

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 PRELIMINARY RESPONSE

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<i>Volvo Penta of the Americas, LLC v. Brunswick Corp.,</i> 81 F.4th 1202 (Fed. Cir. 2023)	50

Rules / Statutes

35 U.S.C. § 325(d)	3, 62
37 C.F.R. § 42.107(e)	2

EXHIBIT LIST

No.	Exhibit
2001	Declaration of Vadim Backman, Ph.D.
2002	<i>Curriculum vitae</i> of Vadim Backman, Ph.D.
2003	Prosecution file history for application number 15/634,607, issued as patent number 11,845,991
2004	Prosecution file history for application number 17/936,335, issued as patent number 11,634,781
2005	Prosecution file history for application number 18/179,945, issued as patent number 11,970,746
2006	Portion of prosecution file history for application number 18/919,170
2007	Declaration of June Ann Munford
2008	Appendix to Declaration of June Ann Munford
2009	Sidney J. Winawer and Ann G. Zauber, <i>The Advanced Adenomas as the Primary Target of Screening</i> , 12(1) Gastrointestinal Endosc. Clin. N. Am. 1, 1-9 (2002)
2010	Daniel C. Chung, <i>The Genetic Basis of Colorectal Cancer: Insights Into Critical Pathways of Tumorigenesis</i> , 119 Gastroenterology 854, 854-865 (2000)
2011	Hermann Brenner et al., <i>Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840 149 screening colonoscopies</i> , 56(11) Gut 1585, 1585-1589 (2007)
2012	David L. Zack et al., <i>Colorectal Cancer Screening Compliance by Medicine Residents: Perceived and Actual</i> , 96(10) Am. J. Gastroenterology 3004, 3004-3008 (2001)
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2017	Geneoscopy, “Geneoscopy Submits Premarket Approval Application to U.S. food and Drug Administration for its Noninvasive Colorectal Cancer RNA Biomarker Screening Test,” https://www.geneoscopy.com/geneoscopy-submits-premarket-approval-application-to-fda-for-its-noninvasive-colorectal-cancer-rna-biomarker-screening-test/ (January 24, 2023)
2018	United States Department of Health and Human Services, “Increase the proportion of adults who get screened for colorectal cancer — C-07,” https://health.gov/healthypeople/objectives-and-data/browse-objectives/cancer/increase-proportion-adults-who-get-screened-colorectal-cancer-c-07
2019	Declaration of Peter Wood
2020	Transcript of October 10 Deposition of Duncan Whitney, Ph.D. in connection with IPR2024-00459
2021	Geneoscopy, Series C Investor Presentation, available at (password protected link) https://nephronnext.open-exchange.net/stream/531120 (April 10, 2024)
2022	FDA, ColoSense™ Approval letter, available at https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001A.pdf
2023	CDC “Vital Signs: Colorectal Cancer Tests Save Lives,” available at https://archive.cdc.gov/www_cdc_gov/vitalsigns/colorectalcancerscreening/index.html
2024	Exact Sciences Form 10-K for the year ending December 31, 2004
2025	Exact Sciences Form 10-K for the year ending December 31, 2008
2026	Exact Sciences Form 10-K for the year ending December 31, 2014

2027	Exact Sciences Form 10-K for the year ending December 31, 2016
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2029	Exact Sciences Form 10-K for the year ending December 31, 2023
2030	Printout from Exact Sciences' Internal Survey Database
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2032	Exact Sciences, "Cologuard® Wins Popular Science Magazine's 2014 'Best of What's New' Award," https://www.exactsciences.com/newsroom/press-releases/cologuard-wins-popular-science-magazines-2014-best-of-whats-new-award (November 12, 2014)
2033	Everyday Health, Inc., "Everyday Health Awards for Innovation Winners Announced at 2015 International CES®," https://www.prnewswire.com/news-releases/everyday-health-awards-for-innovation-winners-announced-at-2015-international-ces-300017454.html (January 7, 2015)
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2038	John B. Kisiel et al., <i>Multitarget Stool DNA for Average Risk Colorectal Cancer Screening Major Achievements and Future Directions</i> , 30 Gastrointest Endoscopy Clin N Am 553, 553-568 (2020)

2039	Jason D. Eckmann et al., <i>Multi-Target Stool DNA Testing for Colorectal Cancer Screening: Emerging Learning on Real-world Performance</i> , 18 Curr Treat Options Gastro 109, 109-119 (2020)
2040	ColoSense Product information available at https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001C.pdf
2041	Disclaimer in a Patent Under 37 CFR 1.321(a) of claims 1 and 2 of U.S. Patent No. 11,970,746
2042	Request for Ex Parte Reexamination under 37 C.F.R. § 1.510 of U.S. Patent No. 11,634,781

I. INTRODUCTION

U.S. Patent No. 11,970,746 (the “’746 patent”) covers the use of Exact Sciences’ revolutionary Cologuard® colorectal cancer (“CRC”) screening kits. The technology protected by the ’746 patent has given millions of people a noninvasive and convenient approach to CRC screening, and has been a resounding commercial success.

Petitioner’s challenge to the ’746 patent comes almost a decade after the commercial release of the Cologuard test and relies on classic hindsight to extract selective claim elements from various prior art references. However, the cited references neither teach nor suggest the convenient and effective home-collection method of the ’746 patent. The cited references likewise provide no motivation to combine the references generally, and particularly no motivation to combine only the cherry-picked portions of each reference on which Petitioner relies to cobble together the elements of the claimed invention.

Both the cited references and Petitioner’s declarant, Dr. Duncan Whitney, acknowledge that sensitivity **and specificity** are critical performance parameters for diagnostic tests. *See, e.g.* EX1002 ¶28 (“Sensitivity and specificity are important metrics of diagnostic performance.”); EX1004 at 6 (“Highly sensitive, specific, and easily analyzable markers are required for noninvasive stool-based

CRC screening.”). Yet, in asserting that a POSA would have been motivated to combine the cited reference, Petitioner improperly relies exclusively on the potential for improved sensitivity without addressing the demonstrated, negative effect on specificity shown in the same cited references. Petitioner compounds this error by also ignoring the multiple other ways in which the cited references would have dissuaded Petitioner’s proposed combinations. Petitioner’s reliance on sensitivity alone violates the “longstanding principle that the prior art must be considered for all its teachings, not selectively.” *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Exact Sciences has now disclaimed claims 1 and 2,¹ so only claims 3-4 and 12-19 are at issue. 37 C.F.R. § 42.107(e); EX2041. Ground V concerns only now disclaimed claims 1 and 2 and therefore does not need to be considered. The remaining Grounds fail to establish either (1) how or why a POSA would have selected only the specific claim elements from the cited references, to the exclusion of other aspects of the cited references, or (2) why a POSA would have been motivated to develop a method of at home collection of fecal sample to be tested for two different classes of markers—blood protein and nucleic acid.

¹ Claims 1 and 2 were disclaimed to streamline issues for the Board, particularly where Patent Owner relies on Claim 3 in its pending motion for Preliminary Injunction in the related District Court litigation.

Further, the objective evidence of non-obviousness easily outweighs Petitioner's flawed obviousness arguments. Such evidence includes at least the commercial success of Cologuard, failed attempts prior to Cologuard to solve the need for CRC screening technology with both adequate diagnostic accuracy and patient uptake, long-felt need that was met by the Cologuard test, industry praise for Cologuard, and Petitioner's copying of Exact Sciences' patented approach.

Finally, discretionary denial of institution is appropriate under 35 U.S.C. § 325(d). The Examiner considered the very same art and arguments that Petitioner advances here before issuing the challenged claims.

II. BACKGROUND OF THE COLOGUARD TEST AND '746 PATENT

A. CRC Screening Techniques Prior to the Cologuard Test

For decades, CRC has been known as a leading cause of cancer-related deaths. *See, e.g.*, EX1034 at 1; EX1004 at 1. By the '746 patent's priority date, colonoscopy had become the primary screening test for CRC because of its high sensitivity and specificity, and because polyps can be removed during the procedure. EX1001 at 1:65-67. However, while both sensitive and specific, colonoscopy is also "invasive, costly, has limited availability and includes certain risks such as induction of infection and perforation of the bowel." *Id.* at 2:1-3. Although the risk of severe complications from colonoscopy is low, it does present an approximately 0.1% risk of perforation requiring surgery. EX2001 ¶35; EX1042

at 5. There are also multiple practical barriers to more widespread CRC screening by colonoscopy. EX2001 ¶¶36-37.

By 2009, various approaches for screening for CRC that were less invasive than colonoscopy, including fecal occult blood tests (“FOBT”) and nucleic acid screening tests, were also being used and further developed. *See* EX1001 at 2:4-3:40. Each of the less invasive tests had limitations, including limited sensitivity, specificity, patient acceptability, or a combination of all three. *See id.* FOBT tests in particular are limited by the intermittent nature of colorectal bleeding. *Id.* at 2:41-43. The sensitivity of FOBT tests is therefore dependent on “the number of samples taken and the frequency of testing.” *Id.* Those working in the field sought to balance sensitivity and specificity in a test that could be made widely available, and that would be acceptable to users. EX2001 ¶39.

A primary goal with CRC screening is to identify cancer or precancerous lesions as early as possible. The earlier the detection, the greater the reduction in mortality. *See, e.g.,* EX1001 at 1:43-46; EX1004 at 1; EX2001 ¶30. Accordingly, those working in the field recognized that, in addition to early-stage CRC, precancer indications, such as adenomas, should be a target of screening. EX2009 at 1; EX2001 ¶¶30-31.

As Petitioner’s own declarant Dr. Duncan Whitney acknowledges, both “[s]ensitivity and specificity are important metrics of diagnostic assay

performance.” EX1002 ¶28; *see also id.* ¶31 (“Effective diagnostic tests must be sensitive and specific for the disease of interest.”); EX2020 at 133:11-15 (“required of a good test...is to have high specificity in order to avoid false positives and to have high sensitivity to avoid false negatives.”). High sensitivity is desirable because false negatives result in disease not being detected. EX1002 ¶29. High specificity is desirable “because patients who wrongly test positive are often subjected to an unnecessary medical procedures [sic] and potentially unnecessary treatment.” *Id.* ¶30. A person working in this field would understand that, in view of the high cost of colonoscopy, even minor reductions in specificity could have a large negative impact on the overall cost-effectiveness of screening using the test. EX2001 ¶¶37, 112. Further, false positives have significant patient impact. *Id.* ¶¶36, 112; EX1034 at 12-13. If a screening test has low specificity, then both health care providers and patients understand that a positive test result may not be indicative of disease. This, in turn, may reduce incentive to follow up with the recommended colonoscopy after a positive screening test result. EX2001 ¶112. Or, if the patient does follow-up as recommended, in addition to the risks and costs of the colonoscopy procedure, there is also the intangible impact on the patient of the stress of waiting for the results of the follow-up colonoscopy, only to eventually learn that the initial test result was a false positive and that the patient does not have cancer or precancerous lesions. *Id.*

By the February 2009 priority date, there remained a long-felt unmet need for effective, efficient, non-invasive CRC screening tests. EX2001 ¶¶170-179. A person of ordinary skill in the art (“POSA”) would recognize that any such tests would need (i) to have sufficient sensitivity to detect indications of cancer and precancerous lesions, (ii) to have sufficient specificity to minimize false positives that result in unnecessary colonoscopies, and (iii) to be both accessible to, and acceptable to, patients. *Id.* ¶¶29-39; 147.

B. The Invention of the ’746 Patent

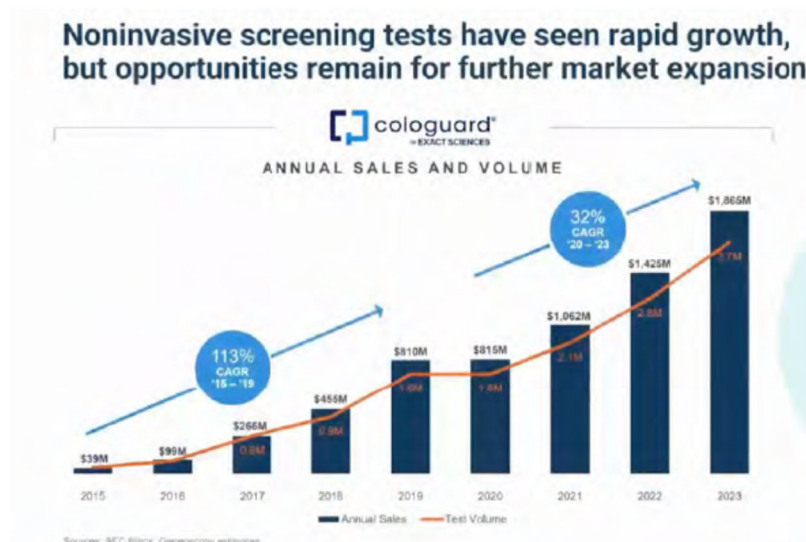
The Cologuard test using the ’746 patented technology accomplished these goals. Indeed, use of the Cologuard test achieved 92.3% sensitivity and 86.6% specificity. EX1077 at 1; EX2001 ¶42. The Cologuard test revolutionized home CRC screening. Under the ’746 patent’s novel and innovative approach, a fecal sample that will be tested for both nucleic acid and blood can be conveniently collected in the privacy of a patient’s own home and shipped without freezing from virtually anywhere. EX1076 at 13-31. The ’746 patent is the innovative combination of at-home collection that is acceptable to patients, use of buffers that avoid the need for freezing, and testing for both nucleic acids and fecal occult blood that resulted in enhanced performance. *See generally* EX1001. The Cologuard test using the ’746 patent’s invention enables many patients to get

screened for CRC, patients who would otherwise go unscreened. EX2001 ¶183; EX2019 ¶39.

The invention of the '746 patent, as embodied in the Cologuard product, provides a patient-friendly, effective means of collecting and processing fecal samples for screening. Under the patented method, a patient collects a fecal sample in the privacy of their own home. EX1076 at 15-19; EX2001 ¶¶151-152. The patient then removes a portion of the sample to a separate sealable container, resulting in a first and second portion. EX1076 at 20-23; EX2001 ¶153. The patient adds a stabilizing buffer to the first portion. EX1076 at 8, 22-23; EX2001 ¶154. The separate sealable container with the second portion contains a buffer that prevents denaturation or degradation of blood proteins. EX1076 at 8, 20-21; EX2001 ¶156. The containers are both sealed and shipped to a lab at room temperature—without freezing prior to shipping. EX1076 at 21, 23, 30; EX2001 ¶¶151, 154, 156, 158. The lab obtains the two containers with the two portions, extracts nucleic acid from the first portion, and the extracted nucleic acid is tested for an amount of human nucleic acid. EX1080 at 4; EX2001 ¶¶160-162. The second portion is tested for an amount of blood protein. EX1080 at 4; EX2001 ¶163.

The Cologuard test was the first FDA-approved commercially available multitarget stool-based blood and nucleic acid test for CRC screening. EX1025 at

1. The Cologuard test was also the first product to successfully undergo the FDA-CMS parallel review program resulting in simultaneous FDA approval and a proposed Medicare national coverage determination. EX2019 ¶¶14. The Cologuard test has been used by millions since its August 2014 approval. *Id.* ¶¶38. Indeed, Petitioner has pointed to the rapid increase in use of the Cologuard test in its own presentations to investors.



EX2021 at 11.

In May of 2024—almost a decade after Cologuard received FDA approval—Petitioner received FDA premarket approval for its ColoSense™ test. EX2022 at 1. ColoSense copies the innovative, successful approach of the '746 patent for at-home collection of fresh fecal samples to be tested for both nucleic acid and blood protein. EX2001 ¶¶186-194.

III. PROSECUTION HISTORY

The '746 patent issued on April 30, 2024, from Application No. 18/179,945. EX1001. The '945 application was a continuation of application No. 17/936,335 (the "'335 application") which issued as Patent No. 11,634,781 (the "'781 patent"). *Id.*; EX2004 at 1. The '335 application was a continuation of application No. 15/634,607 (the "'607 application"), which issued as U.S. Patent No. 11,845,991 on December 19, 2023. EX2004 at 14; EX2003 at 1.

Petitioner suggests that the '746 patent issued without significant prosecution history. Pet. at 10-11. This largely ignores the history of office actions during prosecution of the related '607 application, in which the Patent Owner overcame multiple rejections, including rejections based on Petitioner's Shuber² reference. EX2003 at 315-320; 353-358. The '746 patent is subject to terminal disclaimer over the '781 patent and the '991 patent. EX1019 at 6; EX2005 at 59-61.

During prosecution of the '746 patent, Patentee submitted an Information Disclosure Statement ("IDS") that included Petitioner's Petition for *Inter Partes* Review of the '781 parent patent (the "'781 Petition") as well as all references and

² Petitioner relies on International Patent Application Publication Number WO2005/113769 as "Shuber." EX1008. Petitioner has acknowledged that reference US 2008/0124714 A1 (Shuber et al.) cited during prosecution is the same reference. EX1031 at 84.

materials cited in the '781 Petition. EX2005 at 492-499. The '781 Petition included the same arguments as the current Petition with respect to the cited Lenhard, Vilkin, Itzkowitz, and Shuber references. *See* EX2031 at 11-65. The submitted materials from '781 Petition also included the Inbar reference that is identified in Grounds VI and VII in the present Petition. EX2005 at 492. The Examiner indicated that all references in the IDS were considered except where lined through. EX2005 at 76-82. Nothing was lined through, thus the Examiner considered all of Petitioner's cited art and Petitioner's same arguments concerning obviousness before issuing the '746 patent. *Id.*

IV. THE ASSERTED PRIOR ART

1. Lenhard (EX1004)

Lenhard is a 2005 article that focuses on comparison of a single gene methylation (epigenetic) marker with a guaiac method of FOBT (gFOBT) for purposes of distinguishing between patients with CRCs and those without. EX1004 at 1 (Background & Aims); EX2001 ¶55.

Samples in Lenhard “were collected before cathartic preparation for scheduled surgery or colonoscopy” and were “received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80° C.” EX1004 at 2; EX2001 ¶¶55-56. The samples were subjected to gFOBT “immediately on receipt and before freezing.” EX1004 at 4; EX2001 ¶56. The gFOBT testing of Lenhard

involved spreading stool sample onto cards, letting the sample dry for a day, then applying a peroxide catalyst to the card. *Id.*; EX2001 ¶58.

In its comparison of the specific HIC1 methylation marker with gFOBT, Lenhard notes the combined results of the two individual tests. EX1004 at 2, 6; EX2001 ¶57. Petitioner relies heavily on those combined results, particularly that “the combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.” *See, e.g.*, Pet. at 9, 13. Petitioner ignores much of the Lenhard reference and does not address how a POSA would consider the reference as a whole. *See* Pet. at 13, 19-34.

To begin, a POSA would consider that in Lenhard, “[m]ost patients with CRCs had been referred with a known diagnosis,” with 16 of the 26 CRC patients having symptomatic cases. EX1004 at 2; EX2001 ¶60. In addition, the “two thirds of CRCs” detected by the specific HIC1 and gFOBT combination discussed in Lenhard were largely late-stage cancers. EX1004 at 2, Table 1; EX2001 ¶60. Thus, the combined HIC1/gFOBT results in Lenhard showed relatively poor sensitivity of only 65% of CRCs that were predominantly late-stage. EX2001 ¶60.

A POSA looking at the results together would also consider the effect, if any, on detection of adenomas. EX2001 ¶¶59, 62. Lenhard itself teaches that “a stool-based screening assay also should detect relevant premalignant lesions (ie, adenoma).” EX1004 at 6. This is because “[d]etection of early disease and

precancerous adenomatous lesions leads to a decrease of CRC-related mortality.”

Id. at 1. Lenhard reported that the specific HIC1/gFOBT combination showed “no increase in the sensitivity for adenoma.” *Id.* at 6; EX2001 ¶59.

Further, consistent with Lenhard’s own teachings, a POSA would not consider sensitivity without also considering specificity. Lenhard repeatedly states that markers must have **both** high sensitivity and specificity. EX1004 at 1, Background & Aims (“markers with high sensitivity and good specificity are needed”), 2 (“identification of both sensitive and highly specific methylation markers is required ...”), 6 (“Highly sensitive, specific, and easily analyzable markers are required for noninvasive stool-based CRC screening.”); *see also* EX2001 ¶63. Lenhard further explains that “low specificity of a test results in a low positive predictive value” and “in high rates of unnecessarily performed colonoscopies.” *Id.* at 7. The sensitivity for “two thirds of CRCs” on which Petitioner relies came with a reduction in specificity. EX2001 ¶¶64-65; *see also* EX1004, Table 3 (showing additional false positives from gFOBT for control subjects 40, 47, 82 and 84).

A POSA considering Lenhard would consider the 65% sensitivity of the combined HIC1/gFOBT results in the context of the sensitivity of other markers. EX2001 ¶66. For example, Lenhard discusses other methylation markers found in stool, including SFRP2, which detected 77%-90% of CRCs—more than the 65%

detected by HIC1 methylation analysis combined with gFOBT. EX1004 at 2.

Lenhard notes, however, that the “specificity of SFRP2 methylation was quite poor, at 77%.” *Id.*

Lenhard concludes that the study shows “HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 *with a few additional sensitive and specific methylation markers* may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas.”

EX1004 at 7 (emphasis added). Thus, Lenhard teaches that the logical next path to explore would be combining different methylation markers, not combining nucleic acid-based testing with FOBT as Petitioner asserts. EX2001 ¶¶67-68.

2. Vilkin (EX1005)

Vilkin is a 2005 article that concerns testing a particular desktop immunochemical FOBT (“iFOBT”) that demonstrated a “high sensitivity of 76.5% for all significant colorectal neoplasia and acceptable specificity of 95.3%” based on three samples per subject. EX1005 at 7. The tested population in Vilkin was “ambulatory persons who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high-risk for CRC and invited for colonoscopy.” *Id.* at 4; EX2001 ¶69.

Vilkin required that the subject prepare three consecutive daily samples. EX1005 at 3 (Methods), 4. According to Vilkin, the “best results were obtained

when all three tests were performed and utilized for analysis.” *Id.* at 6. Table 3 of Vilkin reveals a range of sensitivities between the three different sample sets.

Table 3. Sensitivity for Significant Colorectal Neoplasia (N = 34)*
for Each I-FOBT[†] Prepared

I-FOBT Positive	Cancer (%)	Cancer + AAP (%)
Sample 1	83.3	52.9
Sample 2	66.7	52.9
Sample 3	100	61.8
Samples 1 and 2	83.3	64.7
Samples 1, 2, and 3	100	76.5

*Six colorectal cancers (CRC) and 28 advanced adenomatous polyps (AAP).

[†]At the 100 ng Hb/mL threshold.

Id. at 7. Vilkin reports that the authors would continue with three fecal tests per subject, as they had “confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” *Id.* at 8; EX2001 ¶69.

For sample handling, Vilkin describes that a fecal probe with a serrated tip is “poked into the stool,” and that the tip is then put back into the sampling device that contains “Hb stabilizing buffer.” EX1005 at 4. Vilkin required that samples are “kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.” *Id.* Vilkin also states that “storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability.” *Id.* at 8. Thus, although Vilkin states that the tip of the sample

collection probe is “put in a closed amount of Hb stabilizing buffer,” Vilkin teaches that refrigeration was required to prevent decay. *Id.* at 4; EX2001 ¶70.

3. Itzkowitz (EX1006)

Itzkowitz focuses on testing what it identified as “version 2” of Exact Sciences’ own fecal DNA test for CRC, a test with “improved DNA stabilization / isolation techniques and a new promoter methylation marker.” EX1006 at 1. As disclosed in Itzkowitz, the “optimal combination of vimentin methylation plus DIA resulted in 87.5% sensitivity and 82% specificity.” *Id.* Further “cancers were detected regardless of stage or location.” *Id.*; EX2001 ¶¶74-75.

Itzkowitz recognizes the need for “availability of a noninvasive screening test that is convenient, safe, and easy to perform at home without bowel preparation or dietary restriction” to increase participation in CRC screening. EX1006 at 5. As Itzkowitz notes, “[i]nherent in the success of any screening test is patient acceptance.” *Id.* at 6. Itzkowitz also refers to a “previous multicenter study in which subjects preferred fecal DNA testing to both the fecal occult blood test and colonoscopy.” *Id.* at 7; EX2001 ¶76.

Itzkowitz provides no data concerning adenomas, stating that “[h]ow well the new fecal DNA assay might perform for detecting adenomas is not yet known, but will be the subject of future investigations.” EX1006 at 7; EX2001 ¶77.

Consistent with various other references, Itzkowitz refers to gFOBT tests as a point of comparison, noting that “[f]ecal DNA testing has shown greater sensitivity than guaiac-based occult blood tests” for non-invasive CRC screening. EX1006 at 1. Itzkowitz does not suggest combination of FOBT with nucleic acid testing. *See generally Id.*; EX2001 ¶78.

Itzkowitz concludes that “[a]n improved fecal DNA test that incorporates only 2 markers shows much higher sensitivity for CRC. The new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening.” EX1006 at 1; EX2001 ¶79.

4. Kanaoka (EX1007)

Petitioner relies on Kanaoka in Grounds II, IV, and VII. *See* Pet. at 12. Kanaoka describes a “method of detecting a tumor marker for diagnosing colon cancer which comprises collecting biological sample which is immediately frozen using liquid nitrogen in some cases.” EX1007 (Abstract). Kanaoka sought to “provide a non-invasive and convenient tumor marker detecting method for diagnosing colon cancer, which is superior in sensitivity and specificity to the existing fecal occult blood test.” *Id.* at [0015]. Kanaoka also includes results from an iFOBT “for comparison and reference.” *Id.* at [0057]; EX2001 ¶81.

Kanaoka discloses that the tested COX-2 marker had 90% sensitivity while the comparison iFOBT had 82.1% sensitivity. *Id.* at [0065]-[0066]; EX2001 ¶81.

The iFOBT test had three false positives among the control cases (specificity 86.3%), where the COX-2 test had no false positives in the control cases (specificity 100%). EX1007 at [0065]-[0066]; EX2001 ¶82. If the results from these two tests are considered together, they show an insignificant increase in sensitivity with a more significant decrease in specificity. EX2001 ¶¶82-84.

5. Shuber (EX1008)

Shuber is a patent application with two named inventors, Anthony Shuber and Petitioner's declarant, Dr. Whitney. EX1008. The Shuber priority date is May 14, 2004 and the applicant is the Patent Owner here, Exact Sciences. *Id.*

Shuber concerns preparing samples for use in nucleic acid-based testing. EX1008 (Field of the Invention). Shuber describes a method for stabilizing nucleic acids in biological samples, including stool samples, to facilitate analysis in a nucleic acid integrity assay. *Id.* at 2:5-9. According to Shuber, “[i]n one embodiment, the invention may be useful to avoid or reduce the number of false negative results in a screen of a population of individuals for one or more indicia of adenoma or early stage cancer (e.g., using a DNA integrity assay, a multiple mutation assay, a hypermethylation assay, or any combination thereof).” *Id.* at 28:23-27. Each of these is a nucleic acid-based test. EX2001 ¶88.

Shuber acknowledges that “detecting adenomas is particularly useful for identifying early signs or risks of colorectal cancer (e.g., cancerous and

precancerous lesions or growths in the colon).” EX1008 at 13:7-8. According to Shuber, testing for various combinations of nucleic acid markers could detect adenomas with 60%, 74%, 90% and even “greater than 95% sensitivity (e.g., greater than 98% sensitivity).” *Id.* at 14:1-16; EX2001 ¶89.

Shuber says very little about sample collection, stating that “a sample (e.g., a stool sample) may be directly deposited into a container (e.g., a sealable container [sic])” that either already contains a stabilization solution or to which a stabilization solution may be added. EX1008 at 29:7-19. Shuber does not specifically mention home collection. *See generally* EX1008; EX2001 ¶90.

6. Inbar (EX1009)

Inbar is an international patent application published in 1997. EX1009 at 1. Inbar describes a “system for collecting, storing and transporting” specimens of a “pasty material” including stool. *Id.* Inbar does not describe at home collection of the fecal sample. EX2001 ¶93. Petitioner concedes as much, asserting only that a POSA “would recognize” that the collection process of Inbar “would occur at a subject’s home.” Pet. at 54. Petitioner’s only basis for this unfounded assumption is that the samples of Inbar are shipped to a laboratory for testing. *Id.* Petitioner ignores that the sample collection described in Inbar could take place in a doctor’s office or clinic, and that Inbar says nothing to suggest otherwise. EX2001 ¶93.

Inbar notes that, at times different entities have to be assayed, and that “[t]his is the case, for example, in stool, where it is generally desired to assay both bacteria and parasites, which as noted above, require different media.” EX1009 at 4:13-16. Where the different entities to be assayed “require” different media, then the system includes two containers, each with a different “preservation medium.” *Id.* at 4:16-18.

Inbar includes a single reference to “cryptic blood” in the background of the invention where it states that “[c]ollection and transportation of a pasty material, such as stool, food samples, soil samples, and the like for purposes of laboratory manipulation such as detection of microorganism being bacteria or parasites, detection of cryptic blood, preparation of a biochemical profile, etc., is an essential component of modern medicine, health care and environmental management.” *Id.* at 1:7-12. Inbar also states that composition of the preservation medium depends on the substance to be preserved, for example, “if the entity is a chemical substance, the medium will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration.” *Id.* at 4:4-8. Inbar does not disclose a “solution that prevents denaturation or degradation of blood protein” in a fecal sample. *See generally id*; *see also* EX2001 ¶¶93-94.

Inbar says nothing about preserving, extracting, and/or testing for nucleic acid in fecal samples. *See generally* EX1009; EX2001 ¶97.

V. CLAIM CONSTRUCTION IS NOT NECESSARY TO DENY INSTITUTION

Petitioner proposes no claim constructions. Patent Owner does not believe that the Board must construe any claim terms in order to deny institution. Patent Owner reserves the right to assert claim construction positions should the Board institute IPR.

VI. PETITIONER’S GROUNDS FAIL ON THE MERITS

The Grounds presented in the Petition are deficient for at least the following reasons, and the Board should deny institution.

A. Level of Ordinary Skill in the Art

In its challenges to the ’746 patent and its parent, the ’781 patent, the Petitioner has offered two, significantly different, proposed levels of skill for the person of ordinary skill. EX2001 ¶¶48-50. Geneoscopy asserted in its reexamination request concerning the ’781 patent that a person of ordinary skill in the art (“POSA”) in the relevant field of the invention of the ’781 patent:

would have had at least a Bachelor of Science degree in Biology (or a similar major) and several years of experience in the processing of biological samples, such as fecal samples from a human. Such a person would have been well-acquainted with methods of collecting fecal samples, preserving proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, and subsequently evaluating the fecal samples for proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, as of February 3, 2009.

EX2042 at 7; EX2001 ¶49. In the Petition, Petitioner contends that a “POSA relevant to the ’746 Patent would have a Ph.D. in chemistry, biochemistry, biology, or a related field and at least five years of experience designing and performing diagnostic assays on fecal samples.” Pet. at 12.

Patent Owner disagrees with both of Petitioner’s proposals. Although Petitioner’s proposed level of skill in the reexamination touches on the breadth of potentially relevant topic areas, the education level of a Bachelor of Science degree is less than is typical for individuals of ordinary skill in this field. EX2001 ¶50. On the other hand, the level of skill set forth in the Petition requires an extraordinary level of skill within an overly narrow focus. *Id.* The proper level of ordinary skill in somewhere between the two and takes into consideration the full scope of the claimed invention. Specifically, a POSA would have a doctoral degree in medicine, chemistry, biochemistry, biology, or a related field and 1-2 years of experience in the processing and analysis of biological samples, including fecal samples. *Id.* ¶51. Such a person could have been an individual or a member of a team of scientists addressing fecal sample processing and analysis. *Id.* The Board accepted Patent Owner’s definition for purposes of the Institution Decision in IPR2024-00459. EX1033 at 8.

Patent Owner has submitted with this POPR the declaration of Dr. Vadim Backman. EX2001. No matter which of the three different levels of skill is applied,

Dr. Backman is a person of at least ordinary skill, and it does not change that the claims of the '746 patent would not have been obvious to a person of ordinary skill as of the priority date. *Id.* ¶¶2-9, 53-54.

B. All Grounds: Petitioner Shows No Motivation for User Separation of Fecal Sample into Two Separate Sealable Containers at Home

Petitioner's argument assumes, without support, that a POSA would be motivated to have the user separate the sample into two separate containers with two different buffers. Petitioner offers no reason why a POSA having only the knowledge in the art as of February 2009 would have arrived at the claimed method. EX2001 ¶122.

At most, Petitioner's declarant Dr. Whitney opines that "many assays used different stabilizing buffers to minimize loss of sample integrity." EX1002 ¶75. He then provides examples of some references that discuss buffers to prevent degradation of DNA and of other references that use buffers to stabilize blood protein. *Id.* Notably, the Whitney declaration offers no opinion that a POSA in 2009 would have understood that a "DNA preservation" buffer would be unsuitable to stabilize blood protein, or vice versa. *See id.* At deposition in connection with related IPR2024-00459, Dr. Whitney testified that he had not formed an opinion as to whether or not a single buffer could stabilize both DNA and protein. EX2020 at 148:14-22; 149:18-150:20. Accordingly, Petitioner has not

shown why a POSA would have been motivated to have the user separate the fecal sample at home.

There is nothing in the cited references that would have motivated a POSA to arrive at the claimed method where the at-home user divides the sample into two portions, combines the first portion with a stabilizing buffer, and combines the second portion with a solution that prevents denaturation or degradation of blood proteins. To begin, Lenhard does not teach either at home collection or user interaction with the sample. *See generally* EX1004. To the contrary, Lenhard expressly states that the samples were separated after receipt. *Id.* at 2. (“Samples were received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80°C”). The “iFOBT of Vilkin” used an “amount of Hb stabilizing buffer” in the sample tube. EX1005 at 4. However, Vilkin does not identify the components of the “Hb stabilizing buffer.” *Id.* Itzkowitz also describes use of a buffer, referred to as a “DNA-stabilizing buffer.” EX1006 at 2. Neither Vilkin nor Itzkowitz addresses whether a “DNA-stabilizing buffer” could also be used as an “Hb stabilizing buffer.” Without such teachings, there would have been no motivation for a POSA to develop a test requiring at-home interaction with the sample to combine two separate portions of the sample with different media.

Petitioner’s proposed Shuber/Vilkin and Shuber/Vilkin/Inbar combinations similarly provide no motivation to develop a method for processing freshly-

collected fecal sample where the user must interact with the sample to separate it into two portions at home.

Absent a compelling reason why the fecal sample would have to be separated at the time of at-home collection, a POSA as of the priority date would not have been motivated to develop a test that required user interaction with the stool sample to separate the sample into two containers. EX2001 ¶122. Without the roadmap of the '746 patent claims, the less complex and more patient-acceptable approach would have been to use a nucleic acid stabilizing buffer that also preserves blood protein. *Id.* ¶¶122-124. This would have resulted in a less complex test with fewer components. It also would have eliminated any need for at-home interaction with the sample because, with the use of a single buffer in a single container, the sample would be separated at the lab.

C. Ground I: Petitioner Fails to Establish That Lenhard in View of Vilkin and Itzkowitz Renders Claims 3-4 and 14-19 Obvious

In Ground I, Petitioner argues that it would have been obvious to use “the iFOBT of Vilkin and the fecal collection and DNA stabilization process of Itzkowitz in the fecal screening method of Lenhard to arrive at the method of the challenged claims.” Pet. at 19. Petitioner then relies on select elements of each of the references to assert that a POSA would have been motivated to combine the references to “improve” on Lenhard. When the references are considered in their

entirety, as they must be, they would not have motivated a POSA to arrive at the claimed invention. Rather, the combined teachings of the references would suggest to a POSA that the modifications proposed by Petitioner would result in a less specific, more costly, and less patient friendly test.

1. The Lenhard, Vilkin, and Itzkowitz Combination Does Not Teach or Suggest the Claimed Invention

Petitioner asserts that Lenhard discloses “a method of processing a fecal sample that includes collecting it from a subject, testing a first portion for cancer-specific DNA and testing a second portion for blood proteins.” Pet. at 19. To begin, Petitioner mischaracterizes Lenhard—the gFOBT of Lenhard tests for heme, not for blood protein. EX2001 ¶58. Petitioner then picks and chooses from both Vilkin and Itzkowitz to argue that a POSA would have been motivated to make multiple significant modifications to Lenhard including (i) replacing the laboratory collection and sample separation of Lenhard with at-home collection and sample separation, (ii) using fresh rather than frozen samples, (iii) using the specific at-home collection device of Itzkowitz, (iv) using the specific iFOBT stool probe of Vilkin to, at home, remove a portion of the sample from the at-home collection device of Itzkowitz, and (v) sending the sample for testing for both blood protein and nucleic acid. Pet. at 19-28. A POSA would not have come to these multiple

changes to Lenhard without the roadmap of the '746 patent and impermissible hindsight.

As Petitioner acknowledges, Lenhard provides “few details regarding sample collection.” Pet. at 22. Lenhard discloses laboratory collection of samples that were then frozen before testing for nucleic acid. EX1004 at 2; EX2001 ¶56. Vilkin requires that each subject prepare three consecutive daily samples. EX1005 at 3 (Methods), 4; EX2001 ¶69. Vilkin also requires refrigeration for sample preservation. EX1005 at 4 (samples are “kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.”), 8 (“storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability”); EX2001 ¶70. Itzkowitz describes direct defecation into a “special stool collection kit.” EX1006 at 2. Itzkowitz does not describe any separation or removal of stool from that collection kit. *Id.* Itzkowitz also discloses that subjects preferred fecal DNA testing to FOBT. *Id.* at 7 (referring to a “previous multicenter study in which subjects preferred fecal DNA testing to both the fecal occult blood test and colonoscopy.”); EX2001 ¶¶76, 117. One significant distinction between the collection kit of Itzkowitz and FOBT, including the stool probe of Vilkin, is that the user directly defecates into the sealable Itzkowitz collection kit, thus requiring no interaction with the stool sample. EX2001 ¶119; EX1006 at 2; EX1005 at 4.

Petitioner's use of the sample collection device of the Vilkin iFOBT with the DNA-only test of Itzkowitz to arrive at the particular features of the claims reflects classic impermissible hindsight. Even if Petitioner had shown a motivation to combine stool nucleic acid-based CRC tests with iFOBT as of the priority date, which they have not, the combination would not have resulted in the specific at-home collection method of the claims.

2. Petitioner Fails to Establish That A POSA Would Have Been Motivated to Combine Lenhard with Vilkin and Itzkowitz

Petitioner's argument begins from the premise that a POSA would have been motivated to combine a nucleic acid test with FOBT based on Lenhard's statement that the "combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs," and that use of both the HIC1 methylation markers and gFOBT in Lenhard "increased detection rates for CRCs" and "detected all localized cancers." Pet. at 19. Stated differently, Petitioner asserts that the reported increased sensitivity of Lenhard's specific HIC1/gFOBT combination over the sensitivity of either HIC1 or gFOBT individually would have provided motivation to combine tests for different types of markers. Petitioner's argument improperly ignores the other teachings of Lenhard, Vilkin, and Itzkowitz as well as the teachings of the background references on which Petitioner relies. *See, e.g.,*

Arctic Cat, Inc. v. Bombardier Recreational Products, Inc., 876 F.3d 1350, 1360 (Fed. Cir. 2017) (“it is error to fail to consider the entirety of the art.”).

Petitioner further argues that a POSA would have been motivated to modify Lenhard to “include Vilkin’s iFOBT” because Vilkin teaches advantages of iFOBT over gFOBT, including “higher sensitivity than gFOBT,” eliminating the need for dietary restrictions associated with gFOBT, and that iFOBT is quantitative. Pet. at 20. Here too Petitioner ignores all of the aspects of Vilkin that would have discouraged combination with “Vilkin’s iFOBT,” including the need for three samples that are taken over three days and refrigerated over that time. EX1005 at 3-4, 6, 8. Neither the references nor Petitioner’s arguments set forth any rationale for how a POSA in 2009 would have chosen the specific elements of the ’746 patent claims from three different references—to the exclusion of the other teachings of those references—to arrive at the claimed invention.

- (a) Lenhard Would Not Have Suggested to a POSA that Testing for Different Classes of Markers Would Result in Greater Sensitivity for CRC Screening Than a Single Class of Markers

Petitioner relies on Lenhard’s disclosure of 65% sensitivity using the combined results from a single DNA methylation marker and gFOBT to argue that a POSA would have been motivated to combine iFOBT with nucleic acid-based testing. Pet. at 19. Petitioner has no explanation for why a POSA would pursue the

more complex solution of developing a test for two different classes of markers rather than pursuing improvements to either iFOBT alone or nucleic acid testing alone. This is particularly so where the specific HIC1/gFOBT combination has lower sensitivity than had been disclosed for FOBT-only or nucleic acid-only tests that did not add the complexity of combination. Petitioner's increased sensitivity argument also ignores that Lenhard's combined HIC1/gFOBT results showed no improved sensitivity in screening for advanced adenomas, a fact that Lenhard found worth noting. EX1004 at 6 ("Although the combined test detected all localized cancers, no increase in the sensitivity for adenoma was seen."); EX2001 ¶62.

When Lenhard is considered as a whole, it does not provide motivation to develop a combined test for both nucleic acid and fecal occult blood, particularly not based on Petitioner's asserted motivation of increased sensitivity. EX2001 ¶¶55-68, 101-103, 110-112. Petitioner relies on Lenhard's statement that the "combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs." Pet. at 13, 19. However, Lenhard discloses that another methylation marker alone, SFRP2, was more sensitive, "detecting 77%-90% of CRCs," although Lenhard also notes that the "specificity of SFRP2 methylation was quite poor, at 77%." EX1004 at 2; EX2001 ¶103. Lenhard concludes that the study shows "HIC1 as a sensitive and specific marker well suited for stool-based

CRC screening. Combination of HIC1 with a few additional sensitive and specific methylation markers may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas.” *Id.* at 7. Thus, Lenhard expressly suggests multiple methylation markers. EX2001 ¶¶108. Without the benefit of hindsight and the ’746 patent as a roadmap, a POSA considering Lenhard would have pursued a combination of additional sensitive and specific methylation markers.

Further, the specific HIC1/gFOBT combination discussed in Lenhard showed no increase in sensitivity for advanced adenomas. EX1004 at 6; EX2001 ¶101. Table 2 of Lenhard provides data for thirteen patients with large, advanced adenomas. *Id.* at 3. The single advanced adenoma that was detected by FOBT was also detected through the HIC1 methylation analysis. *Id.*; EX2001 ¶62. The combination on which Petitioner relies thus provided no improved sensitivity for this critical element of CRC screening tests. EX2001 ¶¶62, 101.

Vilkin and Itzkowitz also each disclose tests that were more sensitive than the combined HIC1/gFOBT results reported in Lenhard. The Vilkin authors achieved sensitivity of 76.5% with “acceptable specificity” of 95.3% for a combination of both CRCs and advanced adenomas using an iFOBT threshold of 100 ng Hb/mL and testing three samples from each subject. EX1005 at 7-8. Vilkin concludes that a particular desktop iFOBT test is highly sensitive and specific: “we have found this desktop, automated-developed and quantified Hb version of the

immunochemical fecal occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with an acceptable specificity and consequent high negative predicative value.” *Id.* at 8. According to Vilkin, its results mean “that in this group of high-risk and symptomatic patients, all cases of cancer and most advanced adenomas would be detected and a negative test would provide a very high degree of certainty that there was no clinically significant colorectal neoplasia at this round of screening.” *Id.*; EX2001 ¶104.

Itzkowitz describes data from two DNA-only based tests, both of which showed greater sensitivity than the HIC1/gFOBT combination of Lenhard. First, Itzkowitz describes an increase in sensitivity from 52% to 72.5% in version 1 of Exact Sciences’ DNA-only based test. EX1006 at 6. The increase was attributed to the improved methods of stabilization and extraction. *Id.* Itzkowitz notes that this improvement in version 1 was achieved at a “relatively minor decrease in specificity from 94.4% to 89.3%.” *Id.* Itzkowitz then focuses on version 2 of the Exact Sciences panel, finding that, “[t]he combination of vimentin plus DIA-DY resulted in an optimal sensitivity of 85.5% (95% CI, 73.9%-94.5%). This optimal combination detected most cancers, including early stage (stage I) lesions, regardless of their location in the colon.” *Id.* Itzkowitz concludes that its “results suggest that with only 2 markers (vimentin + DY) providing a sensitivity of 88%, the 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.” *Id.* at 7. Accordingly, Itzkowitz describes a series of improvements in DNA-based testing and concludes that a combination of DNA-based markers could achieve acceptable sensitivity with reduced complexity. EX2001 ¶¶105-106.

Further, a POSA in 2009 would recognize that whether and how much any particular combination would improve sensitivity was highly unpredictable. By 2009, it was already well established that a combination of biomarkers often performs worse than individual biomarkers. EX2001 ¶¶110. For example, as demonstrated by the adenoma results reported in Lenhard, a combination could result in no improvement in sensitivity coupled with reduced specificity. *Id.* ¶¶110-111. Therefore, a POSA seeking to improve a CRC screening test as of the priority date would not have been motivated by Lenhard, Vilkin, and Itzkowitz to combine different classes of markers, even before the multiple other factors that would have weighed against combination are taken into account. *Id.* ¶¶101-109. Rather, a POSA would have avoided the pitfalls of combination and instead pursued improvements to either FOBT alone or nucleic acid testing alone. *Id.*

(b) A POSA Would Have Been Dissuaded by Reduced Specificity

As discussed above, Petitioner argues that the sensitivity of Lenhard’s HIC1/gFOBT combination provides the motivation to combine. In its Institution

Decision concerning the related '781 patent, the Board noted that the claims “do not require a particular level of sensitivity or specificity.” EX1033 at 18. However, Patent Owner’s point concerning specificity is that, whether or not Lenhard provides a motivation to combine cannot be based on a single parameter, but must instead take into account the prior art as a whole and whether it suggests the combination. *See Arctic Cat*, 876 F.3d at 1363 (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”). A POSA would not have considered potential increased sensitivity alone, but would have also considered impact on specificity and other factors, such as increased complexity. EX2001 ¶¶110-124. Petitioner’s own expert testified in connection with IPR2024-00459 that “sensitivity and specificity, in my opinion, should always be looked at in combination.” EX2020 at 169:13-17. Yet the Petition does not even attempt to address reduced specificity. *See generally* Pet.

Considered in its entirety, Lenhard teaches that its specific HIC1/gFOBT combination reduced the specificity for CRC from 98% (HIC1 alone) to 89% (HIC1 and gFOBT). EX2001 ¶¶64, 111. Lenhard also expressly teaches that “methylation markers as well as genetic markers need to be selected carefully to achieve both high sensitivity and specificity.” EX1004 at 7. Lenhard further points out that “low specificity of a test results in a low positive predictive value and consecutively in high rates of unnecessarily performed colonoscopies.” *Id.*

Petitioner's own cited references support that a POSA would not be motivated by sensitivity without also considering impact on specificity. For example, Petitioner asserts that a 2007 review article concerning iFOBT noted that iFOBT “provides for an improved sensitivity/specificity ratio; in other words, they can achieve better sensitive *without an unacceptable deterioration in specificity.*” Pet. at 21, citing EX1020 at 29 (emphasis added).

A POSA would not have been motivated by the teachings of Lenhard to combine classes of markers where the specific HIC1/gFOBT combination (1) resulted in lower specificity, (2) was still less sensitive than existing DNA-only or FOBT-only tests, and (3) showed no improvement in detecting advanced adenomas. EX2001 ¶¶103, 110-112.

(c) A POSA Would Have Been Dissuaded by the Requirements of Vilkin, Including the Need for Multiple Samples and Refrigeration

Petitioner asserts that a POSA would have combined the “iFOBT of Vilkin” with Lenhard and Itzkowitz and that it would have been obvious to “replace the gFOBT of Lenhard with the iFOBT of Vilkin” because of certain purported advantages of iFOBT over gFOBT. Pet. at 20-21. One such “advantage” according to Petitioner was “collecting fewer fecal samples.” *Id.* at 21. Petitioner points to Young which states that most branded versions of iFOBT “require fewer than three fecal samples, the recommended number for GFOBT.” EX1020 at 4. Yet the

iFOBT of Vilkin requires that the subject prepare three consecutive daily fecal samples. EX1005 at 3 (Methods), 4. Vilkin also discloses that the “best results were obtained when all three tests were performed and utilized for analysis.” *Id.* at 6. Vilkin reports that they would continue to collect three fecal tests per subject as they had “confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” *Id.* at 8. Thus, the iFOBT of Vilkin did not provide the advantage of requiring fewer fecal samples than gFOBT. Further, Petitioner asserts that modifying Lenhard to use “the sample collection and stabilization method of Itzkowitz and the iFOBT of Vilkin” would produce “two samples.” Pet. at 24. However, considering that Vilkin requires collection of three samples over three days, the combination of Itzkowitz and the iFOBT of Vilkin would result in a minimum of four samples, one for DNA and three for iFOBT, and up to six samples, if collection were done for both tests on each of the three days of sample collection that Vilkin teaches.

In addition, and unlike gFOBT, use of the iFOBT of Vilkin requires that samples be “kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.” EX1005 at 4; EX2001 ¶¶70, 114. According to Vilkin, “storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability.” EX1005 at 8; EX2001

¶¶70, 114. Vilkin also notes “screeners’ hesitancy about keeping the prepared test transiently in their home refrigerator.” *Id.*; EX2001 ¶¶71, 115.

The “iFOBT of Vilkin” on which Petitioner relies required both testing of three separately-collected daily samples and refrigeration of those samples in the test subject’s home refrigerator over multiple days. EX1005 at 4, 8. These requirements would have dissuaded combination of the iFOBT of Vilkin with any other form of test. EX2001 ¶¶113-116.

(d) A POSA Would Not Have Been Motivated to Increase Complexity and Cost with a Combination of Multiple Classes of Markers

Petitioner’s proposed combination would result in a test with increased cost and complexity. A POSA seeking to improve CRC screening tests would not have been motivated to pursue an approach that would increase both cost and complexity unless there was a significant likelihood of substantial performance gains that could not be achieved otherwise. EX2001 ¶¶117-124. Here, the cited references do not suggest the likelihood of any meaningful performance gains from combining tests for two different classes of markers, and a POSA would have had no motivation to make the combination. *Id.*

As noted in Itzkowitz, “[i]nherent in the success of any screening test is patient acceptance.” EX1006 at 6. Itzkowitz’s “preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirm[ed]

a very high degree of patient satisfaction.” *Id.* at 6-7. “These findings support results from the previous multicenter study in which ***subjects preferred fecal DNA testing to both the fecal occult blood test*** and colonoscopy.” *Id.* at 7 (emphasis added); EX2001 ¶117.

In addition, requiring a patient to remove a portion of stool from the sample for the FOBT test increases complexity at the collection site and significantly reduces the advantage of the direct defecation device of Itzkowitz that avoids the patient having to interact with their stool. EX2001 ¶119. A POSA’s knowledge concerning user reluctance would have further discouraged the collection method claimed in the ’746 patent in this area where patient acceptance is critical to success. *Id.*

A POSA would not have been motivated to add an FOBT test to the patient-preferred test of Itzkowitz to arrive at the claimed invention of the ’746 patent. Combining a nucleic acid test with an FOBT test requires, among other things, more collection components and separate testing once the samples are delivered to the lab. EX2001 ¶¶118, 121. This requires two sets of equipment for the two different types of tests as well as different skill sets and training for the lab personnel responsible for testing the samples. *Id.* Each of these adds cost, complexity, and an increased potential for error, all of which would have weighed against combination. *Id.*

Although Petitioner relies on a specific combination with the “iFOBT of Vilkin,” Petitioner also argues that a POSA would have been motivated more generally by “advantages of iFOBT over gFOBT” that were purportedly known by the priority date. Pet. at 20. The 2008 Levin reference on which Petitioner relies contradicts that argument. EX1013. Levin looked at studies that compared the then currently-marketed most sensitive gFOBT with iFOBT (referred to as fecal immunochemical tests or “FIT” in Levin). EX1013 at 7. Based on data from six studies, Levin concludes that there were “no clear patterns of superior performance [...] between a high-sensitivity guaiac-based test (Hemoccult SENSE) and a variety of FIT.” *Id.* Levin also notes “higher costs associated with FIT compared with gFOBT.” *Id.*; EX2001 ¶137.

Nothing in the references on which Petitioner relies suggests that testing for two different classes of markers would improve diagnostic performance over a single class of markers, let alone that such a combination would have sufficiently improved diagnostic performance to warrant the increased complexity and cost. In light of the advancements disclosed in the cited references for each of iFOBT and nucleic acid testing individually, and considering the express teachings of the cited references, there would have been no reason for a POSA to increase cost and complexity by combining tests for two classes of markers. There would also have been no motivation for a POSA to combine nucleic acid testing with the iFOBT of

Vilkin where the Vilkin test relied on testing three samples per subject and required sample refrigeration. Further, even assuming that a POSA would consider a combination of classes of markers based on Lenhard, Petitioner's own cited references reveal that by 2008 there was at least one gFOBT test over which iFOBT tests had no clear performance advantages. Petitioner has not demonstrated any reason why a POSA at the time would have combined only the specific, selected aspects of Lenhard, Vilkin, and Itzkowitz to arrive at the claimed invention. EX2001 ¶¶122-124.

D. Ground III: Petitioner Fails to Establish That Shuber in View of Vilkin Renders Claims 3-4 and 14-19 Obvious

Petitioner's Ground III relies on a combination of Shuber and Vilkin. The Shuber patent application is assigned to Patent Owner Exact Sciences. EX1008. The two named inventors on the Shuber application, one of whom is Petitioner's declarant Dr. Whitney, were both employed by Exact Sciences as of that application's 2004 priority date. *Id.*; *see also* EX1003 at 3. Vilkin was published in 2005. EX1005. Yet four more years went by before the priority date of the '746 patent in 2009. Petitioner cites numerous references concerning CRC screening that were published during those four years, including references describing continued work by teams at Exact Sciences. *See* Pet. at viii-xv. Considering the widely recognized need for improved CRC screening, logic suggests that only with

the benefit of hindsight would Shuber and Vilkin be combined to arrive at the claimed invention.

When considered as a whole, the cited references do not teach or suggest the claimed method of the '746 patent, nor do they provide motivation to combine the nucleic acid-based test of Shuber with the iFOBT of Vilkin. EX2001 ¶125-140. Moreover, even if such motivation were found, nothing in Shuber, Vilkin, or the other cited references suggests the specific configuration of the claimed invention. EX2001 ¶141.

1. The Shuber and Vilkin Combination Does Not Teach or Suggest the Claimed Invention

Petitioner asserts that Shuber “describes the possibility of using multiple tests in combination to improve the test’s sensitivity for detection of CRC.” Pet. at 17. Shuber states that “[i]n one embodiment, the invention may be useful to avoid or reduce the number of false negative results in a screen of a population of individuals for one or more early stage cancer (e.g., using a DNA integrity assay, a multiple mutation assay, a hypermethylation assay, or any combination thereof.”) EX1008 at 28:23-27. On its face, Shuber suggests combination of nucleic acid-based tests only—not a combination with blood-based tests or with any other category of test. EX2001 ¶127. In fact, Shuber discloses that testing only for various combinations of nucleic acid markers could detect adenomas with 60%,

74%, 90% and even “greater than 95% sensitivity (e.g., greater than 98% sensitivity).” EX1008 at 14:1-16; EX2001 ¶128.

As discussed above, Vilkin describes, *inter alia*, a particular desktop test instrument and the testing of three samples per patient where the “best results were obtained when all three tests were performed and utilized for analysis.” EX1005 at 6.

Petitioner’s combination of Shuber and Vilkin to arrive at the specific elements of the claimed invention is based on impermissible hindsight knowledge of the claims. For example, the claims require at home collection by the subject. EX1001 at 45:59-61. The claims also require two separate sealable vessels, each containing a portion of the fecal sample where the first portion is combined with a stabilizing buffer and the second portion is combined with a solution that prevents denaturation or degradation of blood proteins. EX1001 at 45:63-67; 46:56-57. Shuber says little about sample collection and nothing about at-home collection by a patient. EX1008 at 29:8-19; EX2001 ¶129. Vilkin describes using stool probes to collect samples over three consecutive days. EX1005 at 4; EX2001 ¶130. Neither reference discloses or suggests that the subject separate one stool sample such that there is a first portion and a second portion, each in a separate sealable container, where the first portion is tested for nucleic acid and the second portion for blood protein, as required by the claims. EX1005; EX1008; EX2001 ¶¶129-131. Thus,

the proposed combination of Shuber with Vilkin fails to teach or suggest all of the claimed elements as arranged in the claims.

2. Petitioner Fails to Establish That A POSA Would Have Been Motivated to Combine Shuber with Vilkin

Petitioner argues that a POSA would have been motivated to combine Shuber with Vilkin “to arrive at a CRC diagnostic test with improved sensitivity.” Pet. at 38. As with the previous combination, Petitioner ignores the portions of the cited references that would have dissuaded a POSA from such a combination, including the potential for an unacceptable decrease in specificity and the increased complexity of a test for multiple marker classes. *See Arctic Cat*, 876 F.3d at 1363 (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”).

(a) The References on Which Petitioner Relies Do Not Suggest Enhanced Performance from Combining Tests for Different Classes of Markers and Would Not Have Motivated the Combination of Shuber with Vilkin

In an attempt to justify the proposed combination, Petitioner incorrectly asserts that “the advantages of combining such stool DNA and blood protein assays were well understood in the art” by the priority date. Pet. at 38. Petitioner relies on various select quotes from references going back to 2002. Taken in the context of the references as a whole, and in the context of the knowledge in the art as of the priority date, the statements on which Petitioner relies would not have

motivated a POSA to combine Shuber with the iFOBT of Vilkin, and certainly not in a way that would result in the claimed invention. EX2001 ¶¶132-139.

Petitioner first relies on a sentence from the 2002 Nishikawa reference. Pet. at 38-39, citing EX1011. Nishikawa concludes that the tested method of detecting *K-ras* point mutations “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. The statement in this 2002 reference is pure speculation without reference to any data or support. *Id.* Notably, seven years passed between Nishikawa and the invention of the ’746 patent without anyone else arriving at the claimed invention before the priority date. EX2001 ¶133. Further, as discussed below, the other art on which Petitioner relies that was published between 2002 and the priority date suggested that a combination of marker classes would not result in improved diagnostic performance where a potential increase in sensitivity would have to be balanced against any decrease in specificity. *Id.* ¶¶134-140.

Petitioner also cites to Lenhard as providing purported motivation to combine Shuber with Vilkin. Pet. at 39. However, as discussed above, consideration of the complete Lenhard reference would have dissuaded a POSA from combining a nucleic acid marker test with FOBT for CRC screening. EX2001

¶¶55-68, 134. As is also discussed above, Lenhard itself concludes that the study shows “HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 with a few additional sensitive and specific methylation markers may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas.” EX1004 at 7. There is no teaching, suggestion, or motivation to combine FOBT with nucleic acid testing for CRC screening in Lenhard.

Petitioner also cites to the 2005 Kutzner reference for purported motivation. Kutzner describes a retrospective study of frozen samples. Kutzner poses an unanswered question of “whether both [MD and gFOBT] methods should be used together in broad diagnostic screening programs.” EX1012 at 8. The Kutzner authors acknowledge that their “retrospective data *do not allow* any conclusion on the potential of this approach in diagnostic screening. Prospective comparative studies, which include a very high number of individuals, have to prove the value of the combined application of MD and FOBT.” *Id.* (emphasis added). More importantly, by posing the question, Kutzner reveals that the answer was neither obvious nor predictable. It would not have been obvious to a POSA to combine nucleic acid-based testing with FOBT with any reasonable expectation that the combination would result in improved performance over tests for a single class of markers. EX2001 ¶¶135, 140. In addition, as discussed above, any potential for

improved performance would also need to be weighed against the negative aspects of requiring increased user interaction with the sample as well as notable increases in test complexity and cost that would result from a combined test.

The Petitioner also cites Levin as purportedly providing motivation to combine. Pet. at 40. However, Levin does nothing more than pose a question for potential investigation. *Id.* at 40. Levin posits that “[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 (emphasis added). Thus, Levin indicates that a POSA would not be motivated to combine nucleic acid tests with FOBT considering the results shown in Lenhard and Kanaoka, both of which show adverse effects on specificity when results from nucleic acid testing and FOBT were considered together. EX2001 ¶¶136, 138-139. Further, as discussed above, Levin concludes that there were “no clear patterns of superior performance between a high-sensitivity guaiac-based test (Hemoccult SENSAs) and a variety of FIT.” *Id.* ¶137. In addition, Levin notes “higher costs associated with FIT compared with gFOBT.” *Id.* Nothing in Levin’s speculation as to “whether or not” including “a sensitive gFOBT or FIT” would improve sensitivity without adversely affecting specificity would have motivated the combination of the iFOBT test of Vilkin with Shuber, particularly not when considered in the context of the other cited references. *Id.* ¶¶136-139.

(b) Petitioner’s Purported Motivation to Combine Would Not Have Improved Shuber’s Disclosed Sensitivity

As discussed above, Petitioner argues generally that a POSA would have been motivated to combine Shuber with Vilkin to attempt to improve sensitivity. *See* Pet. at 38. However, Shuber itself discloses that testing for its set of disclosed nucleic-acid markers could be used to detect adenomas with “greater than 95% sensitivity (e.g., greater than 98% sensitivity).” EX1008 at 14:15-16. A POSA would not have been motivated to combine the nucleic acid testing of Shuber with the iFOBT of Vilkin where, based on the disclosures of Shuber, there could be little, if any, improved sensitivity, and where any such combination would make the test more complicated and would likely reduce specificity. EX2001 ¶¶118-121, 125-131.

(c) A POSA Would Have Been Dissuaded by the Requirements of Vilkin, Including the Need for Multiple Samples and Refrigeration

Petitioner asserts that a POSA would have combined Shuber with the iFOBT of Vilkin to arrive at the methods of the challenged claims. Pet. at 37-41. As with the proposed combination in Ground I, Petitioner again ignores that Vilkin requires the collection of three samples over three days as well as the refrigeration of those samples. Petitioner does not explain how or why a POSA would have chosen to combine nucleic acid testing with the iFOBT of Vilkin that required multiple

samples and where the different samples resulted in substantially different sensitivity. A POSA would not have been motivated to combine the nucleic-acid test of Shuber with the iFOBT of Vilkin. EX2001 ¶¶69-73, 113-116, 130-131.

(d) A POSA Would Not Have Been Motivated to Increase Complexity and Cost

Contrary to Petitioner’s conclusions, a POSA seeking to “improve the sensitivity of CRC diagnosis” prior to the priority date would have focused on improving either DNA-based analysis or FOBT analysis, not combining tests for two different classes of markers. EX2001 ¶ 139. Among other aspects, as discussed above, a POSA seeking to improve CRC screening tests would not have been motivated to choose a path that would increase both cost and complexity unless there was a considerable likelihood of sufficient performance gains. EX2001 ¶¶117-124, 139.

As with Ground I, nothing in the references on which Petitioner relies in Ground III suggests that testing for two different classes of markers would improve diagnostic performance over a single class of marker, let alone sufficiently improved diagnostic performance to warrant the increased complexity of the combination. In light of the advancements described in the cited references concerning each of iFOBT and nucleic acid testing individually, and considering the express teachings of the cited references, there would have been no reason for a

POSA to add cost and complexity by combining tests for two classes of markers.

There would also have been no motivation for a POSA to combine the nucleic acid testing of Shuber with the iFOBT of Vilkin where the Vilkin test relied on testing of three samples and required refrigeration of those samples. EX2001 ¶¶126-140.

Petitioner has not demonstrated any motivation to combine Shuber with Vilkin to arrive at the specific elements of the claimed invention. EX2001 ¶141.

E. Ground VI: Petitioner Fails to Establish That Inbar, Shuber, and Vilkin Render Claims 3-4 and 14-19 Obvious

In Ground VI—the proposed combination of Inbar, Shuber, and Vilkin—Petitioner refers back to Section VII(C) of the Petition concerning the proposed combination of Shuber’s nucleic acid testing and Vilkin’s iFOBT “to arrive at a CRC diagnostic test with improved sensitivity.” Pet. at 57. For the same reasons discussed above, a POSA would not have considered the potential for improved sensitivity in isolation. The addition of Inbar to the proposed Shuber and Vilkin combination does not change that there would have been no motivation for a POSA to combine these references to arrive at the claimed invention as of the priority date. EX2001 ¶142.

Inbar does not describe at-home sample collection. *See generally* EX1009; EX2001 ¶93. Further, Inbar teaches that the sample collection system should include two containers with different preservation media only when the analytes

“require” different media. EX1009 at 4:16-18; EX2001 ¶ 96. As discussed above, Petitioner has not established that a POSA in 2009 would have understood that nucleic acids and blood protein in stool required different preservation media.

Moreover, Inbar does not disclose a “solution that prevents denaturation or degradation of blood protein” in a fecal sample. *See generally* EX1009; EX2001 ¶94. Inbar also says nothing about preserving, extracting, and/or testing for nucleic acid in fecal samples. *See generally* EX1009; EX2001 ¶¶95-97.

F. Grounds II, IV and VII Also Fail

Petitioner’s Grounds II, IV and VII address only dependent claims 12 and 13. Those Grounds fail for the same reasons Grounds I, III, and VI fail.

In addition, for Claims 12 and 13, Petitioner argues that Kanaoka provides further motivation to combine to improve sensitivity. Pet. at 35, 48. Petitioner is once again impermissibly considering one aspect of a reference without considering the entire reference. *See, e.g., Arctic Cat*, 876 F.3d at 1363. The results reported in Example 1 of Kanaoka show that testing for COX-2 and using an iFOBT test resulted in one additional true positive test from the iFOBT that was not identified with the COX-2 test. EX1007 at [0067]. However, the iFOBT test also had three false positives among the control cases (specificity 86.3%), where the COX-2 test had no false positives in the control cases (specificity 100%). EX1007 at [0065][0066]; EX2001 ¶144. The combination of Kanaoka thus

resulted in an insignificant increase in sensitivity, with a more significant decrease in specificity. EX2001 ¶144. As with *Lenhard*, consideration of the Kanaoka reference as a whole would have discouraged a combination of nucleic acid-based and FOBT tests. *Id.*

VII. SECONDARY INDICIA SUPPORT NONOBVIOUSNESS

Objective evidence of nonobviousness can establish that “an invention appearing to have been obvious in light of the prior art was not,” and may be “the most probative and cogent evidence in the record.” *Apple Inc. v. Int’l Trade Comm’n*, 725 F.3d 1356, 1366 (Fed. Cir. 2013) (internal citations omitted). This evidence “guards against the use of hindsight because it helps turn back the clock and place the claims in the context that led to their invention.” *Id.* (internal citations omitted).

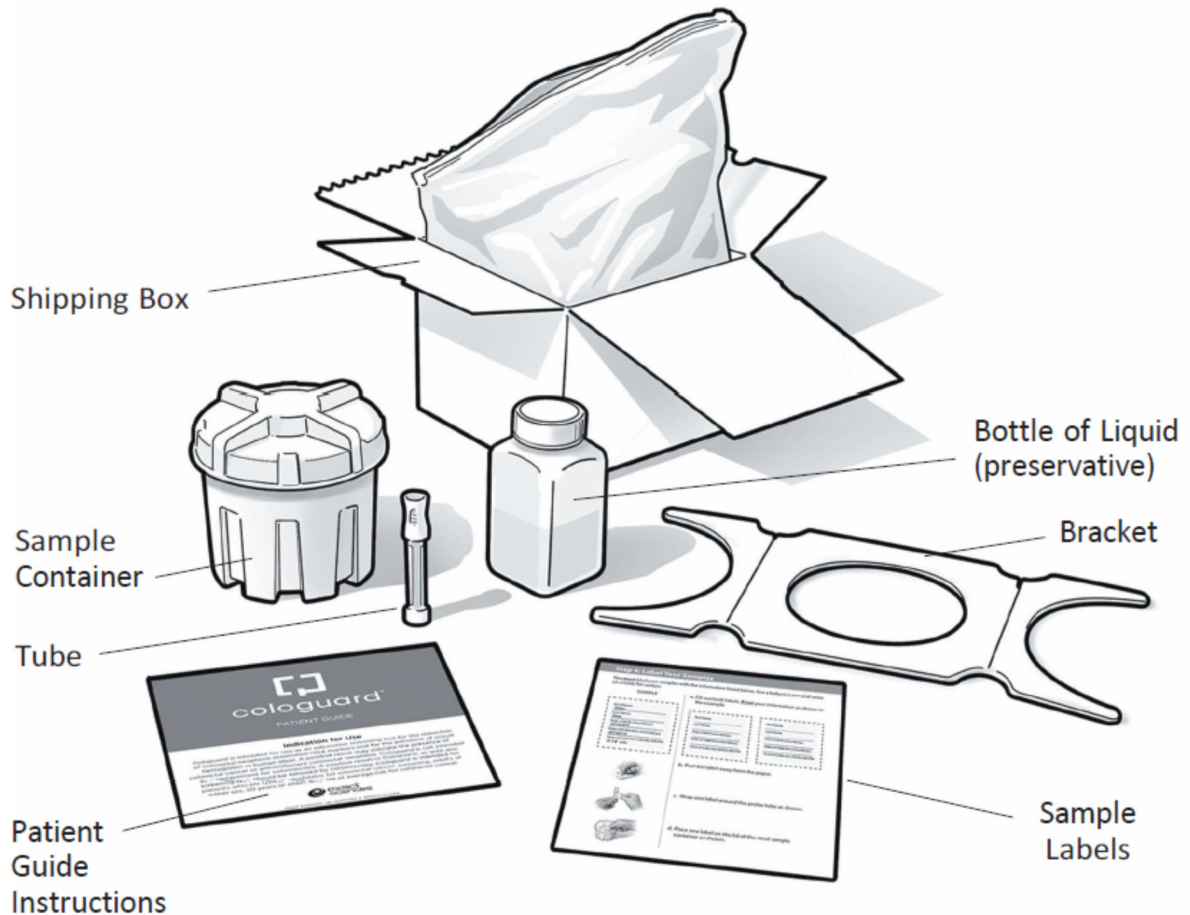
A. There is a Nexus Between the Cologuard Product and the Patent Invention

Petitioner does not contest that the Cologuard Product practices the claimed invention. Rather, Petitioner argues that Cologuard product is not “co-extensive” with the claimed invention. Pet. at 67. But nexus can be established where “the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’” *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023). Petitioner conclusorily

asserts that Cologuard is covered by multiple other patents. Pet. at 67. But even if so, this does not demonstrate a lack of nexus with the '746 patent, nor has Petitioner shown otherwise. *See, e.g., Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991) (“It is not necessary ... that the patented invention be solely responsible for the commercial success” for nexus to exist.).

There can be no dispute that patient acceptance and ease of use are critical to any screening test. *See, e.g.,* EX1020 at 4 (“Population participation is essential for cancer detection.”). The method of at least Claim 3 of the '746 patent is fundamental to use of the Cologuard test as described in detail in Exact Sciences' product literature. EX2001 ¶¶149-163. The Cologuard Patient Guide provides detailed instructions for the collection of a fecal sample that is shipped without freezing. EX2001 ¶151; EX1076 at 24-28, 30-31. The patient receives a Cologuard Collection Kit (the “Collection Kit”) that includes everything that the patient needs for at home collection of fecal sample, separation of the sample into two portions in separate sealable containers, and combination of the first portion with a stabilizing buffer and second portion with a solution that prevents denaturation or degradation of blood protein.

What Is Inside the Cologuard Collection Kit



- The bottle of liquid contains a preservative (less than 10% EDTA in Tris buffered solution).
- The tube contains a 10% albumin in Tris buffered detergent solution with an antimicrobial agent.

EX1076 at 8; EX2001 ¶¶151-160.

The two separate portions are obtained by a lab where nucleic acid is extracted from the first portion and tested and where second portion is tested for an amount of blood protein. EX1080 at 4; EX2001 ¶¶160-163.

B. The Commercial Success of the Cologuard Product Objectively Demonstrates Non-Obviousness

Cologuard test sales have grown from approximately four thousand tests in 2014 to roughly 4 million tests in 2023. EX2019 ¶38. More than 14 million Cologuard tests have been performed since its launch in 2014. *Id.*

The Cologuard test remained Exact Sciences' only product for the years 2014 through 2018, and Exact Sciences' revenue for those years reflects the products' success: \$1,798,000 in 2014; \$39,437,000 in 2015; \$99,376,000 in 2016; \$265,989,000 in 2017; and \$454,462,000 million in 2018. EX2019 ¶¶36-37. Petitioner's own presentation also supports the continued, and increasing, commercial success of the Cologuard test, showing the "rapid growth" of Cologuard sales to almost 4 million tests in 2023. EX2021 at 11.

The Cologuard test would not have achieved commercial success if it did not satisfy two critical aspects of screening tests: diagnostic accuracy and uptake. EX2001 ¶164. The claimed invention of the '746 patent is essential to both aspects. *Id.* The addition of buffers to each of the first and second portions of the sample and testing for both nucleic acids and fecal occult blood all contribute to the test's diagnostic performance. *Id.* The Cologuard test kit itself, using the '746 patented method, allows convenient, at-home collection in a way that patients have accepted. *Id.*

Exact Sciences has achieved this success with the Cologuard test notwithstanding patient reluctance, existing biases, and negative perceptions of earlier CRC screening mechanisms. EX2001 ¶¶165-169; EX2019 ¶¶ 29-31. A 2005 article observed that “[n]egative attitudes toward the tests themselves are also prevalent. Fecal occult blood testing (FOBT) is widely perceived as embarrassing or distasteful.” EX2036³ at 1; EX2001 ¶166. Itzkowitz observed that “[c]oncerns about test discomfort, invasiveness, embarrassment, and self-efficacy have been identified as important barriers to more effective screening.” EX1006 at 5; EX2001 ¶167. Itzkowitz further stated the obvious, that “[i]nherent in the success of any screening test is patient acceptance.” EX1006 at 6; EX2001 ¶167.

When the Cologuard test was launched in 2014, it faced a commercial environment where doctors and patients had to be educated concerning the Cologuard test to overcome the existing negative attitudes. EX2001 ¶¶166-169; EX2019 ¶¶ 29-31. Exact Sciences has expended substantial resources on this education effort with marketing focused on the availability, advantages, and ease of use of the Cologuard test. EX2019 ¶¶31-32. Exact Sciences’ efforts have contributed to increased compliance by individuals who previously had not been screened. *Id.* ¶39; EX2029 at 5; EX2039 at 4-5.

³ Exhibit 2036 is a true and correct copy of Schroy. EX2007 ¶¶60-63.

C. Others Had Tried and Failed to Develop a CRC Screening Test with Satisfactory Diagnostic Accuracy and Uptake, and The Cologuard Product Satisfies a Long-Felt, Previously Unmet Need

As the Federal Circuit has explained, “[l]ongfelt need is closely related to the failure of others.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012). Evidence is particularly probative of nonobviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand. *Id.*

By 2009, it had long been recognized that early screening and detection reduced CRC mortality. EX2001 ¶¶29-31. The references submitted with the Petition demonstrates the extensive and differing failed attempts to develop CRC screening tests with sufficient diagnostic accuracy that could realistically screen large portions of the population. The technologies that existed at the time of the invention, such as colonoscopy and noninvasive tests including gFOBT and iFOBT, each had their own limitations and had not adequately reduced the numbers of unscreened individuals. *Id.* ¶¶32-37.

Although colonoscopy was considered the gold standard for testing as of 2009, it has significant drawbacks. EX2001 ¶¶34-37, 173. It is an invasive procedure that carries a risk, although a low one, of complications including perforation that would require surgery. *Id.* ¶35. It also requires preparation through

colonic purge before the procedure. *Id.* ¶36. In addition, colonoscopy must be performed at a medical facility which requires patient time and potential travel as well as availability of trained medical personnel to perform the procedure. *Id.* ¶37.

GFOBT, iFOBT, and previous nucleic acid based tests also failed to satisfy the need. For example, the sensitivity and predictive value of gFOBT were suboptimal with approximately 10% sensitivity for advanced adenomas. EX2001 ¶174; EX1042 at 7-8.

Fecal DNA analysis had also been explored. However, DNA analysis at the time offered only marginal increase in sensitivity for advanced neoplasia, including advanced adenomas and CRC, to 18.2%, the benefit of which was offset by increased cost per test. EX2001 ¶175; EX1042 at 7-8.

Exact Sciences' own history highlights earlier failed efforts to develop CRC screening tests with sufficient diagnostic accuracy and that would be used by patients. By 2004, a team at Exact Sciences had developed the company's first non-invasive, DNA based test used for screening for CRC. EX2024 at 2, 6. That test, which is identified as version 1 in Itzkowitz, was the subject of the 2004 Imperiale article comparing fecal DNA testing with gFOBT. *See* EX1042; EX1006. Although the sensitivity of that first Exact Sciences test was far superior to gFOBT, the overall sensitivity for invasive cancers plus adenomas was a disappointing 40.8%. EX1042 at 1; EX2001 ¶176.

Exact Sciences continued its development efforts, and by 2007 a team at Exact Sciences had developed the second generation DNA-based stool test that is described in Itzkowitz. EX1006. That test also failed to satisfy the long-felt need for a CRC screening test with sufficient diagnostic accuracy and the company's future was in question. By December 31 of 2008, Exact Sciences was down to 4 employees. EX2019 ¶¶38; EX2025 at 18.

As of the February 2009 priority date of the '746 patent, a high proportion of individuals within the group for whom guidelines recommended screening still had not undergone CRC screening and there remained a longstanding, unmet need for effective, efficient, non-invasive CRC screening tests. EX2001 ¶178.

These low screening levels of individuals within the recommended screening group persisted until the introduction of the Cologuard test by Exact Sciences, which through the combination of fecal DNA analysis and identification of blood proteins in the stool offered excellent sensitivity and specificity for early-stage CRCs and robust sensitivity and excellent specificity for advanced adenomas. The test had strong uptake by patients and patient accessibility due to its non-invasive nature and lack of complications, thus addressing all major limitations of the other attempts at CRC screening. EX2001 ¶179; *see also* EX2019 ¶¶37, 39.

Various publications have credited the Cologuard test for significant increases in CRC screening rates. For example, one publication observed that in

2019 alone, 1.7 million patients were successfully screened using Cologuard. EX2037⁴ at 2; EX2001 ¶181. Another study described better adherence from patients using the Cologuard test where, in the Medicare population, 71% of beneficiaries who had a Cologuard test order completed the test, with 91% completing the test within 60 days, far exceeding the 45% adherence rate for other fecal CRC tests. EX2038⁵ at 10; EX2001 ¶182.

Other studies further confirm that the Cologuard test is being used by a patient population whose needs were previously unmet by the then-available screening options. A study published in 2020 found that 24% of patients with a positive Cologuard test who subsequently had a screening colonoscopy were over 10 years overdue for screening. EX2039⁶ at 4-5; EX2001 ¶183. In addition, internal studies by Exact Sciences have shown that approximately 40% of surveyed Cologuard users were previously unscreened for CRC. EX2019 ¶39; EX2029 at 5. The volume of Cologuard test sales, increased screening rates overall, and the number of Cologuard test users who were never previously screened all demonstrate that the Cologuard test is meeting the previously unmet need.

⁴ Exhibit 2037 is a true and correct copy of Miller-Wilson. EX2007 ¶¶64-67.

⁵ Exhibit 2038 is a true and correct copy of Kisiel. EX2007 ¶¶68-70.

⁶ Exhibit 2039 is a true and correct copy of Eckmann. EX2007 ¶¶71-74.

D. The Cologuard Product Has Received Industry Praise and Recognition

The Cologuard product has received significant recognition and numerous awards. For example, for its groundbreaking innovation, the Cologuard test won the prestigious Prix Galien USA Award for best medical technology product in 2016. EX2031⁷; EX2019 ¶21. In addition, in 2014, the year Cologuard received FDA approval, the Cologuard test won a “Best of What’s New” award from Popular Science. EX2032; EX2019 ¶22.

In January 2015, the Cologuard test won an Everyday Health Award for Innovation, which recognizes services and technologies that are “dedicated to improving overall health and wellbeing.” Everyday Health’s then Vice President and Chief Operating Officer Paul Slavin stated in a press release, “these awards continue to bring the most inventive and creative digital health technologies and services to the forefront,” and “[e]ach of the winners demonstrated an incredible understanding about where the digital health marketplace is going and how we can propel it forward.” EX2033⁸; EX2019 ¶23. Cologuard was also awarded a

⁷ Exhibits 2031-2032, 2034-2035 are true and correct copies of press releases that are accessible at Exact Sciences’ website, <https://www.exactsciences.com/newsroom/press-releases>. EX2019 ¶¶21-22, 24-25; EX2007 ¶¶45-50, 54-59.

⁸ Exhibit 2033 is a true and correct copy of a press release by Everyday Health. EX2019 ¶23; EX2007 ¶¶51-53.

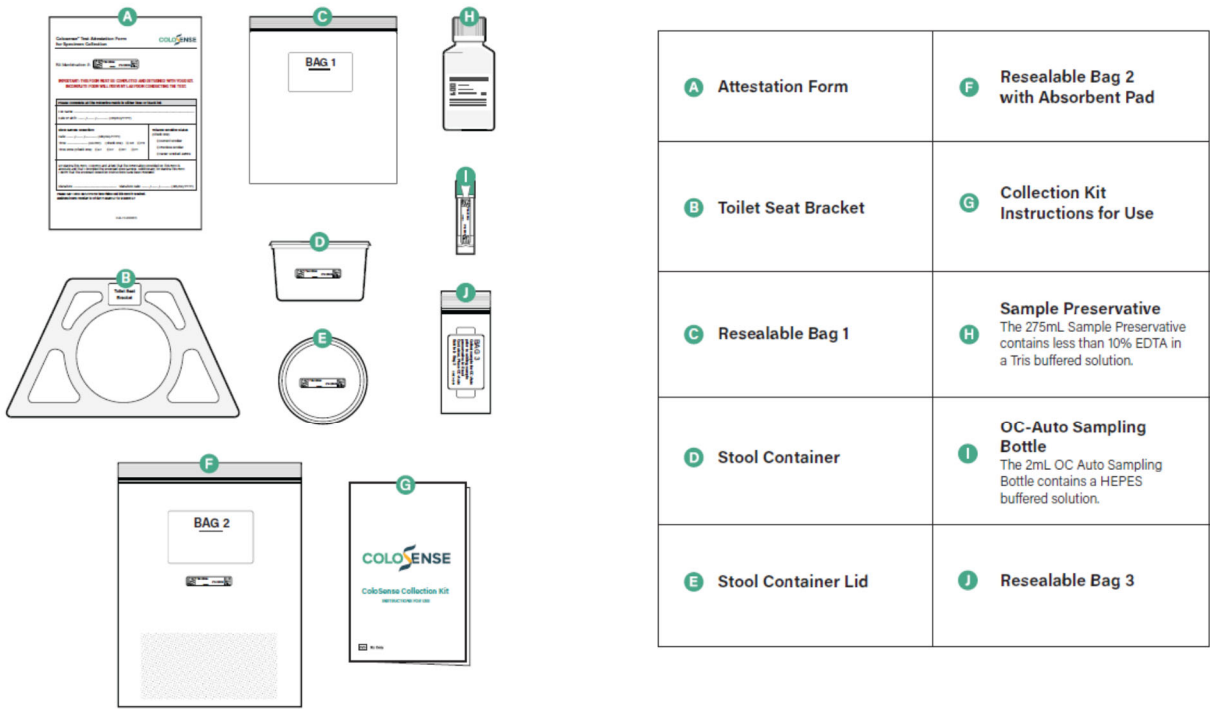
Wisconsin Innovation Award (WIA) in the “Healthcare/Health IT” category in 2015. EX2034; EX2019 ¶24.

In 2016, Exact Sciences received the Business Intelligence Group’s 2016 Company of the Year BIG Award for Business in the Health Care category. EX2035; EX2019 ¶25. At the time all of the above awards were received, the Cologuard test was Exact Sciences’ only product. EX2019 ¶26.

E. Petitioner’s Recently Approved “ColoSense” Product Copies the Claimed Invention

Despite the variety of past and present approaches to CRC screening, Petitioner’s ColoSense test copies the ’781 patented invention. To begin, the ColoSense Collection Kit contains the same elements as Exact Sciences’ successful Cologuard Collection Kit. EX2001 ¶¶186-194; EX2040.

ColoSense Collection
Kit Contents



EX2001 ¶187; EX2040 at 34.

Petitioner’s Product Information describes the method. EX2001 ¶¶187-194.

And, as with the Cologuard product, after collection with a ColoSense collection kit a lab obtains the two containers with the first and second portions and tests the second portion for a blood protein. EX2001 ¶194; EX2040 at 56. Nucleic acid is extracted from the first portion and the nucleic acid is tested for an amount of nucleic acid. EX2001 ¶194; EX2040 at 54-55.

VIII. THE BOARD SHOULD EXERCISE ITS DISCRETION AND DENY INSTITUTION UNDER § 325(D)

The Board should exercise its discretion to deny institution under 35 U.S.C. § 325(d). Each of Petitioner's cited references was considered by the Examiner during prosecution. EX2005 at 76-82. Indeed, the '781 Petition and the accompanying January 10, 2024 Whitney Declaration—containing the same arguments and discussion of the prior art that Petitioner advances here— were considered by the Examiner. *Id.*; EX1031.

Section 325(d) allows discretionary denial where the “same or substantially the same” art or arguments were considered during prosecution. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, 2020 WL 740292, at *3 (P.T.A.B. Feb. 13, 2020) (precedential, designated March 24, 2020). Every reference on which Petitioner now relies as well as Petitioner's complete '781 Petition and accompanying declarations were considered during prosecution. EX2005 at 76-82; *see also* Pet. at 69. This is sufficient to establish that the same art was previously presented. *Biocon Pharma Ltd. v. Novartis Pharmaceuticals Corp.*, 2021 WL 608300, at *4 (P.T.A.B. Feb. 16, 2021) (accepting that the examiner considered a reference that was “listed on the IDS and the Examiner signed the IDS with the statement ‘all references considered except where lined through.’”); *see also Google LLC v. Valtrus Innovations, Inc.*, IPR2022-01197,

Paper 18 (P.T.A.B. June 13, 2023). Accordingly, prong 1 of the *Advanced Bionics* framework is satisfied. 2020 WL 740292, at *3.

Notwithstanding that the Examiner indicated that all art was considered, Petitioner argues that Examiner erred in “overlooking the asserted art.” Pet. at 70. Petitioner bases its argument concerning purported Examiner error on the Board’s institution decision concerning the related ’781 patent. Pet. at 70. The fact of the institution decision does not establish that the Examiner erred. Indeed, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Advanced Bionics*, 2020 WL 740292, at *3.

Moreover, in the ’781 Institution Decision, the Board noted that the claims “do not require a particular level of sensitivity or specificity.” EX1033 at 18. The issue, however, is not the scope of the claims, but Petitioner’s reliance on sensitivity in a vacuum as a purported motivation to combine. As discussed in detail above, whether the references provide a motivation to combine cannot be based on a single parameter, but must instead consider the prior art as a whole and whether it suggests the combination. *See Henny Penny*, 938 F.3d at 1332 (benefits “both lost and gained, should be weighed against one another” when considering

motivation to combine); *Arctic Cat*, 876 F.3d at 1363 (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”). When the prior art is considered as a whole, the disadvantages of a potential combination outweigh potential benefits, and there is no motivation to combine.

The Board also noted in the ’781 Institution Decision that Patent Owner had not presented evidence of secondary considerations in its Preliminary Response. EX1033 at 19, fn. 9. As discussed above, secondary considerations also support the nonobviousness of the claimed invention.

IX. CONCLUSION

For the foregoing reasons, the Board should deny institution of the Petition.

Date: November 26, 2024

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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 13,767 words and thus complies with the applicable word limit.

Date: November 26, 2024

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Pursuant to 37 C.F.R. § 42.6, I hereby certify that on November 26, 2024 the foregoing Preliminary Response from Patent Owner was served via email on the following counsel of record for the Petitioner:

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