EX1080, EX2027 at 24:4-10.

III. CONCLUSION

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

Date: March 10, 2025

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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 5,526 words and thus complies with the applicable word limit.

Date: March 10, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on March 10, 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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