

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

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

PATENT OWNER'S RESPONSE

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<i>ATD Corp. v. Lydcall, Inc.</i> , 159 F.3d 534 (Fed. Cir. 1998)	21
<i>Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	21
<i>Eurand, Inc. v. Mylan Pharms., Inc.</i> 676 F.3d 1063 (Fed. Cir. 2012)	58
<i>Harmonic Inc. v. Avid Tech., Inc.</i> , 815 F.3d 1356 (Fed. Cir. 2016)	21
<i>KSR Intern. Co. v. Teleflex Inc.</i> 127 S.Ct. 1727 (2007)	21
<i>Natera, Inc. v. NeoGenomics Labs. Inc.</i> , 106 F.4th 1369 (Fed. Cir. 2024)	31
<i>W.L. Gore & Assoc. v. Garlock, Inc.</i> , 721 F.2d 1540 (Fed. Cir. 1983)	65

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	European Patent Application Publication No. EP1266715A1 to DeLuca et al.
2007	Zohar Levi et al., <i>A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test</i> , 23(9) <i>Aliment Pharmacol Ther.</i> , 1359, 1359–1364 (2006)
2008	Thomas F. Imperiale et al., <i>Multitarget Stool DNA Testing for Colorectal-Cancer Screening</i> , 370(14) <i>N. Eng. J. Med.</i> , 1287, 1287–1297 (2014)(“Imperiale 2014”)
2009	Sidney J. Winawer and Ann G. Zauber, <i>The Advanced Adenomas as the Primary Target of Screening</i> , 12(1) <i>Gastrointestinal Endosc. Clin. N. Am.</i> 1, 1–9 (2002)
2010	Daniel C. Chung, <i>The Genetic Basis of Colorectal Cancer: Insights Into Critical Pathways of Tumorigenesis</i> , 119 <i>Gastroenterology</i> 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) <i>Gut</i> 1585, 1585–1589 (2007)
2012	David L. Zack et al., <i>Colorectal Cancer Screening Compliance by Medicine Residents: Perceived and Actual</i> , 96(10) <i>Am. J. Gastroenterology</i> 3004, 3004–3008 (2001)
2013	Amnon Sonnenberg and Fabiola Delcò, <i>Cost-effectiveness of a Single Colonoscopy in Screening for Colorectal Cancer</i> , 162(2) <i>Arch Intern Med.</i> 163, 163–168 (2002)

2014	Peter B. Cotton et al., <i>Computed Tomographic Colonography (Virtual Colonoscopy): A Multicenter Comparison With Standard Colonoscopy for Detection of Colorectal Neoplasia</i> , 291(14) JAMA 1713, 1713–1719 (2004)
2015	Nathalie Schoofs, et al., <i>A. PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study</i> . Endoscopy 38, 971-977 (2006)
2016	Exact Sciences, “Cologuard™ Patient Guide” (2014)
2017	Exact Sciences, “FDA Approves Exact Sciences’ Cologuard®; First and Only Stool DNA Noninvasive Colorectal Cancer Screening Test,” https://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2014/FDA-Approves-Exact-Sciences-Cologuard-First-and-Only-Stool-DNA-Noninvasive-Colorectal-Cancer-Screening-Test/default.aspx (August 12, 2014)
2018	Exact Sciences, “Get Off the Bench: Hoops Themed Campaign Urges Colorectal Cancer Screening,” https://www.exactsciences.com/newsroom/news-and-stories/get-off-the-bench-hoops-themed-campaign-urges-colorectal-cancer-screening-#:~:text=March%2007%2C%202024-,Get%20Off%20the%20Bench%3A%20Hoops%2DThemed%20Campaign%20Urges%20Colorectal%20Cancer,&text=Shortly%20after%20basketball%20star%20Jamal,he%20got%20some%20tough%20news (March 07, 2024)
2019	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)
2020	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

2022	Declaration of Vadim Backman, Ph.D. in Support of Patent Owner’s Response to Petition for <i>inter partes</i> Review of U.S. Patent 11,634,781
2023	Declaration of Peter Wood
2024	Declaration of June Ann Munford
2025	Appendix to Declaration of June Ann Munford
2026	Intentionally omitted
2027	Transcript of October 10 Deposition of Duncan Whitney, Ph.D.
2028	Intentionally omitted
2029	Geneoscopy, Series C Investor Presentation, available at (password protected link) https://nephronnext.open-exchange.net/stream/531120 (April 10, 2024)
2030	FDA, ColoSense™ Approval letter, available at https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001A.pdf
2031	CDC “Vital Signs: Colorectal Cancer Tests Save Lives,” available at https://archive.cdc.gov/www_cdc_gov/vitalsigns/colorectalcancerscreening/index.html
2032	Exact Sciences, Cologuard™ Product Information, available at https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017c.pdf
2033	U.S. Patent Application No. 18/919,170
2034	Exact Sciences Form 10-K for the year ending December 31, 2004
2035	Exact Sciences Form 10-K for the year ending December 31, 2008
2036	Exact Sciences Form 10-K for the year ending December 31, 2014
2037	Exact Sciences Form 10-K for the year ending December 31, 2016
2038	Exact Sciences Form 10-K for the year ending December 31, 2018
2039	Exact Sciences Form 10-K for the year ending December 31, 2021
2040	Exact Sciences Form 10-K for the year ending December 31, 2023
2041	Printout from Exact Sciences’ Internal Survey Database
2042	Exact Sciences, “Exact Sciences’ Cologuard Wins Prestigious Prix Galien Award For Best Medical Technology Product,”

	https://www.exactsciences.com/newsroom/press-releases/exact-sciences-cologuard-wins-prestigious-prix-galien-award (October 28, 2016)
2043	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)
2044	Everyday Health, Inc., “Everyday Health Awards for InnovationWinners Announced at 2015 InternationalCES®,” https://www.prnewswire.com/news-releases/everyday-health-awards-for-innovation-winners-announced-at-2015-international-ces-300017454.html (January 7, 2015)
2045	Exact Sciences, “Exact Sciences Wins Wisconsin Innovation Award,” https://www.exactsciences.com/newsroom/press-releases/wisconsin-innovation-award-2015 (August 19, 2015)
2046	Exact Sciences, “Exact Sciences Honored As 2016 Big Award Company Of The Year In Health Care,” https://www.exactsciences.com/newsroom/press-releases/published/2021/03/10/08/57/2-years-since-cologuards-fda-approval-0 (October 2, 2016)
2047	Intentionally omitted
2048	Paul C. Schroy 3 rd et al., <i>Patient perceptions of stool-based DNA testing for colorectal cancer screening</i> , 28(2) Am J. Prev. Med. 208, 208-214 (2005)
2049	Lesley-Ann Miller-Wilson et al., <i>Cross-sectional adherence with the multi-target stool DNA test for colorectal cancer screening in a large, nationally insured cohort</i> , 36 International Journal of Colorectal Disease 2471, 2471-2480 (2021)
2050	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)
2051	Rebecca Swartz et al., <i>Colorectal Cancer Screening: Compliance with Multi-Target Stool DNA Testing Among Medicare Beneficiaries</i> , S-601 Gastroenterology Su1660 (2020)
2052	Jason D. Eckmann et al., <i>Multi-Target Stool DNA Testing for Colorectal Cancer Screening: Emerging Learning on Real-</i>

	<i>world Performance</i> , 18 Curr Treat Options Gastro 109, 109-119 (2020)
2053	ColoSense Product information available at https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001C.pdf

I. INTRODUCTION

U.S. Patent No. 11,634,781 (the “’781 patent”) covers the use of Exact Sciences’ revolutionary Cologuard® colorectal cancer (“CRC”) screening kits. The technology protected by the ’781 patent has given millions of people a noninvasive and convenient approach to CRC screening, and has been a resounding commercial success.

For decades, CRC has been known as a leading cause of cancer deaths. *See, e.g.*, EX1033 at 1; EX1004 at 1. It was also already well known before the ’781 patent’s priority date that screening and early detection reduce CRC mortality. *See, e.g.*, EX1004 at 1. Yet, although various screening methods had been developed, as of 2008 more than half of adults in the United States still had not been screened at that time. *Id.* The Cologuard test addressed this long-felt, unmet need for CRC screening that patients would accept.

Petitioner’s challenge to the ’781 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 ’781 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.

In addition, the objective evidence of non-obviousness should be considered and would easily outweigh 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.

II. TECHNICAL BACKGROUND – CRC SCREENING

By the '781 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." *Id.* at 2:1-3. For example, while the risk of severe complications from colonoscopy is low, it does present an approximately 0.1% risk of perforation requiring surgery. EX2022 ¶34; EX1043 at 5. There are also practical barriers to more widespread CRC screening by colonoscopy, including patient reticence due to bowel preparation, discomfort, financial costs, and limitations to access. EX2022 ¶¶35-36.

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. 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. *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. EX2022 ¶¶38-39.

A primary goal with CRC screening is to identify cancer or precancerous lesions as early as possible. The earlier the pre-cancer or cancer is detected, the greater the reduction in mortality. *See, e.g.*, EX1001 at 43-46; EX1004 at 1; EX2022 ¶29. Accordingly, those working in the field recognized that, in addition to early-stage CRC, precancer indications, such as adenomas, should also be a target of screening because detection and removal of adenomas provides an opportunity to prevent CRC. EX2009 at 1; EX2022 ¶29. FOBT tests did not satisfy this need because they had low sensitivity for colorectal adenomas where “neoplasms may not bleed and thus cannot be detected in this way.” EX1043 at 2.

As Petitioner's declarant Dr. Duncan Whitney acknowledges, both "[s]ensitivity and specificity are important metrics of diagnostic assay performance." EX1002 ¶27; *see also* EX2027 at 133:12-15 ("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."). Low sensitivity results in disease not being detected. EX2022 ¶30. Low specificity results in an unacceptable number of false positives. *Id.* Assuming that a patient with a positive test result follows medical recommendations, then each false positive results in an unnecessary colonoscopy. *Id.*; *see also* EX1002 ¶29. A person working in this field would understand that even minor reductions in specificity could have a large negative impact on the overall cost-effectiveness of screening using the test. EX2022 ¶¶36, 106. Further, false positives have significant patient impact. *Id.* ¶107; EX1033 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. EX2022 ¶107. On the other hand, when a patient does follow-up as recommended, in addition to the risks and costs of the colonoscopy procedure outlined above, there is also the intangible impact 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. EX2022 ¶¶31-40, 169. 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.* ¶¶29-30, 38, 41.

III. THE INVENTION OF THE '781 PATENT

The Cologuard test using the '781 patented technology accomplished these goals. Indeed, use of the Cologuard test achieved 92.3% sensitivity and 86.6% specificity for CRC. EX2008¹ at 1; EX2022 ¶41. The Cologuard test revolutionized CRC screening. Under the '781 patent's novel and innovative approach, a fecal sample that will be tested for both nucleic acid and blood protein can be conveniently collected in the privacy of a patient's own home and shipped without freezing from virtually anywhere. EX2032 at 13-31; EX2022 ¶¶143-154. The '781 patent is the innovative combination of at-home collection that is

¹ Exhibit 2008 is a true and correct copy of Imperiale 2014. EX2024 ¶¶6-9.

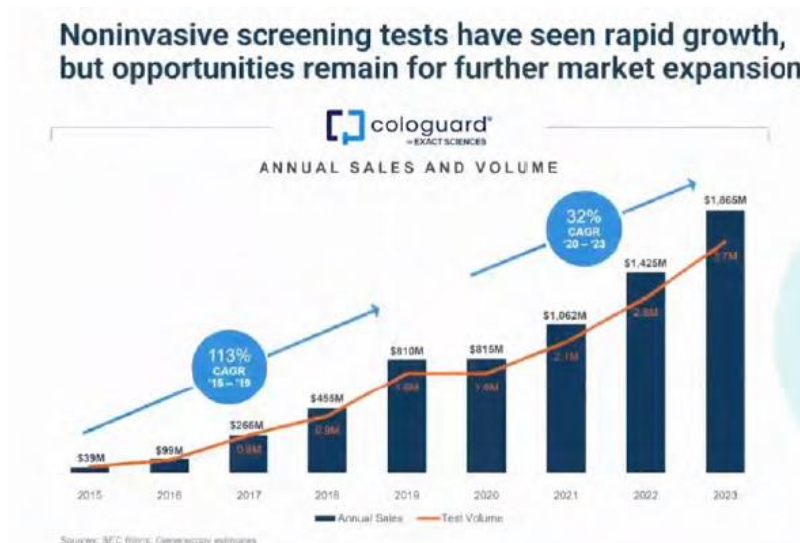
acceptable to patients, use of buffers that avoid the need for freezing, and testing for both nucleic acids and fecal occult blood that resulted in enhanced performance. *See generally* EX1001. The Cologuard test using the '781 patent's invention enables many patients to get screened for CRC, patients who would otherwise go unscreened. EX2022 ¶175; EX2023 ¶39; EX2040 at 5.

More specifically, the invention of the '781 patent, as embodied in the Cologuard product, provides a patient-friendly, effective means of collecting and processing freshly-collected fecal samples for screening. Under the patented method, a patient collects a fecal sample by direct defecation into a convenient container in the privacy of their own home. EX2032² at 15-19; EX2022 ¶¶143-144. The patient then removes a portion of the sample to a separate sealable container, resulting in both a removed portion and a remaining portion. EX2032 at 20-23; EX2022 ¶145. The separate sealable container contains a buffer that prevents denaturation or degradation of blood proteins. EX2032 at 8, 20-21; EX2022 ¶146. The patient also adds a stabilizing buffer to the remaining sample in the first container. EX2032 at 8, 22-23; EX2022 ¶147. The containers are both sealed and shipped to a lab at room temperature—they are not ever frozen. EX2032 at 21, 23,

² Exhibit 2032 is a true and correct copy of the ColoGuard product information accessible at the FDA website at https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017c.pdf. EX2023 ¶9.

30; EX2022 ¶149. The lab obtains the two containers with the two portions and tests the removed portion for a blood protein. EX2032 at 6; EX2022 ¶¶149-152. Nucleic acid is extracted from the remaining portion and the nucleic acid is tested for an amount of nucleic acid. EX2032 at 6; EX2022 ¶¶153-154.

The Cologuard test was the first FDA-approved commercially available multitarget stool-based blood and nucleic acid test for CRC screening. EX2017 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. EX2023 ¶14. The Cologuard test has been used by millions since its August 2014 approval. EX2018 at 3. Indeed, Petitioner has pointed to the rapid increase in use of the Cologuard test in its own presentations to investors.



EX2029 at 11.³

In May of 2024—almost a decade after Cologuard received FDA approval—Petitioner received FDA premarket approval for its ColoSense™ test. EX2030 at 1. ColoSense copies the innovative, successful approach of the '781 patent for at-home collection of fresh fecal samples to be tested for both nucleic acid and blood protein.

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 testing (gFOBT) for purposes of distinguishing between patients with CRCs and those without. EX1004 at 1; EX2022 ¶55. Lenhard states that samples “were collected before cathartic preparation for scheduled surgery or colonoscopy” and that the samples were “received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80° C.” EX1004 at 2; EX2022 ¶56. The samples were subjected to gFOBT “immediately on receipt and before freezing.” *Id.* at 4. The gFOBT testing

³ Exhibit 2029 is a true and correct copy of an April 2024 Geneoscopy presentation titled “Series C Investor Presentation,” as downloaded from <https://nephronnext.open-exchange.net/stream/531120>. EX2023 ¶33.

of Lenhard involved spreading stool sample onto cards, letting the sample dry for a day, then applying a peroxide catalyst to the card. *Id.*; EX2022 ¶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; EX2022 ¶57. Petitioner relies heavily on select statements concerning those combined results, particularly that “the combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.” Pet. at 14; EX1004 at 2, 6. Petitioner ignores much of the Lenhard reference and does not address how a POSA would consider the reference as a whole. *See* Pet. at 14, 20-33. Among other things, a POSA would also consider the following from the Lenhard reference: (1) the advanced stage of the known CRC patients tested in Lenhard; (2) the lack of any improvement in detecting adenomas; (3) that the improved sensitivity of the HIC1/gFOBT combination adversely affected specificity; (4) the fact that certain methylation markers were already known to have higher sensitivity than the specific combination of HIC1 and gFOBT; and (5) Lenhard’s own conclusions that combination of methylation markers may allow for highly sensitive and specific stool based detection of CRCs and adenomas. EX2022 ¶¶59-68.

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; EX2022 ¶60. In addition, the “two thirds

of CRCs” detected by the specific HIC1 and gFOBT combination discussed in Lenhard were largely late-stage cancers. As shown in Table 1, half of the patients with CRC, 13 of 26, were in stage IV. EX1004 at 2, Table 1; EX2022 ¶60. Of the remaining thirteen patients, seven were in stage III, five in stage II, and only one in stage I. *Id.* Thus, the combined results from HIC1 and gFOBT in Lenhard showed relatively poor sensitivity of only 65% of CRCs that were predominantly late-stage. EX2022 ¶60.

A POSA would also consider the effect, if any, on detection of adenomas. Lenhard itself states that “a stool-based screening assay also should detect relevant premalignant lesions (ie, adenoma).” EX1004 at 6. Table 2 of Lenhard reports results for thirteen patients with advanced adenomas. EX1004 at 3; EX2022 ¶62. Only four of the thirteen were detected by the HIC1 methylation marker, and only one—one that was also detected by the HIC1 methylation marker—was detected by gFOBT. EX2022 ¶62.

Table 2. Clinicopathologic Data and HIC1 Methylation Status of Patients With Adenomatous Polyps

No.	Sex	Age (y)	Diagnosis	HIC1 methylation	FOBT
27	M	72	Tubular adenoma, ascending colon, 3 cm	+	—
28	F	63	Tubulovillous adenoma, ascending colon, hepatic flexure, sigmoid colon, 1–1.5 cm	—	—
29	M	63	Tubulovillous adenoma, ascending colon, 2 cm	—	—
30	M	76	Tubulovillous adenoma, ascending and transverse colon, 1, 3, 4 cm	+	+
31	M	83	Tubulovillous adenoma, transverse colon, 3 cm	—	—
32	F	65	Tubulovillous adenoma, sigmoid colon, 1.5 cm	—	—
33	M	72	Tubulovillous adenoma, ascending colon, 1 cm	—	—
34	F	60	Tubular adenoma, sigmoid colon, 1.5 cm	—	—
35	M	69	Tubular adenoma, 1.5 cm, ascending colon	—	—
36	M	70	Tubulovillous adenoma, sigmoid colon, 1 cm	—	—
37	M	64	Tubulovillous adenoma, rectum, 1 cm	—	—
38	M	72	Adenoma, cecum, 2 cm	+	—
39	F	63	Tubulovillous adenoma, sigmoid colon, 2 cm	+	—

M, male; F, female.

EX1004, Table 2 (highlighting added). The significance is highlighted by Lenhard’s observation that the specific HIC1/gFOBT combination showed “no increase in the sensitivity for adenoma.” *Id.* at 6; EX2022 ¶62. The significance is further highlighted by Lenhard’s description of the need for CRC screening and statement that “[d]etection of early disease and precancerous adenomatous lesions leads to a decrease of CRC-related mortality.” *Id.* at 1.

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.”); EX2022 ¶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. Notably, the sensitivity for “two thirds of CRCs” on which Petitioner relies came with a reduction in specificity. EX2022 ¶¶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’s statement that the specific combination of HIC1 and gFOBT “allowed for detection of two thirds of cancers,” would consider that 65% sensitivity in the context of the sensitivity of other markers. EX2022 ¶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. EX2022 ¶67. This is consistent

with how a POSA at the time would have considered Lenhard as a whole, either alone or in combination with the other cited references. *Id.* ¶¶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. Vilkin reports both sensitivity and specificity at differing hemoglobin levels. *Id.*, Table 2. 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; EX2022 ¶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 the analysis.” *Id.* at 6. Notably, Table 3 of Vilkin reveals a wide 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 they would continue with three annual fecal tests, as they had “confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” *Id.* at 8; EX2022 ¶69.

With respect to 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; EX2022 ¶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.*; EX2022 ¶¶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; EX2022 ¶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; EX2022 ¶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.*; EX2022 ¶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; EX2022 ¶79.

4. Kanaoka (EX1007)

Petitioner relies on Kanaoka in Grounds II and V. *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]. Kanaoka discloses that the tested COX-2 marker had 90% sensitivity with 100% specificity, while the comparison iFOBT had 82.1% sensitivity with 86.3% specificity. *Id.* at [0065]-[0066]; EX2022 ¶81.

Petitioner contends that the combined results of COX-2 and iFOBT in Kanaoka indicate that “the combination of the two tests had a higher sensitivity than either test alone.” Pet. at 19. 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]; EX2022 ¶82. Thus, if the results from these two separate tests are considered together, they show an insignificant increase in sensitivity with a more significant decrease in specificity. EX2022 ¶¶82-84.

5. Derks (EX1008)

Petitioner relies on Derks in Grounds III and VI. Derks explores “the timing of promoter methylation and relationship with mutations and chromosomal alterations” in CRC. EX1008 at 2. Derks evaluated the promoter methylation status of certain markers. Derks concludes that “[s]ince promoter methylation was already present in nonprogressed adenomas without chromosomal alterations...promoter methylation can be regarded as an early event preceding *TP53* mutation and chromosomal abnormalities in colorectal cancer development.” *Id.*; EX2022 ¶87.

Consistent with the other references on which Petitioner relies and the knowledge in the art at the time, Derks emphasizes the need for early detection. Derks states that the “association between gene methylation and pre-malignant lesions is highly relevant for methylation-marker based colorectal cancer screening.” EX1008 at 10. Derks concludes that “[g]iven that aberrant DNA methylation can also be detected in stool DNA, studying methylation as common

event in pre-malignant lesions is promising to provide novel specific biomarkers for risk assessment and secondary prevention.” *Id.*; EX2022 ¶88.

6. Shuber (EX1009)

Shuber is a patent application with two named inventors, Anthony Shuber and Petitioner’s declarant, Dr. Whitney. EX1009. 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. EX1009 (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. EX2022 ¶90.

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).” EX1009 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.

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. EX1009 at 29:7-19. Shuber does not specifically mention home collection by a patient. *See generally* EX1009; EX2022 ¶92.

V. LEVEL OF ORDINARY SKILL IN THE ART

Petitioner contends that a POSA “relevant to the ’781 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. In its previous, failed reexamination request concerning the ’781 patent, Geneoscopy asserted that a 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.

EX1021 at 7.

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. EX2022 ¶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 is 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. Paper 9 at 8.

Patent Owner has submitted with this POR the declaration of Dr. Vadim Backman in support of this section of the POR. EX2022. 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 '781 patent would not have been obvious to a person of ordinary skill as of the priority date. *Id.* ¶53.

VI. CLAIM CONSTRUCTION

Patent Owner does not believe that claim construction is necessary to resolve patentability.

VII. PETITIONER HAS FAILED TO PROVE UNPATENTABILITY

In an *inter partes* review, “the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citation omitted). This burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Petitioner relies on select portions of each of the cited references without providing any reason why a POSA would have chosen those specific aspects of the references, while rejecting others. This is improper. *See ATD Corp. v. Lydcall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998). Even if each separate claim element could be extracted from a piece of prior art, a “patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art.” *KSR Intern. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1741 (2007).

A. Ground I: Petitioner Fails to Establish That Lenhard in View of Vilkin and Itzkowitz Renders Claims 1-9, 11, and 14-20 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 20-21. 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 that would still be less sensitive than the nucleic acid-only or FOBT-only tests described in Lenhard, Vilkin, and Itzkowitz.

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 a fecal sample from the subject, removing a portion of it to test for blood proteins and then testing the remaining portion for cancer-specific DNA.” Pet. at 21. 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 of Lenhard with at-home collection, (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 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 26-32. A POSA would not have come to these multiple changes to Lenhard without the roadmap of the '781 patent and impermissible hindsight.

As Petitioner acknowledges, Lenhard provides “few details regarding sample collection.” Pet. at 24. Lenhard discloses laboratory collection of samples that were then frozen before testing for nucleic acid. EX1004 at 2; EX2022 ¶¶56. Vilkin requires that each subject prepare three consecutive daily samples. EX1005 at 3 (Methods), 4. 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.”), 3 (Conclusions) (“[r]efrigerated OC-Sensor samples are stable for 21 days.”); EX2022 ¶¶69-70. 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.”); EX2022 ¶¶76, 112. 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. *Id.* ¶114; 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 using both the HIC1 methylation markers and gFOBT "increased detection rates for CRCs" and "detected all localized cancers." Pet. at 21. 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 “included 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 21-22. 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 ’781 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 a Combination of Test Types Would Result in Greater Sensitivity for CRC Screening Than a Single Test Type

Petitioner relies on Lenhard’s disclosure of 65% sensitivity with the combination of a single DNA methylation marker and gFOBT to argue that a POSA would have been motivated to combine iFOBT with nucleic acid-based

testing. Petition at 21. Petitioner has no explanation for why a POSA would pursue the more complex solution of developing a test for two different types 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 that Petitioner contends provides a motivation has lower sensitivity than disclosed FOBT-only or nucleic acid-only tests that did not have 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.").

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. EX2022 ¶¶96-98, 103-107. 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 14. 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; EX2022 ¶98. 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. EX2022 ¶¶67, 103. Without the benefit of hindsight and the ’781 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. 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.*; EX2022 ¶62. The combination on which Petitioner relies thus provided no improved sensitivity for this critical element of CRC screening tests. EX2022 ¶¶29, 62, 106.

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% 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 predictive 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.*; EX2022 ¶99.

Itzkowitz describes data from two DNA-only based tests, both of which showed greater sensitivity than the HIC1/FOBT 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. EX2022 ¶¶100-101.

Taken individually and together, the sensitivity results reported in Lenhard, Vilkin, and Itzkowitz do not suggest the combination of different classes of markers to achieve improved sensitivity:

Reference and Marker(s)	Reported Sensitivity	Source
Lenhard – HIC1 and gFOBT [CRC only]	65%	EX1004 at 5 (Table 4)
Lenhard – SFRP2	77-90%	EX1004 at 2
Vilkin – iFOBT [combined results from three samples – CRC only]	100%	EX1005 at 7 (Table 3)
Vilkin – iFOBT [combined results from three samples and including advanced adenomas]	76.5%	EX1005 at 7 (Table 3)
Itzkowitz – describing Exact Sciences’ improved version 1 DNA-based test	72.5%	EX1006 at 6
Itzkowitz – describing Exact Sciences’ version 2 – vimentin methylation plus DIA DNA-based test	87.5%	EX1006 at 6

See also EX2022 ¶¶98-100.

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. EX2022 ¶¶105, 115. 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.* ¶¶105-106. Therefore, a POSA seeking to improve sensitivity of 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.* ¶¶96-107. Rather, a POSA would have avoided the pitfalls of combination and instead pursued improvements to either FOBT alone or nucleic acid testing alone. *Id.* ¶¶104-107.

(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 the Institution Decision, the Board noted that the claims "do not require a particular level of sensitivity or specificity." Paper 9 at 18. Here, Patent Owner's point with respect to specificity is that, whether Lenhard provides 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 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.”); *see also Natera, Inc. v. NeoGenomics Labs. Inc.*, 106 F.4th 1369, 1378 (Fed. Cir. 2024) (“[u]nclaimed factors relevant to the feasibility of creating a useful claimed invention can impact the motivation to combine analysis if a skilled artisan would reasonably consider them.”) (citation omitted). 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. EX2022 ¶¶105-119. Indeed, Petitioner’s own expert testified that “sensitivity and specificity, in my opinion, should always be looked at in combination.” EX2027 at 169:13-17.

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). EX2022 ¶¶61, 106. As discussed above, the sensitivity of that specific HIC1/gFOBT combination is still worse than the sensitivities of the nucleic-acid only or FOBT-only tests described in the cited references. 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.* Lenhard would not have motivated a combination of classes of markers to increase sensitivity where the combination resulted in lower specificity

and when that combination was still less sensitive than existing DNA-only or FOBT-only tests. EX2022 ¶¶95, 105-107.

Petitioner's own arguments 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 22, citing EX1024 at 29 (emphasis added).

A POSA would not have been motivated by the teachings of Lenhard to combine classes of markers where Lenhard itself teaches that the specific HIC1/gFOBT combination reduced specificity and that other methylation markers alone achieved greater sensitivity. EX2022 ¶95. That a POSA would not have been motivated by Lenhard is particularly true where the reported increase in sensitivity was only in detection of CRC and where Lenhard's specific HIC1/gFOBT combination showed no improvement in detection of advanced adenomas. *Id.* ¶¶95-97.

(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 used in Lenhard with the iFOBT of Vilkin” because of certain purported advantages of iFOBT over gFOBT. Pet. at 21-22. One such “advantage” according to Petitioner was “collecting fewer fecal samples.” *Id.* at 22. Petitioner points to Young which states that most branded versions of iFOBT “require fewer than three fecal samples, the recommended number for GFOBT.” EX1024 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 the analysis.” *Id.* at 6. Vilkin reports that they would “continue with collecting three annual fecal tests” 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 stabilization method of Itzkowitz and the iFOBT of Vilkin” would produce “two samples.” Pet. at 26. However, where 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.

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. According to Vilkin, “storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability.” *Id.* at 8. Vilkin also notes “screeners’ hesitancy about keeping the prepared test transiently in their home refrigerator.” *Id.*; EX2022 ¶¶109-110.

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. EX2022 ¶¶108-111.

(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. EX2022 ¶¶112-115. 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); EX2022 ¶112.

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. EX2022 ¶114. A POSA’s knowledge concerning user reluctance would have further discouraged the collection method claimed in the ’781 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 ’781 patent. Combining a nucleic acid test with an FOBT test as claimed requires, among other things, more collection components and separate testing once the samples are

delivered to the lab. EX2022 ¶113. 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 22. The 2008 Levin reference on which Petitioner relies contradicts that argument. 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 SENSА) and a variety of FIT.” *Id.* Levin also notes “higher costs associated with FIT compared with gFOBT.” *Id.*

Nothing in the references on which Petitioner relies suggests that testing for two different classes of markers would have improved 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

associated with testing for two different classes of markers. 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 those 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 of three samples and required sample refrigeration. Further, even assuming that a POSA would consider a combination 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 Lenhard with Vilkin and Itzkowitz to arrive at the claimed invention.

3. Petitioner Fails to Establish Any Motivation for User Separation of Fecal Sample into Two Separate Sealable Containers at Home

As discussed above, a POSA would not have been motivated to increase test cost or complexity and would further not have been motivated to increase patient interaction with the fecal samples. Petitioner's cobbling together of Lenhard, Vilkin, and Itzkowitz assumes, based in part on Lenhard's comparison of gFOBT with HIC1 methylation testing, that the sample will be separated. Pet. at 21.

Nowhere does Lenhard teach that the patient separates the sample. *See generally* EX1004. Lenhard describes that samples were received, aliquoted, then stored at -80° C. *Id.* at 2. Those samples were “subjected to FOBT” “immediately upon receipt and before freezing.” *Id.* at 4. Further, sample treatment in Lenhard differed substantially from the method of the claims. The Lenhard samples were spread on cards for gFOBT, and were not put into stabilizing buffer solutions. EX2022 ¶58. The “iFOBT of Vilkin” in contrast used an “amount of Hb stabilizing buffer” in the sample tube. EX1005 at 4. Vilkin does not specify 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. Petitioner’s argument assumes that a POSA would be motivated to have the user separate the sample into two separate containers with two different buffers, but Petitioner offers no reason as to why a POSA with only the knowledge in the art as of 2009 would have arrived at the claimed method. EX2022 ¶117.

At most, Petitioner’s declarant Dr. Whitney opines that “many assays used different stabilizing buffers to minimize loss of sample integrity.” EX1002 ¶74. He then provides examples of references that discuss buffers to prevent degradation of DNA and buffers to stabilize blood protein. *Id.* Notably, the Whitney declaration contains no opinion that a POSA in 2009 would have understood that one could not have used a “DNA preservation” buffer to also stabilize blood protein. *See id.*

At deposition, Dr. Whitney testified that he had not formed an opinion as to whether or not a single buffer could stabilize both DNA and protein. EX2027 at 148:14-22; 149:18-150:20.

Absent a compelling reason why the stool sample would have to be separated by the user at the time of 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. EX2022 ¶¶117. Without the roadmap of the '781 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.* ¶¶118-119. 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 as, with the use of a single buffer in a single container, the sample would be separated for two separate tests at the lab.

B. Ground IV: Petitioner Fails to Establish That Shuber in View of Vilkin Renders Claims 1-9, 11, and 14-20 Obvious

Petitioner's Ground IV relies on a combination of Shuber and Vilkin. The Shuber patent application is assigned to Patent Owner Exact Sciences. EX1009. 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.* Vilkin was published in 2005. EX1005. Yet

four years went by before the priority date of the '781 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-xvi. Considering the widely recognized need for improved CRC screening, logic suggests that Shuber and Vilkin would be combined to arrive at the claimed invention only with the benefit of hindsight.

When considered as a whole, the cited references do not teach or suggest the claimed method of the '781 patent, nor do they provide motivation to combine the nucleic acid-based test of Shuber with the iFOBT of Vilkin. Moreover, even if such motivation were found, nothing in Shuber, Vilkin, or the other cited references suggests the specific configuration of the claimed invention.

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 20. In purported support of that assertion, Petitioner quotes a portion of Shuber that states “[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.”) EX1009 at 28:18-

27; Pet. at 20. 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. 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).” EX1009 at 14:1-15; EX2022 ¶90.

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 the analysis.” EX1005 at 6.

Petitioner’s arguments that the two could be combined to arrive at the specific elements of the claimed invention is based on impermissible hindsight knowledge of the claims. For example, the claims require collection at home by defecation directly into a sealable collection vessel.” EX1001 at 45:23-26. Shuber says little about sample collection and nothing about at-home collection by a patient. EX1009 at 29:8-19. The claims also require removing a portion of the sample from the sealable collection vessel to a separate sealable container. EX1001 at 45:27-29. Vilkin describes using stool probes to collect samples over three consecutive days but does not describe where the stool is located when a portion is collected with the stool probe. EX1005 at 4. Neither reference discloses or suggests that the patient separate one stool sample such that there is a remaining

portion and a removed portion, both in sealable containers, to be tested for two different classes of markers as required by the claims. EX2022 ¶¶69-73, 89-93. 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

In arguing motivation to combine Shuber with Vilkin, Petitioner relies on various statements concerning the potential for improved sensitivity. Pet. at 47-51. As with the previous combination, Petitioner again 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 48. 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 of those skilled in the art, 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. EX2022 ¶¶120-136.

Petitioner first relies on a sentence from the 2002 Nishikawa reference. Pet. at 48, 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. Notably, seven years passed between Nishikawa and the invention of the '781 patent without anyone else arriving at the claimed invention before Exact Sciences. EX2022 ¶128. 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 sufficient improved diagnostic performance where a potential increase in sensitivity would have to be balanced against any decrease in specificity. *Id.* ¶¶129-136.

Petitioner also cites to Lenhard as providing purported motivation to combine Shuber with Vilkin. Pet. at 49. 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. EX2022 ¶¶95-107, 129. 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 6. There is no teaching, suggestion, or motivation to combine FOBT with nucleic acid testing for CRC screening in Lenhard. Lenhard itself concludes that HIC1 should be combined with additional methylation markers, **not** with the gFOBT test that it used to compare with HIC1. EX2022 ¶67.

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 not obvious, and that 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. EX2022 ¶130. 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 for providing motivation to combine. Pet. at 49-50. However, Levin does nothing more than pose a question for potential investigation. *Id.* at 49. 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 tests in light of data such as that in Lenhard and Kanaoka, both of which show adverse effects on specificity. EX2022 ¶131. 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.* ¶132. 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.* ¶¶131-132.

(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 48-50. 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).” EX1009 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. EX2022 ¶¶120-134.

(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 47. As with the proposed combination in Ground I, Petitioner again ignores that Vilkin requires the collection of three samples over three days and 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.

(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. EX2022 ¶134. 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.

As with Ground I, nothing in the references on which Petitioner relies in Ground IV suggests that testing for two different classes of markers would have improved 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. Petitioner has not demonstrated any motivation to combine Shuber with Vilkin to arrive at the claimed invention.

3. Petitioner Fails to Establish Any Motivation for User Separation of Fecal Sample into Two Separate Sealable Containers at Home

For the same reasons discussed above in connection with the Lenhard, Itzkowitz, and Vilkin combination, Petitioner has failed to show any motivation for a POSA as of the priority date to arrive at the claimed invention where the sample is separated at home.

C. Grounds II, III, V, and VI

Petitioner's Grounds II and V address only dependent claims 12 and 13.

Those Grounds fail for the same reasons Grounds I and IV fail. Petitioner's Grounds III and VI address only dependent claim 10. Those Grounds also fail for the same reasons Grounds I and IV fail.

In addition, for Claims 12 and 13, Petitioner argues that Kanaoka provides further motivation to combine to increase sensitivity. Pet. at 44, 63. 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]; EX2022 ¶138. The combination of Kanaoka thus resulted in an insignificant increase in sensitivity, with a more significant decrease in specificity. *Id.* As with Lenhard, consideration of the Kanaoka reference as a whole would have discouraged a combination of nucleic acid-based and FOBT tests. EX2022 ¶138.

VIII. OBJECTIVE INDICIA FURTHER DEMONSTRATE THAT THE CLAIMS OF THE '781 PATENT WERE NOT OBVIOUS IN FEBRUARY 2009

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. The '781 Patented Method is Fundamental to Use and Acceptance of the Cologuard Test

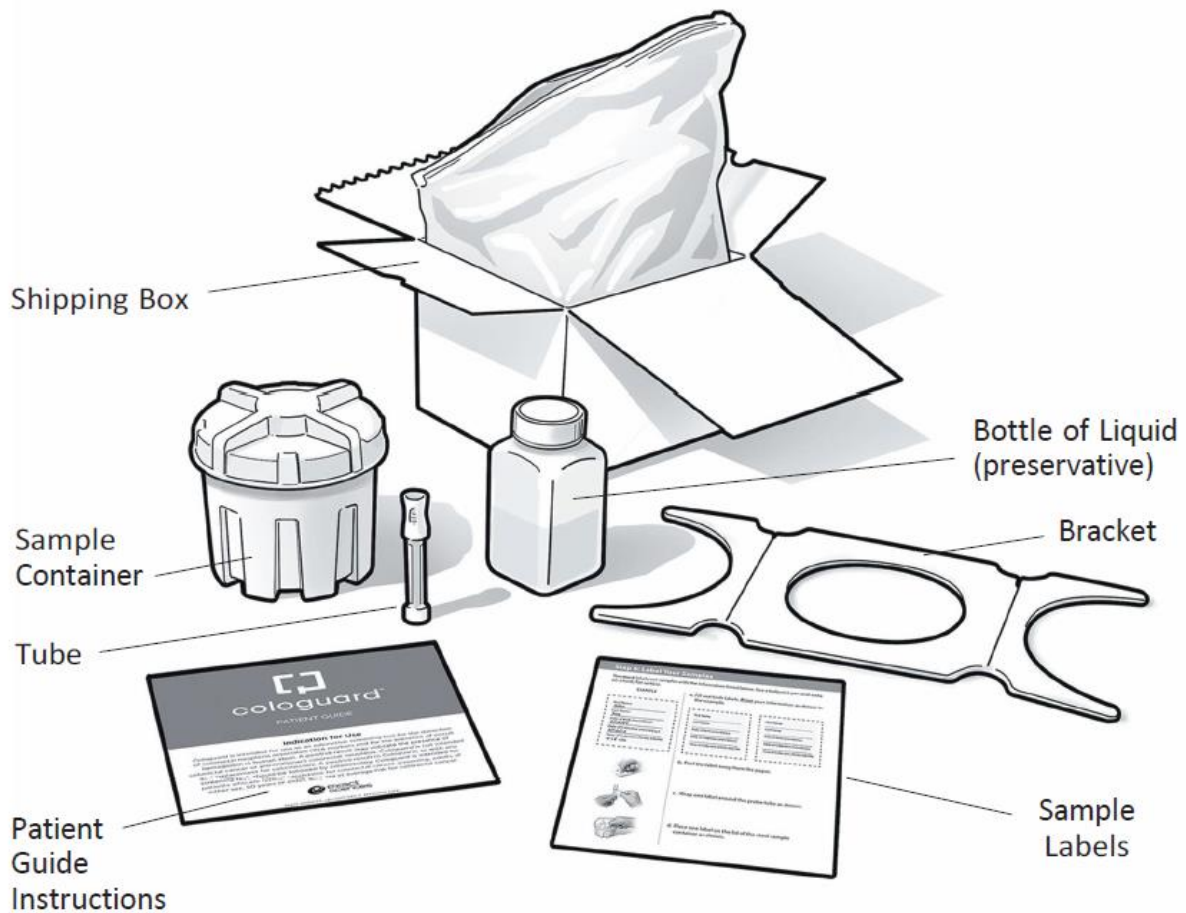
Patient acceptance and ease of use is critical to any screening test. *See, e.g.*, EX1024 at 4 (“Population participation is essential for cancer detection.”). As the CDC itself has stated, “[t]he best test is the test that gets done.” EX2031. The methods of at least Claims 1 and 3 of the '781 patent are fundamental to use of the Cologuard test as described in detail in Exact Sciences’ product literature. The Cologuard Patient Guide (the “Patient Guide”) tracks the sample processing method of Claim 1.

1. 1 [pre]: A method of processing a freshly-collected fecal sample without freezing, the method comprising:

The Patient Guide provides detailed instructions for the collection of a fecal sample that is shipped without freezing. EX2022 ¶143; EX2032 at 24-28, 30-31.

The patient receives a Cologuard Collection Kit (the “Collection Kit”) that includes everything that the patient needs:

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.

EX2022 ¶143; EX2032 at 8.

2. 1[a]: collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;

The Collection Kit includes a sealable sample container and the Patient Guide includes instructions for the patient to defecate directly into that sealable container. EX2022 ¶144; EX2032 at 14, 17-18, 23.

3. 1[b]: removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;

The Collection Kit also includes a sealable tube—a separate sealable container—that contains a probe. EX2022 ¶145; EX2032 at 14, 20. The probe is used to remove a portion of the fecal sample from the sealable collection vessel. EX2032 at 20-21. The probe is then returned to the separate sealable tube. *Id.* Removal of a portion of the fecal sample with the probe results in a removed portion in the tube and a remaining portion of the fecal sample in the collection vessel. EX2022 ¶145; EX2032 at 20-22.

4. 1[c]: combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and

The separate sealable tube in the Collection Kit contains a buffer that prevents denaturation or degradation of blood proteins—a 10% albumin in Tris buffered detergent solution with an antimicrobial agent. EX2022 ¶146; EX2032 at 8. The Patient Guide instructs the user to place the probe with the removed portion

of stool sample into the tube that contains the buffer and turn the cap. EX2022 ¶146; EX2032 at 21. Placing the probe in the buffer-containing separate sealable tube combines the fecal sample with the buffer, and turning the cap seals the container. *Id.*

5. 1[d]: combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.

The Collection Kit also contains a bottle containing a stabilizing buffer—the “bottle of liquid contains a preservative (less than 10% EDTA in Tris buffered solution).” EX2022 ¶147; EX2032 at 8. The Patient Guide instructs the patient to pour all of the contents of the bottle containing the stabilizing buffer over the sample in the sealable collection vessel and to seal the vessel after adding the stabilizing buffer. EX2022 ¶147; EX2032 at 22-23.

6. 3[pre]: A method of processing a fecal sample, the method comprising:

The Cologuard test is a method of processing a fecal sample. EX2032 at 6 (“After you collect your stool sample following the instructions in this Patient Guide, the collection kit will be delivered to a lab. The lab will test your stool sample...”); EX2022 ¶148.

7. 3[a]: obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:

The pair of portions of the fecal sample are collected from a human subject pursuant to the instruction in the Patient Guide, as set forth in connection with claim elements 1[a] and 1[b] above. The pair of portions is sent to a lab that obtains and tests the portions. EX2022 ¶149; EX2032 at 6, 24-28.

8. 3[a][i]: a sealed sealable container containing a removed portion of a fecal sample and a buffer; and

The pair of portions includes a sealed sealable container, the tube, containing a removed portion of the fecal sample and a buffer. EX2022 ¶150; EX2032 at 8, 20-21, 25.

9. 3[a][ii]: a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer,
the pair of portions obtained by the method of claim 1;

The pair of portions is obtained by the method of claim 1, as described above. The pair of portions includes a sealable container containing a remaining portion and a stabilizing buffer. EX2022 ¶151; EX2032 at 8, 17-18, 22-26.

10. 3[b]: testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;

After obtaining the removed portion of the fecal sample from the patient, the lab tests the removed portion for hemoglobin. EX2032 at 6, 46; EX2022 ¶152.

11. 3[c]: extracting nucleic acid from the remaining portion of the fecal sample; and

After obtaining the remaining portion of the fecal sample from the patient, the lab extracts nucleic acid from that remaining portion. EX2032 at 46 (“patient stool samples are processed at the laboratory to isolate the DNA for testing.”); EX2022 ¶153.

12. 3[d]: testing the nucleic acid for an amount of a human nucleic acid.

After obtaining the remaining portion of the fecal sample from the patient, the lab tests the remaining portion for an amount of human nucleic acid. *See, e.g.*, EX2032 at 6 (“Cologuard is designed to detect the DNA and hemoglobin released from these abnormal cells in your stool.”), 46 (“Amplification and detection of methylated target DNA (NDRG4, BMP3), KRAS point mutations, and ACTB (a reference gene for quantitative estimation of the total amount of human DNA in each sample) is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTS™) technology.”); EX2022 ¶154.

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. EX2023 ¶38; EX2029. More than 14 million Cologuard tests have been performed since its launch in 2014. *Id.*

In its SEC Form 10-K for 2014, Exact Sciences stated that for the foreseeable future, its “ability to generate revenue will depend entirely on the commercial success of Cologuard.” EX2023 ¶36; EX2036⁴ at 15. 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. EX2023 ¶ 37; EX2038 at 40. 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. EX2029 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. EX2022 ¶155. The claimed invention of the ’781 patent is essential to both aspects. *Id.* The addition of buffers to each of the remaining and removed 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 ’781

⁴ Exhibits 2034 through 2040 are true and correct copies of Exact Sciences’ SEC Form 10-Ks for the years 2004, 2008, 2014, 2016, 2018, 2021, and 2023. EX2023 ¶35.

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. EX2022 ¶¶156-157; EX2023 ¶¶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.” EX2048⁵ at 1; EX2022 ¶ 157. 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. Itzkowitz further stated the obvious, that “[i]nherent in the success of any screening test is patient acceptance.” *Id.* at 6.

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. EX2022 ¶¶157; EX2023 ¶¶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. EX2023 ¶¶31-32. Exact Sciences’ efforts have

⁵ Exhibit 2048 is a true and correct copy of Schroy. EX2024 ¶¶67-70.

contributed to increased compliance by individuals who previously had not been screened. *Id.* ¶39; EX2040 at 5; EX2052 at 4-5.

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]ong-felt need is closely related to the failure of others.” *Eurand, Inc. v. Mylan Pharms., Inc.* (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. EX2022 ¶¶29-30. The sheer volume of references that Petitioner submitted with the Petition demonstrate 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. EX2022 ¶¶31-36

Although colonoscopy was considered the gold standard for testing as of 2009, it has significant drawbacks. EX2022 ¶¶32-36. It is an invasive procedure

that carries a risk, although a low one, of complications including perforation that would require surgery. *Id.* ¶34. It also requires preparation through colonic purge before the procedure. *Id.* ¶35. 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.* ¶36.

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. EX2022 ¶39; EX1043 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. EX2022 ¶39; EX1043 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. EX2034. 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* EX1043; 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%. EX1043 at 1; EX2022 ¶167.

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. EX2023 ¶38; EX2035 at 18.

As of the February 2009 priority date of the '781 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. EX2022 ¶169.

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. EX2022 ¶170.

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. EX2049⁶ at 2; EX2022 ¶172. 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. EX2050⁷ at 10; EX2022 ¶173.

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. EX2052⁸ at 4-5; EX2022 ¶174. In addition, internal studies by Exact Sciences have shown that approximately 40% of surveyed Cologuard users were previously unscreened for CRC. EX2023 ¶39; EX2040 at 5. The volume of Cologuard test sales, increased screening rates overall, and the

⁶ Exhibit 2049 is a true and correct copy of Miller-Wilson. EX2024 ¶¶71-74.

⁷ Exhibit 2050 is a true and correct copy of Kisiel. EX2024 ¶¶75-77.

⁸ Exhibit 2052 is a true and correct copy of Eckmann. EX2024 ¶¶82-85.

number of Cologuard test users who were never previously screened all demonstrate that the Cologuard test is meeting the previously unmet need.

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. EX2042⁹; EX2023 ¶¶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. EX2043; EX2023 ¶¶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 “each of the winners demonstrated an incredible understanding about where the digital health marketplace is going and how we can

⁹ Exhibits 2042-2043, 2045-2046 are true and correct copies of press releases that are accessible at Exact Sciences’ website, <https://www.exactsciences.com/newsroom/press-releases>. EX2023 ¶¶21-22, 24-25; EX2024 ¶¶52-57, 61-66.

propel it forward.” EX2044¹⁰; EX2023 ¶23. Cologuard was also awarded a Wisconsin Innovation Award (WIA) in the “Healthcare/Health IT” category in 2015. EX2045; EX2023 ¶24.

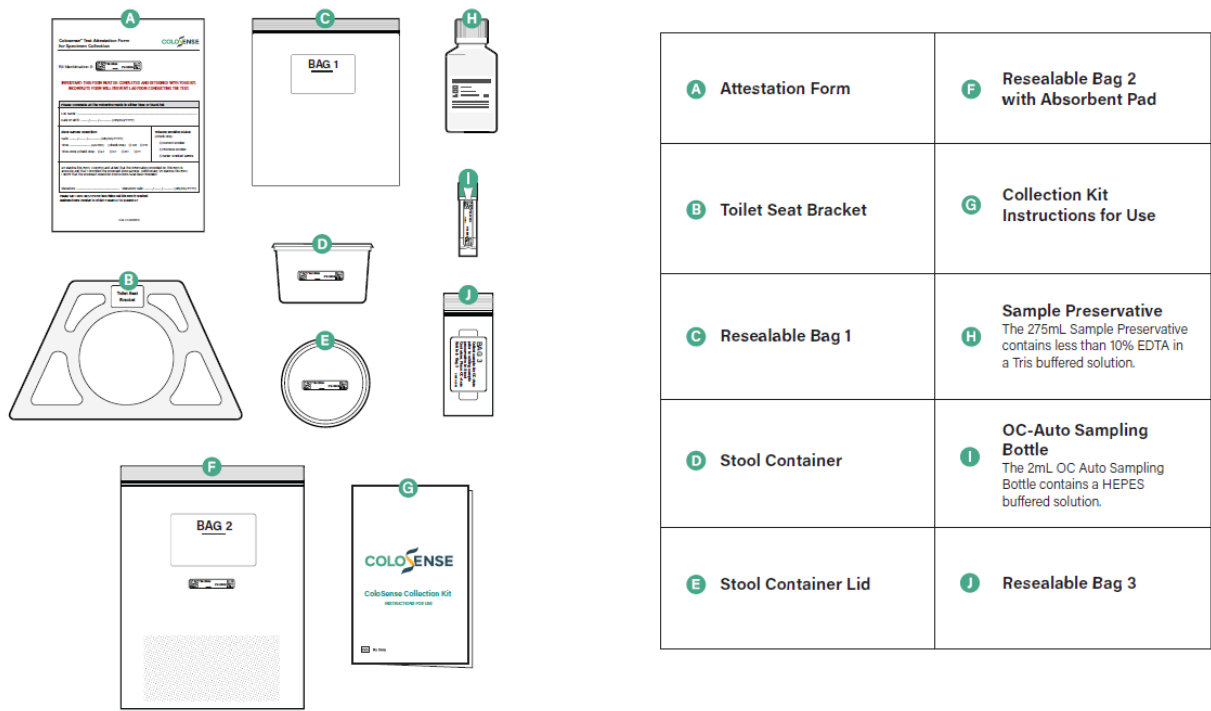
In 2016, Exact Sciences received the Business Intelligence Group’s 2016 Company of the Year BIG Award for Business in the Health Care category. EX2046; EX2023 ¶25. At the time all of the above awards were received, the Cologuard test was Exact Sciences’ only product. EX2023 ¶26.

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. EX2022 ¶¶177-178; EX2053.

¹⁰ Exhibit 2044 is a true and correct copy of a press release by Everyday Health. EX2023 ¶ 23; EX2024 ¶¶58-60.

ColoSense Collection
Kit Contents



EX2022 ¶178; EX2053 at 34.

Petitioner’s user instructions also track the instructions for use of Patent Owner’s Cologuard test, and thus the steps of the patented method. EX2022 ¶177; EX2053. As instructed by Petitioner, a patient collects a fresh fecal sample by direct defecation into a stool container in the privacy of their own home. EX2022 ¶179; EX2053 at 36-37. The patient removes a portion of the sample from the Stool container with a sample probe that is housed in what Petitioner calls a “sampling bottle.” EX2022 ¶180; EX2053 at 37-38. The sampling bottle contains “liquid Sample Preservative”—a buffer that prevents denaturation or degradation

of blood proteins. EX2022 ¶181; EX2053 at 37. The patient returns the probe that is covered with a removed portion of the stool sample to the sampling bottle and seals it. EX2022 ¶182; EX2053 at 38. The patient also adds a stabilizing buffer to the remaining sample in the sample container. EX2022 ¶183; EX2053 at 38. The patient seals that container as well, and both containers are shipped to a lab at room temperature. EX2022 ¶184; EX2053 at 38-40. The lab obtains the two containers with the two portions and tests the removed portion for a blood protein. EX2022 ¶185; EX2053 at 56. Nucleic acid is extracted from the remaining portion and the nucleic acid is tested for an amount of nucleic acid. EX2022 ¶185; EX2053 at 54-55.

These secondary indicia are consistent with the fact that the claimed invention moved in a direction that was contrary to the teaching in the art and weigh heavily against a finding of obviousness. *Cf W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (proceeding “contrary to the accepted wisdom of the prior art” was “strong evidence of nonobviousness.”). Had the claimed invention been obvious, others would have previously thought of it, published it, and brought it to market to save the lives that Exact Science’s technology has saved and to garner the financial success that Exact Sciences has achieved with the Cologuard test. Indeed, had the claimed invention been obvious to a POSA based on the cited references, there is no explanation for why earlier

teams at Exact Sciences—and more specifically the named inventors of Shuber—spent years and millions of dollars on other, failed approaches to the point where Exact Sciences itself almost failed as a company before a new team at Exact Sciences pursued the successful Cologuard approach.

IX. CONCLUSION

For the foregoing reasons, the Board should affirm the patentability of all challenged claims of the '781 patent.

Date: October 25, 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 13,980 words and thus complies with the applicable word limit.

Date: October 25, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on October 18, 2024 the foregoing Response from Patent Owner was served via email on the following counsel of record for the Petitioner:

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