

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

Case No: IPR2024-01330
U.S. Patent 11,970,746

PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. BACKGROUND OF THE COLOGUARD TEST AND ’746 PATENT	3
A. CRC Screening Techniques Prior to the Cologuard Test.....	3
B. The Invention of the ’746 Patent.....	5
III. PROSECUTION HISTORY	8
IV. THE ASSERTED PRIOR ART	9
1. Lenhard (EX1004)	9
2. Vilkin (EX1005)	12
3. Itzkowitz (EX1006).....	14
4. Kanaoka (EX1007)	15
5. Shuber (EX1008)	16
6. Inbar (EX1009)	18
V. LEVEL OF ORDINARY SKILL IN THE ART	20
VI. CLAIM CONSTRUCTION IS NOT NECESSARY	20
VII. PETITIONER HAS FAILED TO PROVE UNPATENTABILITY	20
A. All Grounds: Petitioner Shows No Motivation For At-Home Separation of Sample.....	21
B. Ground I: Petitioner Fails to Establish That Lenhard in View of Vilkin and Itzkowitz Renders Claims 3-4 and 14-19 Obvious	24
1. The Lenhard, Vilkin, and Itzkowitz Combination Does Not Teach or Suggest the Claimed Invention	25

2.	Petitioner Fails to Establish That A POSA Would Have Been Motivated to Combine Lenhard with Vilkin and Itzkowitz.....	27
C.	Ground III: Petitioner Fails to Establish That Shuber in View of Vilkin Renders Claims 3-4 and 14-19 Obvious.....	37
1.	The Shuber and Vilkin Combination Does Not Teach or Suggest the Claimed Invention	38
2.	Petitioner Fails to Establish That A POSA Would Have Been Motivated to Combine Shuber with Vilkin	39
D.	Ground VI: Petitioner Fails to Establish That Inbar, Shuber, and Vilkin Render Claims 3-4 and 14-19 Obvious.....	45
E.	Grounds II, IV and VII: Petitioner Fails to Show Why, or How, A POSA Would Have Combined the Frozen Sample of Kanaoka With Each of the Asserted Combinations.....	47
1.	A POSA Would Not Have Been Motivated to Add the COX-2 RNA Detection of Kanaoka to the Asserted Combinations	47
2.	The Cited References Do Not Support A Reasonable Expectation of Combining the Frozen Processing of Kanaoka in an At-Home Collection Method that Excludes Freezing	49
3.	If Kanaoka Were Added to the Combinations, There Was No Reason to Separate Sample	51
VIII.	SECONDARY INDICIA SUPPORT NONOBVIOUSNESS	51
A.	There is a Nexus Between the Cologuard Product and the Patented Invention.....	52
B.	The Commercial Success of Cologuard Objectively Demonstrates Non-Obviousness	56

C. Others Tried and Failed to Develop a CRC Screening Test with Satisfactory Diagnostic Accuracy and Uptake, and Cologuard Satisfies a Long-Felt, Previously Unmet Need 58

D. Cologuard Has Received Industry Praise and Recognition 62

E. Petitioner’s Recently Approved “ColoSense” Copies the Claimed Invention 63

IX. CONCLUSION.....64

TABLE OF AUTHORITIES

	<u>Page</u>
<u>Cases</u>	
<i>Apple Inc. v. Int’l Trade Comm’n</i> , 725 F.3d 1356 (Fed. Cir. 2013)	51
<i>Arctic Cat, Inc. v. Bombardier Recreational Products, Inc.</i> , 876 F.3d 1350 (Fed. Cir. 2017)	28, 32, 40, 48
<i>ATD Corp. v. Lydcall, Inc.</i> , 159 F.3d 534 (Fed. Cir. 1998)	21
<i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012)	59
<i>Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	20
<i>Harmonic Inc. v. Avid Tech., Inc.</i> , 815 F.3d 1356 (Fed. Cir. 2016)	20
<i>Henny Penny Corp. v. Frymaster LLC</i> , 938 F.3d 1324 (Fed. Cir. 2019)	2
<i>KSR Intern. Co. v. Teleflex Inc.</i> 127 S.Ct. 1727 (2007)	21
<i>Polaris Indus., Inc. v. Arctic Cat Inc.</i> , 882 F.3d 1056 (Fed. Cir. 2018)	55
<i>Quanergy Sys. Inc. v. Velodyne Lidar USA, Inc.</i> , 24 F.4th 1406 (Fed. Cir. 2022)	52, 57
<i>Sound View Innovations, LLC v. Hulu, LLC</i> , 818 F. App’x 1009 (Fed. Cir. 2020)	29
<i>Teva Pharms. Int’l GmbH v. Eli Lilly & Co.</i> , 8 F.4th 1349 (Fed. Cir. 2021)	55

Univ. of Strathclyde v. Clear-Vu Lighting LLC,
17 F.4th 155 (Fed. Cir. 2021) 50

Volvo Penta of the Americas, LLC v. Brunswick Corp.,
81 F.4th 1202 (Fed. Cir. 2023) 52

EXHIBIT LIST

No.	Exhibit
2001	Declaration of Vadim Backman, Ph.D.
2002	<i>Curriculum vitae</i> of Vadim Backman, Ph.D.
2003	Prosecution file history for application number 15/634,607, issued as patent number 11,845,991
2004	Prosecution file history for application number 17/936,335, issued as patent number 11,634,781
2005	Prosecution file history for application number 18/179,945, issued as patent number 11,970,746
2006	Portion of prosecution file history for application number 18/919,170
2007	Declaration of June Ann Munford
2008	Appendix to Declaration of June Ann Munford
2009	Sidney J. Winawer and Ann G. Zauber, <i>The Advanced Adenomas as the Primary Target of Screening</i> , 12(1) Gastrointestinal Endosc. Clin. N. Am. 1, 1-9 (2002)
2010	Daniel C. Chung, <i>The Genetic Basis of Colorectal Cancer: Insights Into Critical Pathways of Tumorigenesis</i> , 119 Gastroenterology 854, 854-865 (2000)
2011	Hermann Brenner et al., <i>Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840 149 screening colonoscopies</i> , 56(11) Gut 1585, 1585-1589 (2007)
2012	David L. Zack et al., <i>Colorectal Cancer Screening Compliance by Medicine Residents: Perceived and Actual</i> , 96(10) Am. J. Gastroenterology 3004, 3004-3008 (2001)
2013	Amnon Sonnenberg and Fabiola Delcò, <i>Cost-effectiveness of a Single Colonoscopy in Screening for Colorectal Cancer</i> , 162(2) Arch Intern Med. 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, “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%20Campaigh%20Urges%20Colorectal%20Cancer,'&text=Shortly%20after%20basketball%20star%20Jamal,he%20got%20some%20tough%20news (March 07, 2024)
2017	Geneoscopy, “Geneoscopy Submits Premarket Approval Application to U.S. food and Drug Administration for its Noninvasive Colorectal Cancer RNA Biomarker Screening Test,” https://www.geneoscopy.com/geneoscopy-submits-premarket-approval-application-to-fda-for-its-noninvasive-colorectal-cancer-rna-biomarker-screening-test/ (January 24, 2023)
2018	United States Department of Health and Human Services, “Increase the proportion of adults who get screened for colorectal cancer — C-07,” https://health.gov/healthypeople/objectives-and-data/browse-objectives/cancer/increase-proportion-adults-who-get-screened-colorectal-cancer-c-07
2019	Declaration of Peter Wood
2020	Transcript of October 10 Deposition of Duncan Whitney, Ph.D. in connection with IPR2024-00459
2021	Geneoscopy, Series C Investor Presentation, available at (password protected link) https://nephronnext.open-exchange.net/stream/531120 (April 10, 2024)
2022	FDA, ColoSense™ Approval letter, available at https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001A.pdf
2023	CDC “Vital Signs: Colorectal Cancer Tests Save Lives,” available at https://archive.cdc.gov/www_cdc_gov/vitalsigns/colorectalcancerscreening/index.html
2024	Exact Sciences Form 10-K for the year ending December 31, 2004
2025	Exact Sciences Form 10-K for the year ending December 31, 2008
2026	Exact Sciences Form 10-K for the year ending December 31, 2014
2027	Exact Sciences Form 10-K for the year ending December 31, 2016
2028	Exact Sciences Form 10-K for the year ending December 31, 2018
2029	Exact Sciences Form 10-K for the year ending December 31, 2023

2030	Printout from Exact Sciences' Internal Survey Database
2031	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)
2032	Exact Sciences, "Cologuard® Wins Popular Science Magazine's 2014 'Best of What's New' Award," https://www.exactsciences.com/newsroom/press-releases/cologuard-wins-popular-science-magazines-2014-best-of-whats-new-award (November 12, 2014)
2033	Everyday Health, Inc., "Everyday Health Awards for Innovation Winners Announced at 2015 International CES®," https://www.prnewswire.com/news-releases/everyday-health-awards-for-innovation-winners-announced-at-2015-international-ces-300017454.html (January 7, 2015)
2034	Exact Sciences, "Exact Sciences Wins Wisconsin Innovation Award," https://www.exactsciences.com/newsroom/press-releases/wisconsin-innovation-award-2015 (August 19, 2015)
2035	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)
2036	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)
2037	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)
2038	John B. Kisiel et al., <i>Multitarget Stool DNA for Average Risk Colorectal Cancer Screening Major Achievements and Future Directions</i> , 30 Gastrointest Endoscopy Clin N Am 553, 553-568 (2020)
2039	Jason D. Eckmann et al., <i>Multi-Target Stool DNA Testing for Colorectal Cancer Screening: Emerging Learning on Real-world Performance</i> , 18 Curr Treat Options Gastro 109, 109-119 (2020)
2040	ColoSense Product information available at

	https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230001C.pdf
2041	Disclaimer in a Patent Under 37 CFR 1.321(a) of claims 1 and 2 of U.S. Patent No. 11,970,746
2042	Request for Ex Parte Reexamination under 37 C.F.R. § 1.510 of U.S. Patent No. 11,634,781
2043	Declaration of Anastasia Fernands in Support of Patent Owner's Motion for Pro Hac Vice Admission
2044	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 No. 11,970,746
2045	Second Declaration of June Anne Munford
2046	Appendix to Second Declaration of June Ann Munford
2047	Hidenori Nakama et. al, <i>Colonoscopic Evaluation of Immunochemical Fecal Occult Blood Test for Detection of Colorectal Neoplasia</i> , Hepato-Gastroenterology, vol. 46, January-February 1999.
2048	TechNotes 11(3), "RNAlater® for RNA and Protein Stabilization," available at https://web.archive.org/web/20050204191932/http://www.ambion.com/techlib/tn/113/6.html
2049	Declaration of John Andrews attaching Japanese Patent Application Publication No. H5-99923 and Certified Translation
2050	Intentionally Omitted
2051	Public Transcript of January 9, 2025 Deposition of Duncan Whitney, Ph.D. in District of Delaware C.A No. 23-1319
2052	September 26, 2024 Declaration of Duncan Whitney, Ph.D. in D. Del. C.A. No. 23-cv-1319-MN
2053	Transcript of May 16, 2025 Deposition of Duncan H. Whitney, Ph.D.

I. INTRODUCTION

U.S. Patent No. 11,970,746 (the “’746 patent”) covers the use of Exact Sciences’ revolutionary Cologuard® colorectal cancer (“CRC”) screening kits. The technology protected by the ’746 patent has provided a life-saving long-desired, but previously unmet, noninvasive solution for millions of people seeking CRC screening, and has undisputedly been a resounding commercial success.

Petitioner ignores the realities of how a person of skill in the art (“POSA”) would have viewed the prior art in 2009. First, Petitioner disregards the importance a POSA would have placed on statistically significant data in the cited prior art to provide motivation to combine references. The fact is, the data Petitioner relies on is *not* statistically significant, and the prior art authors chose not to draw Petitioner’s conclusions from that data accordingly. A POSA would disregard it in the same way. Second, Petitioner ignores the everyday realities of patients who would be the intended users of the test. Petitioner’s prior art requires patients to interact with, then keep, their own feces in zip-lock bags for days in their home refrigerator. Third, a POSA would understand that the results of a study depend on the protocols employed—without incorporating a reference’s methodology, one could not expect the benefits of its results. Petitioner fails to explain a motivation behind the proposed combinations, which a POSA would understand to decrease specificity while increasing complexity and cost.

Petitioner's challenge to the '746 patent—almost a decade after the commercial release of Cologuard—improperly relies on hindsight to select particular elements from various references (while ignoring the rest of the disclosures) to map onto the claims. Petitioner's arguments violate the “longstanding principle that the prior art must be considered for all its teachings, not selectively.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Petitioner further fails to show motivation to incorporate yet another reference (Kanaoka), to arrive at the invention of claims 12 and 13 (Grounds II, IV, and VII). Kanaoka requires freezing, preferably with liquid nitrogen, which is fundamentally incompatible with the claimed at-home collection without freezing. A POSA would understand that the results of a published study are necessarily dependent on the methods employed. A POSA would not have expected the results of the Kanaoka study without, *inter alia*, liquid nitrogen-freezing of the samples prior to analysis.

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

II. BACKGROUND OF THE COLOGUARD TEST AND '746 PATENT

A. CRC Screening Techniques Prior to the Cologuard Test

For decades, CRC has been known as a leading cause of cancer-related deaths. *See, e.g.*, EX1034 at 1; EX1004 at 1. By the '746 patent's priority date, colonoscopy had become the primary screening test for CRC because of its high sensitivity and specificity, and because pre-cancerous polyps can be removed during the procedure. EX1001 at 1:65-67. While both sensitive and specific, colonoscopy is also "invasive, costly, has limited availability and includes certain risks such as induction of infection and perforation of the bowel." *Id.* at 2:1-3.

By 2009, various approaches for CRC screening less invasive than colonoscopy, including fecal occult blood tests ("FOBT") and nucleic acid screening tests, were also being used and developed. *See* EX1001 at 2:4-3:40. Each had limitations, including limited sensitivity, specificity, patient acceptability, or a combination of all three. *See 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. EX2044 ¶41; *see also* EX1020 at 3; EX1023 at 2.

FOBTs, which detect blood in feces,¹ are inherently limited by the intermittent nature of bleeding in colorectal cancer. EX1001 at 2:41-43; EX1023 at 5. The

¹ There are generally two approaches to FOBT. Guaiac-based FOBT ("gFOBT") relies on the substance guaiac, which changes color in the presence of heme, a

sensitivity of FOBTs is therefore dependent on “the number of samples taken and the frequency of testing.” *Id.*

A primary goal with CRC screening is to identify cancer or precancerous lesions as early as possible. The earlier the detection, the greater the reduction in mortality. *See, e.g.*, EX1001 at 1:43-46; EX1004 at 1; EX2044 ¶32. Accordingly, those working in the field recognized that, in addition to early-stage CRC, precancer indications, such as adenomas, should be a target of screening. EX2009 at 1; EX2044 ¶¶32-33.

Both “[s]ensitivity and specificity are important metrics of diagnostic assay performance.” EX1002 ¶28; *see also id.* ¶31 (“Effective diagnostic tests must be sensitive and specific for the disease of interest.”); EX2020 at 133:11-15 (“required of a good test...is to have high specificity in order to avoid false positives and to have high sensitivity to avoid false negatives.”). High sensitivity is desirable because false negatives result in failure to detect disease. EX1002 ¶29. High specificity is desirable “because patients who wrongly test positive are often subjected to an unnecessary medical procedures [sic] and potentially unnecessary treatment.” *Id.* ¶30. A POSA would understand that, in view of the high cost and inconvenience of

moiety complexed with hemoglobin in blood. Immunochemical FOBT (“iFOBT,” also known as fecal immunochemical test, or “FIT”) detects the blood protein hemoglobin using antibodies. EX1023 at 2.

colonoscopy, even minor reductions in specificity could have a large negative impact on the overall cost-effectiveness of screening. EX2044 ¶¶37-39, 146. False positives also have significant patient impact. *Id.* ¶¶38-39, 146; EX1034 at 12-13.

By the February 2009 priority date, there remained a long-felt unmet need for effective, efficient, non-invasive CRC screening tests. EX2044 ¶¶31-40; 222-231. A POSA would recognize that any such tests would need to (i) have sufficient sensitivity to detect indications of cancer and precancerous lesions, (ii) have sufficient specificity to minimize false positives that result in unnecessary colonoscopies and decrease confidence in the test, and (iii) be both accessible to, and acceptable to, patients. *Id.* ¶¶31-43; 146; 196.

B. The Invention of the '746 Patent

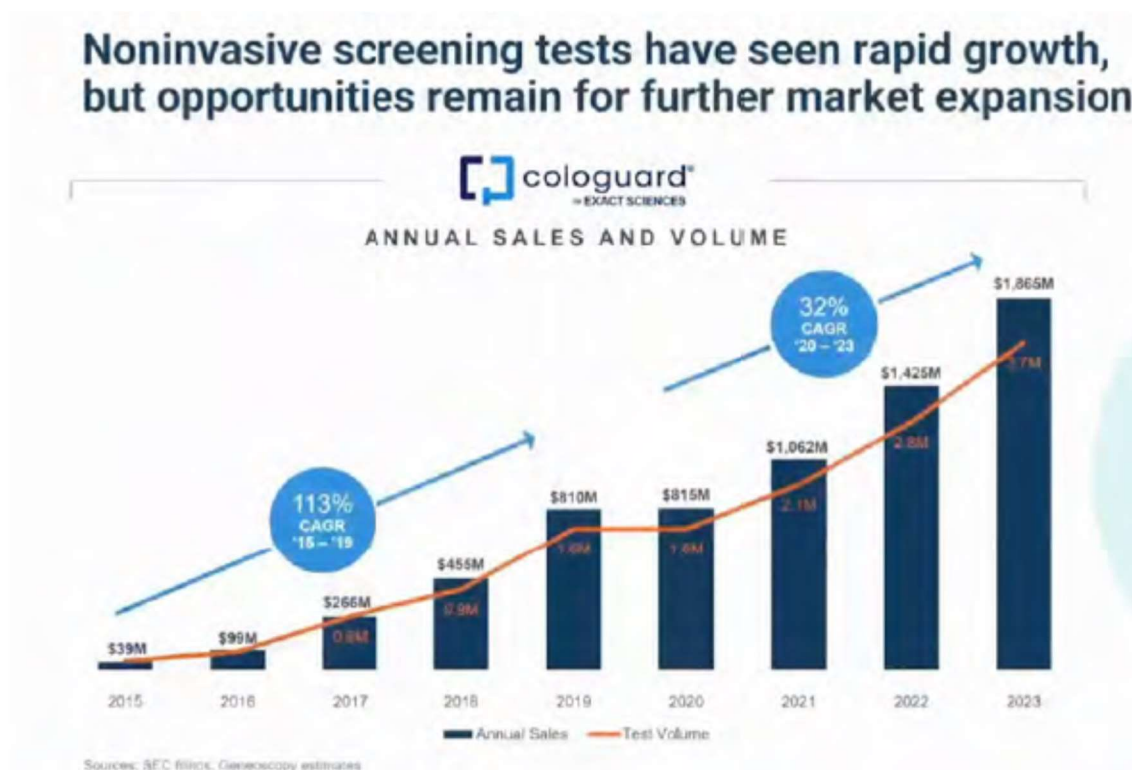
The Cologuard test using the '746 patented technology accomplished these long-felt but unmet goals. EX2044 ¶¶214-221; 232-237. The Cologuard test has achieved 92.3% sensitivity and 86.6% specificity for CRC. EX1077 at 1; EX2044 ¶45. Further, Cologuard significantly outperformed an iFOBT [FIT] in sensitivity for advanced precancerous lesions. EX1077 at 1; EX2044 ¶45.

Cologuard revolutionized at-home CRC screening. Under the '746 patent's novel and innovative approach, a fecal sample that will be tested for both nucleic acid and blood can be conveniently collected in the privacy of a patient's home and shipped without freezing from virtually anywhere. EX1076 at 13-31. The method of

the '746 Patent resolved how to do this without the multiple days of storing zip-lock bags filled with stool samples in a kitchen refrigerator required by the method of Vilkin, or the freezing required by Kanaoka. *See* EX1005 at 8; EX1007 ¶[0057].

The '746 patent is the innovative combination of at-home collection acceptable to patients, use of buffers that avoid freezing, and testing for both nucleic acids and fecal occult blood that resulted in enhanced performance. *See generally* EX1001. The Cologuard test using the '746 patent's invention enables patients to get screened for CRC who would otherwise go unscreened. EX2044 ¶235; EX2019 ¶39. Under the patented method, a patient collects a fecal sample in the privacy of their own home. EX1076 at 15-19; EX2044 ¶¶201-202. The patient removes a portion of the sample to a separate sealable container, resulting in a first and second portion. EX1076 at 20-23; EX2044 ¶203. The patient adds a stabilizing buffer to the first portion. EX1076 at 8, 22-23; EX2044 ¶204. The separate sealable container with the second portion contains a buffer that prevents denaturation or degradation of blood proteins. EX1076 at 8, 20-21; EX2044 ¶206. The containers are sealed and shipped to a lab at room temperature, without freezing. EX1076 at 21, 23, 30; EX2044 ¶¶201, 204, 206, 208. The lab obtains the two containers with the two portions, extracts nucleic acid from the first portion, and tests it for an amount of human nucleic acid. EX1080 at 4; EX2044 ¶¶210-212. The second portion is tested for an amount of blood protein. EX1080 at 4; EX2044 ¶213.

Cologuard was the first FDA-approved commercially available multitarget stool-based blood and nucleic acid test for CRC screening. EX1025 at 1. Cologuard was also the first product to successfully undergo the FDA-CMS parallel review program resulting in simultaneous FDA approval and a proposed Medicare national coverage determination. EX2019 ¶14. Cologuard has been used by millions since its August 2014 approval. *Id.* ¶38. Petitioner has pointed to the rapid increase in use of Cologuard in its own presentations to investors.



EX2021 at 11.

In May of 2024—almost a decade after Cologuard received FDA approval—Petitioner received FDA premarket approval for its ColoSense™ test. EX2022 at 1.

ColoSense copies the innovative, successful approach of the '746 patent for at-home collection of fresh fecal samples to be tested for both nucleic acid and blood protein. EX2044 ¶¶238-246.

III. PROSECUTION HISTORY

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

Petitioner suggests that the '746 patent issued without significant prosecution history. Pet. at 10-11. This ignores the history of office actions during prosecution of the related '607 application, in which the Patent Owner overcame multiple rejections, including rejections relying on Petitioner's Shuber and Kutzner references. EX2003 at 315-320; 353-358, 643-644. The '746 patent is subject to terminal disclaimer over the '781 patent and the '991 patent. EX1019 at 6; EX2005 at 59-61.

IV. THE ASSERTED PRIOR ART

1. Lenhard (EX1004)

Lenhard is a 2005 article that compares performance of a single gene methylation (epigenetic) marker with a gFOBT in distinguishing between patients with CRCs and those without. EX1004 at 1 (Background & Aims); EX2044 ¶58. Notably, the Lenhard data were so poor, the authors were unable to identify over one third of the subjects who had even the most advanced stages of CRC. EX1004; EX2044 ¶¶62-63. Even the authors of Lenhard did not reach the conclusion that combination of DNA and protein markers was the best path forward; rather, they concluded that the combination of two or more DNA markers alone was the better approach. EX1004 at 7. In fact, it would have been scientifically irresponsible for the authors to recommend a combination of DNA and protein based on their statistically insignificant results.

Lenhard also does not describe home collection and separation of stool samples. EX2044 ¶59. Rather, the samples in Lenhard “were collected before cathartic preparation for scheduled surgery or colonoscopy” and were “received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80° C.” EX1004 at 2; EX2044 ¶¶58-59. The samples were subjected to gFOBT “immediately on receipt and before freezing.” EX1004 at 4; EX2044 ¶59. The

gFOBT testing of Lenhard involved spreading stool sample onto cards, letting the sample dry for a day, then applying a peroxide catalyst to the card. *Id.*; EX2044 ¶¶61.

In comparing HIC1 methylation marker with gFOBT, Lenhard includes the combined results of the two individual tests. EX1004 at 2, 6; EX2044 ¶¶60. Petitioner relies heavily on those combined results, particularly that “the combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.” *See, e.g.*, Pet. at 9, 13. But that means **one third of cancers were missed**—in patients who were mostly at advanced stages (meaning the load of cancer cells in their bodies was very high). And the two thirds detection data were not statistically significant as compared to HIC1 alone—with an unreported P-value of 0.13. EX2044 ¶¶64-68. A POSA would recognize this is a suboptimal result. *Id.* ¶¶64-69. Petitioner ignores much of the Lenhard reference and does not address how a POSA would consider it as a whole. *See* Pet. at 13, 19-34.

To begin, a POSA would consider the number of individuals tested and whether any reported results are statistically significant. EX2044 ¶¶63-69. Table 4 of Lenhard on its own shows no statistically meaningful difference between HIC1 alone and the combined results of HIC1 and gFOBT. Lenhard indicates a 95% probability that the sensitivity for HIC1 would fall between 23% and 63%. EX1004, Table 4; EX2044 ¶¶66. For combined HIC1 and gFOBT results, the probability is 95% that sensitivity would fall between 44% and 83%. EX1004, Table 4; EX204 at

¶¶64,66. Because these ranges are vast and overlapping, the data suggests that the real sensitivity of the combined results could be lower than that of HIC1 alone. EX2044 ¶66. Moreover, the P-value of this data was poor at 0.13. *Id.* ¶¶67-68. The notion that a POSA would credit this statistically insignificant data defies common sense.

A POSA considering whether Lenhard would suggest moving forward with an at-home collection CRC screening method would also consider the lack of improvement for adenomas. EX2044 ¶¶62, 71. Lenhard teaches that “a stool-based screening assay also should detect relevant premalignant lesions (ie, adenoma).” EX1004 at 6. This is because “[d]etection of early disease and precancerous adenomatous lesions leads to a decrease of CRC-related mortality.” *Id.* at 1. Lenhard reported that HIC1/gFOBT results combined showed “no increase in the sensitivity for adenoma.” *Id.* at 6; EX2044 ¶62.

Further, a POSA would not consider sensitivity without also considering specificity. Lenhard repeatedly states that markers must have **both** high sensitivity and specificity. EX1004 at 1, Background & Aims (“markers with high sensitivity and good specificity are needed”), 2 (“identification of both sensitive and highly specific methylation markers is required ...”), 6 (“Highly sensitive, specific, and easily analyzable markers are required for noninvasive stool-based CRC screening.”); *see also* EX2044 ¶72. The sensitivity for “two thirds of CRCs” on

which Petitioner relies came with a reduction in specificity. EX2044 ¶¶73-75; *see also* EX1004, Table 3 (showing additional false positives from gFOBT for control subjects 40, 47, 82 and 84).

Lenhard concludes “this 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 methylation markers, not combining nucleic acid-based testing with FOBT as Petitioner asserts. EX2044 ¶¶77-79.

2. Vilkin (EX1005)

Vilkin is a 2005 article that concerns testing a particular desktop immunochemical FOBT (“iFOBT”) that demonstrated a “high sensitivity of 76.5% for all significant colorectal neoplasia and acceptable specificity of 95.3%” based on three samples per subject. EX1005 at 7. The tested population in Vilkin was “ambulatory persons who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high-risk for CRC and invited for colonoscopy.” *Id.* at 4; EX2044 ¶81.

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

all three tests were performed and utilized for analysis.” *Id.* at 6. This makes sense because some CRC patients have intermittent tumor bleeding, and using the Vilkin methodology a cancer might be missed if the sample happens to be taken on a day when the patient’s tumor is not bleeding. EX1023 at 5. Table 3 of Vilkin reveals a range of sensitivities between the three different sample sets.

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

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

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

†At the 100 ng Hb/mL threshold.

Id. at 7. Vilkin taught using three consecutive fecal tests per subject, as they had “confirmed the additive clinical value of repeated occult blood testing in this high-risk population.” *Id.* at 8; EX2044 ¶82.

According to Vilkin, Patients were to handle their own samples using a fecal probe with a serrated tip that is “poked into the stool,” and then put into a 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; EX2044 ¶83.

Vilkin also reported that subjects reacted negatively to the storage protocol. The subjects used double-closing zip-lock bags for storage. However, Vilkin reported that “[t]his packaging could be further improved” because the “double zip-lock bags” only “answered some of the screenees’ hesitancy” about keeping their feces “in their home refrigerator.” EX1005 at 8.

3. Itzkowitz (EX1006)

Itzkowitz focuses on testing what it identified as “version 2” of Exact Sciences’ own fecal DNA test for CRC. EX1006 at 1.

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 patient willingness to participate in CRC screening. EX1006 at 5. “Inherent in the success of any screening test is patient acceptance.” *Id.* at 6. Itzkowitz 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; EX2044 ¶90.

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; EX2044 ¶91; *see also* EX1006 at 7 (results suggest that with only 2 markers (and only one marker type) “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”).

4. Kanaoka (EX1007)

Petitioner relies on Kanaoka in Grounds II, IV, and VII. *See* Pet. at 12. 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” using a “method to prepare a sample for extracting RNA used to detect a tumor marker.” EX1007 at [0015]-[0016]. Kanaoka identifies prior-art limitations of using RNA noting “it was impossible to extract RNA easily and efficiently from a small amount of feces.” *Id.* at [0009]. Kanaoka also teaches that “RNA is more unstable compared with DNA and is always subjected to a danger of decomposition by RNA digesting enzymes...” *Id.* at [0011].

Kanaoka provides 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’s Example 1 states that, “[a]s soon as possible after sampling feces, the feces were separated into 5 ml tubes about 1 g each, were frozen using liquid nitrogen, and were stored at -80°C.” *Id.* at [0057]. Kanaoka provides results from an iFOBT “for comparison and reference.” *Id.*; EX2044 ¶96.

Kanaoka separately discloses results from COX-2 RNA markers and iFOBT. EX1007 at [0065], [0066]. Kanaoka does not discuss combined data for the COX-2 and iFOBT markers. If the results from the two tests are considered together, they show a small increase in sensitivity with a larger decrease in specificity, although neither was statistically significant. EX2044 ¶¶100-103. Considered together, the combined performance was worse overall than COX-2 alone. EX2044 ¶¶100-105.

5. Shuber (EX1008)

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

Shuber concerns preparing samples for use in nucleic acid-based testing. EX1008 (Field of the Invention). Shuber describes a method for stabilizing nucleic acids in biological samples, including stool samples, to facilitate analysis in a nucleic acid integrity assay. *Id.* at 2:5-9. According to Shuber, “[i]n one embodiment, the invention may be useful to avoid or reduce the number of false negative results in a

screen of a population of individuals for one or more indicia of adenoma or early stage cancer (e.g., using a DNA integrity assay, a multiple mutation assay, a hypermethylation assay, or any combination thereof).” *Id.* at 28:23-27. Each of these is a nucleic acid-based test. EX2044 ¶108.

Petitioner ignores the importance of detecting adenomas, but Shuber acknowledges that “detecting adenomas is particularly useful for identifying early signs or risks of colorectal cancer (e.g., cancerous and precancerous lesions or growths in the colon).” EX1008 at 13:7-8. According to Shuber, testing for various combinations of nucleic acid markers could detect adenomas with 60%, 74%, 90% and even “greater than 95% sensitivity (e.g., greater than 98% sensitivity).” *Id.* at 14:1-16; EX2044 ¶109.

Shuber says very little about sample collection, stating that “a sample (e.g., a stool sample) may be directly deposited into a container (e.g., a sealable container [sic])” that either already contains a stabilization solution or to which a stabilization solution may be added. EX1008 at 29:8-19. The “stabilization solution” of Shuber may be at a pH between 7.0 and 9.0 and may include 0.5 mM to 25 mM Tris, 0.01 to 2.5 mM EDTA, and about 100 mM to 200 mM NaCL. EX1008 at 4:1-2; 4:19-21; EX2044 ¶107. Shuber does not specifically mention home collection. *See generally* EX1008; EX2044 ¶110.

6. Inbar (EX1009)

Inbar is an international patent application published in 1997. EX1009 at 1. Petitioner relies on Inbar to assert that a subject separating their own feces into different portions was known in the art. Pet. at 1,17-18, 54-55. This ignores (1) that Inbar does not mention home collection, and (2) the context in which Inbar describes separation of sample. Inbar describes sample separation to test for bacteria and parasites known or suspected to be in a person's body. EX1009 at 2:31-3:3. Incentive for subjects to scoop their own feces into containers for testing is far different for a population experiencing symptoms of having intestinal parasites than for an asymptomatic population with no reason to believe they may or may not have risk of CRC (goal of the patent claims). EX2044 ¶¶125,127.

Inbar describes a “system for collecting, storing and transporting” specimens of a “pasty material” including stool. EX1009 at 1. Inbar does not describe at-home collection of a fecal sample. EX1009; EX2044 ¶113. Petitioner concedes as much, asserting only in conclusory manner that a POSA “would recognize” that the collection process of Inbar “would occur at a subject's home.” Pet. at 54. Petitioner's only basis for this unfounded assumption is that the samples of Inbar are shipped to a laboratory for testing. *Id.* Petitioner ignores that the sample collection described in Inbar could take place in a doctor's office or clinic, and that Inbar says nothing to suggest otherwise. EX2044 ¶113.

Inbar notes that, at times “different entities have to be assayed” and that “[t]his is the case, for example, in stool, where it is generally desired to assay both bacteria and parasites, which as noted above, require different media.” EX1009 at 4:13-16. Where the different analytes to be tested “require” different media, then the system includes two containers, each with a different “preservation medium.” *Id.* at 4:16-18; EX2044 ¶¶115-116.

Inbar includes a single reference to “cryptic blood” in the background where it states that “[c]ollection and transportation of a pasty material, such as stool, food samples, soil samples, and the like for purposes of laboratory manipulation such as detection of microorganism being bacteria or parasites, detection of cryptic blood, preparation of a biochemical profile, etc., is an essential component of modern medicine, health care and environmental management.” EX1009 at 1:7-12. Inbar also states that composition of the preservation medium depends on the substance to be preserved, for example, “if the entity is a chemical substance, the medium will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration.” *Id.* at 4:4-6. Inbar does not disclose a “solution that prevents denaturation or degradation of blood protein” in a fecal sample. *See generally id; see also* EX2044 ¶¶113-114.

Inbar says nothing about preserving, extracting, and/or testing for nucleic acid in fecal samples. *See generally* EX1009; EX2044 ¶117.

V. LEVEL OF ORDINARY SKILL IN THE ART

In its challenges to the '746 patent and its parent, the '781 patent, the Petitioner has offered two, significantly different, proposed levels of skill for the person of ordinary skill. EX2042 at 7; EX2044 ¶¶51-53; Pet. at 12. Patent Owner disagrees with both of Petitioner's proposals. Moreover, the Board accepted Patent Owner's definition for purposes of the Institution Decision. Paper 10 at 8.

Patent Owner has submitted with this POR the declaration of Dr. Vadim Backman. EX2044. No matter which of the three different levels of skill is applied, Dr. Backman is a person of at least ordinary skill, and it does not change that the claims of the '746 patent would not have been obvious to a person of ordinary skill as of the priority date. *Id.* ¶¶2-9, 56-57.

VI. CLAIM CONSTRUCTION IS NOT NECESSARY

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 singled-out portions of each of the cited references without providing any reason why a POSA would have chosen those particular aspects of the references, while ignoring 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). Yet that is precisely what Petitioner is seeking to do here.

A. All Grounds: Petitioner Shows No Motivation For At-Home Separation of Sample

Petitioner’s argument rests on the unsupported assumption that a POSA would be motivated to develop a CRC screening method requiring at-home separation of stool samples. However, even assuming *arguendo* that a POSA would have been motivated to test for different classes of markers, Petitioner offers no reason why a POSA having only the knowledge in the art as of February 2009 would have arrived at a method requiring at-home separation into two separate containers. EX2044 ¶¶119-128.

At most, Petitioner’s declarant Dr. Whitney opines that “many assays used different stabilizing buffers to minimize loss of sample integrity.” EX1002 ¶75. He does not opine that a POSA in 2009 would have understood that a “DNA

stabilization” buffer would be unsuitable to stabilize blood protein, or vice versa. *See id.* At deposition in connection with related IPR2024-00459, Dr. Whitney testified that he had not formed an opinion as to whether or not a single buffer could stabilize both DNA and protein. EX2020 at 148:14-22; 149:18-150:20. A POSA in 2009 would have expected that various buffers, including the common Tris-EDTA as well as commercially available buffers such as RNAlater, could be used to stabilize nucleic acid and protein. EX2044 ¶¶121-124; EX2048²; EX2049³.

Nothing in the cited references provides any reason for at-home sample separation into two containers with different buffers. Lenhard does not disclose (i) home collection, (ii) user interaction with the sample, or (iii) stabilization buffers. *See generally* EX1004; EX2044 at ¶¶58-59,120. The “iFOBT of Vilkin” used an “amount of Hb stabilizing buffer” in the sample tube but does not identify the components of that buffer. EX1005 at 4. Itzkowitz describes use of a buffer, referred to as a “DNA-stabilizing buffer,” and cites to Olson which discloses a buffer composed of 0.5 mol/L Tris, 0.15 mol/L EDTA, and 10mmol/L NaCl (pH 9.0)—which, as explained above, was routinely used to stabilize both DNA and protein.

² Exhibit 2048 is a true and correct copy of an archived webpage concerning RNAlater. EX2045 ¶¶7-9.

³ Exhibit 2049 is attaches a true and correct copy of a Japanese Patent Application Publication No. H5-99923 with certified translation.

EX1006 at 1; EX1022 at 2. Shuber discloses stabilization solutions that could include 0.5 mM to 25 mM Tris, 0.01 to 2.5 mM EDTA, and 100mM to 200 mM NaCl, with pH ranging from 7.0 to 9.0, although pH could be higher or lower—again, routinely used to stabilize both DNA and protein. EX1008 at 4:19-22, 4:1-2. A POSA in 2009 would have expected that a Tris-EDTA buffer such as those disclosed in Olson and Shuber would also prevent the denaturation or degradation of hemoglobin in stool. EX2044 ¶¶120-124; EX2049. Accordingly, a POSA in 2009 would not have been motivated to develop a method requiring at-home *separation* of a stool sample into separate vessels. EX2044 ¶128.

The Melvin and Inbar references confirm that a POSA would not have been motivated to require at-home separation unless the analytes of interest required different buffers. Petitioner relies on an illustration from Melvin describing use of PVA-fixative and formalin for submitting stool specimens to be examined for parasites. Pet. at 7; EX1010 at 32. Melvin explains that more than one preservative may be needed where “[a] single solution is not available for preserving all of the diagnostic forms ...” EX1010 at 85. Inbar states that the “medium required to maintain viable bacteria and the medium required to maintain viable parasites are not only different but are mutual exclusive, i.e., one type of medium damages the other type of organism.” EX1009 at 2:32-3:3. In such circumstances, a system using

separate containers each holding “a different transport or suspension medium” is preferable. EX1009 at 3:3-8.

Absent a compelling reason requiring separation of the fecal sample at the time of at-home collection, a POSA in 2009 would not have been motivated to develop a test that required user interaction with the stool sample to separate the sample into two containers. EX2044 ¶128. Without the roadmap of the '746 patent claims, a POSA would have pursued the less complex and more patient-acceptable approach of using a single stabilizing buffer (such as Tris-EDTA) that also preserves blood protein in a direct defecation device such as that described in Itzkowitz. *Id.* ¶¶119-128. This would have resulted in a less complex test with fewer components that minimized need for at-home patient interaction with the sample. *Id.*

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

In Ground I, Petitioner argues that it would have been obvious to use “the iFOBT of Vilkin and the fecal collection and DNA stabilization process of Itzkowitz in the fecal screening method of Lenhard to arrive at the method of the challenged claims.” Pet. at 19. Petitioner selectively chooses certain 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 suggest that the Petitioner's proposed modifications would not improve either overall performance or acceptability.

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

Petitioner asserts that Lenhard discloses “a method of processing a fecal sample that includes collecting it from a subject, testing a first portion for cancer-specific DNA and testing a second portion for blood proteins.” Pet. at 19. Petitioner picks and chooses from Vilkin and Itzkowitz to argue a POSA would have been motivated to make multiple significant modifications to Lenhard including (i) replacing the Lenhard laboratory collection and sample separation with at-home collection and sample separation, (ii) using fresh not frozen samples, (iii) using the particular at-home collection device of Itzkowitz, (iv) using the particular 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 19-28. A POSA would not have cherry-picked from the references and devised these multiple changes to Lenhard without the roadmap of the '746 patent and impermissible hindsight.

As Petitioner acknowledges, Lenhard provides “few details regarding sample collection.” Pet. at 22. Lenhard discloses laboratory collection of samples that were

frozen before testing for nucleic acid. EX1004 at 2; EX2044 ¶59. Vilkin requires that each subject prepare three consecutive daily samples and refrigerate them at home—which the subjects were hesitant to do. EX1005 at 3 (Methods), 4, 8; EX2044 ¶¶82-84.

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, the latter of which involves stool interaction. *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.”); EX2044 ¶¶90, 152. 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. EX2044 ¶154; EX1006 at 2; EX1005 at 4.

Petitioner’s use of cherry-picked features of the sample collection device of the Vilkin iFOBT with the DNA-only test of Itzkowitz to arrive at the features of the claims reflects 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 it has not, the combination would not have resulted in the 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 motivation argument focuses on "improvement" of sensitivity, whereas the prior art identifies multiple different factors that a POSA seeking to improve CRC screening tests would have considered: "[a]n ideal screening test must be non-invasive, acceptable to patients, simple, have high sensitivity *and specificity*, inexpensive, cost-effective, easy to implement across a large population and should be effective in reducing morbidity and mortality from CRC in the screened population." EX1023 at 2. Petitioner's argument improperly ignores the other teachings of Lenhard, Vilkin, and Itzkowitz as well as the teachings of the cited background references, all of which would have dissuaded a POSA from Petitioner's combinations. *See, e.g., Arctic Cat, Inc. v. Bombardier Recreational Products, Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) ("it is error to fail to consider the entirety of the art.").

Petitioner further argues that a POSA would have been motivated to modify Lenhard to "include Vilkin's iFOBT" because Vilkin teaches advantages of iFOBT over gFOBT, including "higher sensitivity than gFOBT," eliminating the need for dietary restrictions associated with gFOBT, and that iFOBT is quantitative. Pet. at 20. Here too Petitioner ignores the aspects of Vilkin that would have discouraged this, including the need for samples taken over three days and home-refrigerated.

EX1005 at 3-4, 6, 8. A POSA would have taken Vilkin for its word that the subjects were hesitant to do this. EX1005 at 8; EX2044 ¶154. And a POSA would understand that without incorporating the methodology of Vilkin's iFOBT, including home-refrigerating three samples over three days, one could not expect the benefits of Vilkin's results. EX2044 ¶134. Neither the references nor Petitioner's arguments provide any rationale for why a POSA would have chosen only the elements of the '746 patent claims from three different references—to the exclusion of the other teachings of those references—to arrive at the claimed invention.

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

Petitioner has no explanation for why, with knowledge of Lenhard, Vilkin, and Itzkowitz, a POSA would pursue the more complex solution of developing a test for two different classes of markers rather than pursuing improvements to either iFOBT alone or nucleic acid testing alone. EX2044 ¶¶131-146. When considered as a whole, Lenhard does not motivate pursuing a combined test for both nucleic acid and fecal occult blood, particularly not based on Petitioner's asserted motivation of increased sensitivity. EX2044 ¶¶58-79, 131-133, 139-146. While the Federal Circuit does not require that a particular combination be the preferred or most desirable, the "impracticality of the prior art combination may be a factor in determining whether

there would have been a motivation to combine.” *Sound View Innovations, LLC v. Hulu, LLC*, 818 F. App’x 1009, 1013 n.3 (Fed. Cir. 2020).

Petitioner relies on Lenhard’s statement that the “combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.” Pet. at 13, 19. However, Lenhard involved a relatively small cohort of known cancer diagnoses, and the reported difference between HIC1 alone and the combination was ***not statistically significant***. EX2044 ¶¶63-68,132. The HIC1/gFOBT combination discussed in Lenhard also showed no increase in sensitivity for advanced adenomas. EX1004 at 6; EX2044 ¶¶62, 71. The combination on which Petitioner relies thus provided no improved sensitivity for this critical element of CRC screening tests. EX2044 ¶¶62, 131.

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.” *Id.* at 7. Thus, Lenhard expressly suggests multiple methylation markers, disregarding its own statistically insignificant results from the DNA-protein combined data. EX2044 ¶¶137. Without the benefit of hindsight and the ’746 patent as a roadmap, a POSA considering Lenhard would have pursued a combination of multiple sensitive and specific DNA methylation markers.

Vilkin and Itzkowitz also each disclose tests that were more sensitive than the combined HIC1/gFOBT results reported in Lenhard. The Vilkin authors achieved sensitivity of 76.5% with “acceptable specificity” of 95.3% for a combination of both CRCs and advanced adenomas using an iFOBT threshold of 100 ng Hb/mL and testing three samples from each subject. EX1005 at 7-8. Vilkin concludes: “we have found this desktop, automated-developed and quantified Hb version of the immunochemical fecal occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with an acceptable specificity and consequent high negative predicative value.” *Id.* at 8. Vilkin reports that 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.*; EX2044 ¶134.

Itzkowitz focuses on a then newer-version Exact Sciences panel using two DNA markers, observing 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.” EX1006 at 6. 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. EX2044 ¶135.

Further, in the context of purported motivation to combine to improve sensitivity, a POSA in 2009 would recognize that whether and how much a combination of tests from different marker classes would improve sensitivity was highly unpredictable. EX2044 ¶¶139-144. 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.* ¶145. 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.* ¶¶131-138. Rather, a POSA would have avoided the pitfalls of such a combination and instead pursued improvements to either FOBT alone or nucleic acid testing alone. *Id.*

(b) Reduced Specificity Would Have Discouraged Combination

Whether a POSA would have been motivated to combine references must take into account the prior art as a whole and whether it suggests the combination. *See*

Arctic Cat, 876 F.3d at 1363 (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”). A POSA would not have considered potential increased sensitivity in a vacuum; they would have considered overall test performance and other factors, including impact on acceptability and complexity. EX2044 ¶¶145-159. Petitioner’s own expert testified in IPR2024-00459 that “sensitivity and specificity, in my opinion, should always be looked at in combination.” EX2020 at 169:13-17. Yet the Petition does not even attempt to address reduced specificity. *See generally* Pet.

Considered in its entirety, Lenhard teaches that its particular HIC1/gFOBT combination reduced the specificity for CRC from 98% (HIC1 alone) to 89% (HIC1 and gFOBT). EX2044 ¶¶73, 145. Lenhard teaches the importance of high specificity, as do other references on which Petitioner relies. *See, e.g.*, EX1004 at 7 (“methylation markers as well as genetic markers need to be selected carefully to achieve both high sensitivity and specificity.”). A POSA would not have been motivated by Lenhard to combine classes of markers where the particular HIC1/gFOBT combination (1) resulted in lower specificity, (2) was still less sensitive than existing DNA-only or FOBT-only tests (and supported only by statistically insignificant data), and (3) showed no improvement in detecting advanced adenomas. EX2044 ¶¶133, 139-146.

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

Petitioner asserts that a POSA would have combined the “iFOBT of Vilkin” with Lenhard and Itzkowitz and that it would have been obvious to “replace the gFOBT of Lenhard with the iFOBT of Vilkin” because of certain purported advantages of iFOBT over gFOBT. Pet. at 20-21. One such “advantage” according to Petitioner was “collecting fewer fecal samples.” *Id.* at 21. Petitioner contends that the Young reference states that most branded versions of iFOBT “require fewer than three fecal samples, the recommended number for GFOBT.” EX1020 at 4. This ignores the fact that results are based on the methods used to obtain them: the iFOBT of Vilkin required subjects to prepare three consecutive daily fecal samples and keep them in the home refrigerator. EX1005 at 3 (Methods), 4; EX2044 ¶¶83-87. The notion that the iFOBT of Vilkin could have provided the advantage of requiring fewer fecal samples than gFOBT is belied by the reference itself, which required screenees to subject themselves—hesitantly—to keeping days-worth of feces in their refrigerator.

Petitioner asserts without support that modifying Lenhard to use “the sample collection and stabilization methods of Itzkowitz and the iFOBT of Vilkin” would produce “two samples.” Pet. at 24. However, because Vilkin requires collection of three home-refrigerated 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.

Further, iFOBT testing alone routinely required sample collection on at least two consecutive days. EX2044 ¶149.; EX1005 at 8 (contrasting “annual 2-day, average-risk population I-FOBT collection, as routinely used in Japan, United States, and Australia”); EX2047.⁴ Following that routine practice would still result in more than the “two samples” that Petitioner assumes from the proposed Lenhard/Itzkowitz/Vilkin combination.

In addition, and unlike gFOBT, use of the iFOBT of Vilkin requires that samples be refrigerated. EX1005 at 4, 8; EX2044 ¶¶83, 148. Vilkin also notes “screenees’ hesitancy about keeping the prepared test transiently in their home refrigerator.” *Id.*; EX2044 ¶¶84, 150.

The “iFOBT of Vilkin” on which Petitioner relies required both home-refrigeration and testing of three separately-collected samples. EX1005 at 4, 8. These requirements that were necessary to Vilkin’s results would have dissuaded combining the iFOBT of Vilkin with any other form of test. EX2044 ¶¶147-151.

⁴ Exhibit 2047 is a true and correct copy of Nakama. EX2045 ¶¶10-12.

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

Petitioner's proposed combinations would result in a test with increased cost and added complexity for the at-home user. A POSA seeking to improve CRC screening 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. EX2044 ¶¶147-159. 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 Itzkowitz notes, “[i]nherent in the success of any screening test is patient acceptance.” EX1006 at 6. Itzkowitz's “preliminary experience” with the new fecal direct-defecation DNA test “in which patients add stabilization buffer to stool confirm[ed] a very high degree of patient satisfaction.” *Id.* at 6-7. In contrast, requiring a patient to interact with and remove a portion of stool from the sample for FOBT 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. EX2044 ¶154.

A POSA would have also been discouraged by the added number of test components, added complexity, added cost, and increased potential for error.

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. EX2044 ¶¶153-155. 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 testing for two different classes of markers. *Id.*

Nothing in the references on which Petitioner relies suggests that testing for two different classes of markers would improve diagnostic performance over a single class of markers, let alone that such a combination would have sufficiently improved diagnostic performance to warrant the increased user interaction, complexity, and cost. In light of the advancements disclosed in the cited references for each of iFOBT and nucleic acid testing individually, a POSA would not have been motivated to pursue the more costly, more complex two-marker class approach. EX2044 ¶¶152-156 ¶¶. Petitioner has not demonstrated any reason why a POSA would have chosen only the selected aspects of Lenhard, Vilkin, and Itzkowitz, while ignoring other aspects, to arrive at the claimed invention. EX2044 ¶¶157-159.

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

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

When considered as a whole, the cited references do not teach or suggest the claimed method of the '746 patent, nor do they provide motivation to combine the nucleic acid-based test of Shuber with the iFOBT of Vilkin. EX2044 ¶¶160-176. Moreover, even if such motivation were found, nothing in Shuber, Vilkin, or the

other cited references suggests the configuration of the claimed invention. EX2044 ¶177.

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

Petitioner asserts that Shuber “describes the possibility of using multiple tests in combination to improve the test’s sensitivity for detection of CRC.” Pet. at 17. Shuber states that “[i]n one embodiment, the invention may be useful to avoid or reduce the number of false negative results in a screen of a population of individuals for one or more early stage cancer (e.g., using a DNA integrity assay, a multiple mutation assay, a hypermethylation assay, or any combination thereof.)” EX1008 at 28:23-27. This suggests combination of nucleic acid-based tests only—not a combination with blood-based tests or with any other category of test. EX2044 ¶162. In fact, Shuber discloses that testing for combinations of nucleic acid markers could detect adenomas with 60%, 74%, 90% and even “greater than 95% sensitivity (e.g., greater than 98% sensitivity.)” EX1008 at 14:1-16; EX2044 ¶163.

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

Petitioner’s combination of Shuber and Vilkin to arrive at the elements of the claimed invention is based on impermissible hindsight. For example, the claims

require at home collection by the subject. EX1001 at 45:59-61. The claims also require two separate sealable vessels, each containing a portion of the fecal sample where the first portion is combined with a stabilizing buffer and the second portion is combined with a solution that prevents denaturation or degradation of blood proteins. EX1001 at 45:63-67; 46:56-57. Shuber says little about sample collection and nothing about at-home collection by a patient. EX1008 at 29:8-19; EX2044 ¶164. Vilkin describes using stool probes to collect samples over three consecutive days. EX1005 at 4; EX2044 ¶165. Neither reference discloses or suggests that the subject separate one stool sample into a first portion and a second portion, each in a separate sealable container, where the first portion is tested for nucleic acid and the second portion for blood protein, as required by the claims. EX1005; EX1008; EX2044 ¶¶164-166. Thus, the proposed combination of Shuber with Vilkin fails to teach or suggest all of the claimed elements as arranged in the claims.

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

Petitioner argues that a POSA would have been motivated to combine Shuber with Vilkin “to arrive at a CRC diagnostic test with improved sensitivity.” Pet. at 38. As with the previous combination, Petitioner ignores the portions of the cited references that would have dissuaded a POSA from such a combination, including the potential for an unacceptable decrease in specificity and the increased

complexity of a test for multiple marker classes. *See Arctic Cat*, 876 F.3d at 1363 (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”).

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

Relying on select portions of four references, Petitioner incorrectly asserts that “the advantages of combining such stool DNA and blood protein assays were well understood in the art” by the priority date. Pet. at 38. Taken in the context of the references as a whole, and in the context of the knowledge in the art as of the priority date, the statements on which Petitioner relies would not have motivated a POSA to combine Shuber with the iFOBT of Vilkin, and certainly not in a way that would result in the claimed invention. EX2044 ¶¶167-175

Petitioner first relies on a sentence from the 2002 Nishikawa reference. Pet. at 38-39, citing EX1011. Nishikawa concludes that the tested method of detecting *K-ras* point mutations “is highly specific, noninvasive, and cost-effective, and should provide a more sensitive and specific tool for mass screening of colorectal cancer than is currently available, especially if used in combination with fecal occult blood testing and other methods for detecting genetic abnormalities.” EX1011 at 6. The statement is pure speculation without reference to any data or support. *Id.*

Notably, seven years passed between Nishikawa and the invention of the '746 patent without anyone else arriving at the claimed invention before the priority date. EX2044 ¶1683. Further, as discussed below, the other art on which Petitioner relies from between 2002 and the priority date suggested that combining marker classes would not result in improved diagnostic performance. *Id.* ¶¶134-140.

Petitioner also cites Lenhard as providing purported motivation to combine Shuber with Vilkin. Pet. at 39. However, as discussed above, consideration of the complete Lenhard reference would have dissuaded a POSA from combining a nucleic acid marker test with FOBT for CRC screening. EX2044 ¶¶58-79, 169. As is also discussed above, Lenhard itself concludes that the study shows “HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 with a few additional sensitive and specific methylation markers may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas.” EX1004 at 7. Lenhard contains no teaching, suggestion, or motivation to combine iFOBT with nucleic acid testing for CRC screening.

Petitioner also cites to the 2005 Kutzner reference. Kutzner describes a retrospective study of frozen samples. Kutzner poses an unanswered question of “whether both [MD and gFOBT] methods should be used together in broad diagnostic screening programs.” EX1012 at 8. The Kutzner authors acknowledge that their “retrospective data *do not allow* any conclusion on the potential of this

approach in diagnostic screening. Prospective comparative studies, which include a very high number of individuals, have to prove the value of the combined application of MD and FOBT.” *Id.* (emphasis added). More importantly, by posing the question, Kutzner reveals that the answer was neither obvious nor predictable. It would not have been obvious to a POSA to combine nucleic acid-based testing with FOBT with any reasonable expectation that the combination would result in improved performance over tests for a single class of markers. EX2044 ¶¶170, 176. In addition, as discussed above, any potential for improved performance would also need to be weighed against the negative aspects of requiring increased user interaction with the sample as well as notable increases in test complexity and cost that would result from a combined test.

Finally, Petitioner cites Levin as purportedly providing motivation to combine. Pet. at 40. However, Levin does nothing more than pose a question for potential investigation. *Id.* at 40. Levin posits that “[a]nother question worthy of consideration is ***whether or not*** including a sensitive gFOBT or FIT at the time of [sDNA] testing would improve sensitivity ***without adversely affecting specificity***.” EX1013 at 9 (emphasis added). Thus, Levin indicates that a POSA, knowing that both Lenhard and Kanaoka showed adverse effects on specificity, would not be motivated to combine nucleic acid tests with FOBT. EX2044 ¶¶171, 173-175. Levin also concludes that there were “no clear patterns of superior performance between a

high-sensitivity guaiac-based test (Hemoccult SENSА) and a variety of FIT.” EX1013 at 7; EX2044 ¶172. 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 combining the iFOBT test of Vilkin with Shuber, particularly not when considered in the context of the other cited references. EX2044 ¶¶171-173.

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

As discussed above, Petitioner argues generally that a POSA would have been motivated to combine Shuber with Vilkin to attempt to improve sensitivity. *See* Pet. at 38. However, Shuber itself discloses that testing for its set of disclosed nucleic-acid markers could be used to detect adenomas with “greater than 95% sensitivity (e.g., greater than 98% sensitivity.)” EX1008 at 14:15-16; EX2044 ¶¶109, 163. 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 for the user and at the laboratory and would likely reduce specificity. EX2044 ¶¶153-157, 160-166.

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

Petitioner asserts that a POSA would have combined Shuber with the iFOBT of Vilkin to arrive at the methods of the challenged claims. Pet. at 37-41. As with the proposed combination in Ground I, Petitioner again ignores that Vilkin requires the collection of three samples over three days as well as the refrigeration of those samples. Petitioner does not explain how or why a POSA would have chosen to combine nucleic acid testing with the iFOBT of Vilkin that required that the patient collect multiple samples, and where the different samples resulted in substantially different sensitivity. EX2044 ¶¶82-84, 165. A POSA would have understood that Vilkin's results cannot be separated from its methodology and would not have been motivated to combine the nucleic-acid test of Shuber with the iFOBT of Vilkin. EX2044 ¶¶80-87, 147-151, 165-166.

(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. EX2044 ¶139. Among other aspects, as discussed above, a POSA seeking to improve CRC screening tests would not have been

motivated to choose a path that would increase both cost and complexity unless there was a considerable likelihood of sufficient performance gains. EX2044 ¶¶152-159.

As with Ground I, nothing in the references on which Petitioner relies in Ground III suggests that testing for two different classes of markers would improve diagnostic performance over a single class of marker, let alone sufficiently improve 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. EX2044 ¶¶131-138; 152-159. There also would 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. EX2044 ¶¶161-176. Petitioner has not demonstrated any motivation to combine Shuber with Vilkin to arrive at the precise elements of the claimed invention. EX2044 ¶177.

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

In Ground VI—the proposed combination of Inbar, Shuber, and Vilkin—Petitioner refers back to Section VII(C) of the Petition concerning the proposed combination of Shuber's nucleic acid testing and Vilkin's iFOBT “to arrive at a CRC

diagnostic test with improved sensitivity.” Pet. at 57. For the same reasons discussed above, a POSA would not have been motivated to combine Shuber and Vilkin, and even if so motivated, would have had no reason to combine those references to arrive at the elements of the claimed invention. Petitioner then further combines Shuber and Vilkin with the “Inbar system” which Petitioner argues is “designed for the separate preservation of portions of a stool sample.” Pet. at 56-57. Inbar teaches that the sample collection system should include two containers with different preservation media only when the analytes “require” different media. EX1009 at 4:16-18; EX2044 ¶116. As discussed above, nucleic acids and blood protein do not require different preservation media (*see* EX2044 ¶¶123-124), so there would have been no reason for a POSA to use “Inbar’s system” even if the POSA were otherwise motivated to combine Shuber and Vilkin, which they would not have been for all of the reasons discussed above.

A POSA also would not have been motivated to use “Inbar’s system” for at-home collection where Inbar does not mention at-home collection and where sample was separated to test for bacteria and parasites in stool. EX2044 ¶¶112-128; 178; , EX1009 at 2:31-3:3; 4:13-18..

E. Grounds II, IV and VII: Petitioner Fails to Show Why, or How, A POSA Would Have Combined the Frozen Sample of Kanaoka With Each of the Asserted Combinations

Petitioner's Grounds II, IV and VII address dependent claims 12 and 13. Those Grounds fail for the same reasons Grounds I, III, and VI fail and for the additional reasons discussed below.

In Grounds II, IV, and VII, Petitioner adds aspects of the Kanaoka reference to the combinations in each of Grounds I, III, and VI, respectively. Relying on Example I of Kanaoka, Petitioner argues that a POSA would have found it obvious to further modify the asserted combinations to incorporate the COX-2 RNA detection process of Kanaoka. Pet. at 35-36; EX1002 at ¶¶220-224. Petitioner shows neither motivation to add Kanaoka to the various combinations nor reasonable expectation of success in doing so. EX2044 ¶¶179-193.

1. A POSA Would Not Have Been Motivated to Add the COX-2 RNA Detection of Kanaoka to the Asserted Combinations

Kanaoka reports that COX-2 alone had 90% sensitivity with 100% specificity. EX1007 at [0065]; EX2044 at 98-100; . Kanaoka achieved these results using a method where, “[a]s soon as possible after sampling feces, the feces were separated..., were frozen using liquid nitrogen, and were stored at -80° C.” EX1007 at [0057]; EX2044 ¶ 99. The only method Kanaoka describes for stabilizing RNA in fecal samples is immediate freezing. EX1007; EX2044 ¶¶99, 180. A POSA in 2009

would not have been motivated to incorporate the COX-2 RNA testing of Kanaoka in a method of processing a freshly collected fecal sample that excludes freezing. EX2044 ¶¶180-186.-.

Petitioner argues that Kanaoka provides further motivation to combine to improve sensitivity. Pet. at 35, 48. Petitioner once again impermissibly considers one aspect of a reference without considering the entire reference. *See, e.g., Arctic Cat*, 876 F.3d at 1363. Example 1 of Kanaoka shows that, if the results of the iFOBT comparative test are added to the COX-2 RNA test, the combination would have only one additional true positive test from the iFOBT that was not identified with the COX-2 RNA test. EX1007 at [0067]. However, the iFOBT test had three false positives among the control cases (specificity 86.3%), where the COX-2 RNA test had no false positives in the control cases (specificity 100%). EX1007 at [0065]-[0066]; EX2044 ¶¶182-183 Combining Kanaoka's COX-2 and iFOBT data results in an small increase in sensitivity, with a greater decrease in specificity. *Id.* And the overall performance of the combined test was worse than COX-2 alone. *Id.* ¶¶183-184. Therefore, consideration of the Kanaoka reference as a whole would have discouraged combining nucleic acid-based tests and FOBT. *Id.*

2. The Cited References Do Not Support A Reasonable Expectation of Combining the Frozen Processing of Kanaoka in an At-Home Collection Method that Excludes Freezing

A POSA would not have had a reasonable expectation of combining Kanaoka in a home-collection process that excludes freezing. Kanaoka observes that “RNA is more unstable compared to DNA.” EX1007 at [0011]. Kanaoka also describes prior art attempts to use RNA that did not have sufficient sensitivity “because it was impossible to extract RNA easily and efficiently from a small amount of feces.” EX1007 at [0008]-[0009]. Kanaoka stabilizes RNA in the fecal sample by immediate freezing. EX1007; EX2044 ¶199.

Petitioner attempts to overcome Kanaoka’s immediate freezing of samples by relying on a partial quote from Nechvatal. Pet. at 36; EX1024 at 8. The full sentence from which Petitioner selectively quotes states: “[i]n conclusion, this study *suggests* that preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible.” EX1024 at 8 (emphasis added). Nechvatal also notes that while it “focuses on DNA preservation, extraction, and quality, the methods studied were also chosen for their *likely* suitability for preserving RNA as well. *Id.* at 2 (emphasis added).

In fact, Nechvatal did not do any analysis of RNA stability at all—it tested only DNA. *See generally* EX1024; EX2044 ¶¶189-191. Nechvatal did not report any data on RNA stability or any basis upon which a POSA could conclude the DNA-

based results would apply to RNA. *Id.* Nechvatal tested “multiple methods for fecal preservation and DNA extraction.” EX1024 at 2; EX2044 ¶188. The tested preservation methods included, *inter alia*, commercially available RNAlater, drying sample over silica beads, and flash freezing in liquid nitrogen. EX1024 at 2; EX2044 ¶188. Only two of the methods, RNAlater and freezing with liquid nitrogen, were tested on human DNA. EX1024 at 7; EX2044 ¶188.

Considering Kanaoka's statement that RNA is more unstable compared to DNA, Nechvatal's conclusion that the reported study of only DNA “suggests that preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible” would not have provided a reasonable expectation that collection for the RNA analysis of Kanaoka could be done at home and without freezing. EX1024 at 8; EX2044 ¶¶185-193.. A POSA in 2009 would not have had any expectation that they could successfully incorporate Kanaoka's analysis of immediately frozen samples into an at-home collection methodology that expressly excludes freezing based on the limited, speculative statements about RNA in Nechvatal. EX2044 ; EX1024 at 8. *See Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 162 (Fed. Cir. 2021) (references without “evidence or data or other promising information showing” success insufficient to suggest that a skilled artisan would reasonably expect success.)

3. If Kanaoka Were Added to the Combinations, There Was No Reason to Separate Sample

Assuming a POSA would have been motivated to add Kanaoka to the combination in light of the teachings of Nechvatal, there was no motivation for home separation of the sample. EX2044 ¶¶175-193. Nechvatal concluded that the best combination of preservation and extraction methods was “QS-R” which used commercially available RNAlater as the preservation method. EX1024 at 3, 8; EX2044 ¶192. RNAlater was sold for stabilizing both RNA *and* protein. EX2048; EX2044 ¶192. Accordingly, if a POSA had sought to use the COX-2 RNA of Kanaoka modified with the preferred preservation method of Nechvatal – use of RNAlater – there would have been no reason to separate the sample to use different buffers for RNA and blood proteins. EX2044 ¶193.

VIII. SECONDARY INDICIA SUPPORT NONOBVIOUSNESS

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

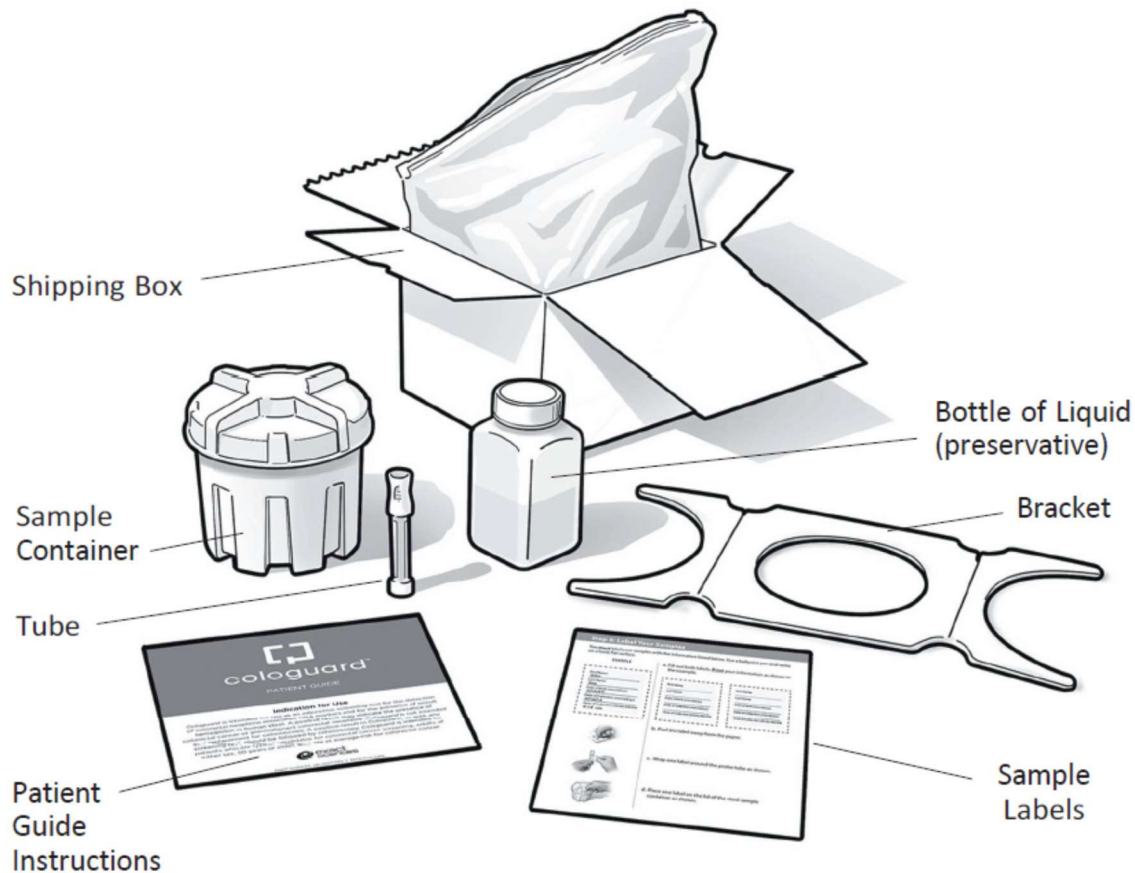
A. There is a Nexus Between the Cologuard Product and the Patented Invention

Petitioner does not contest that the Cologuard Product practices the claimed invention. Rather, Petitioner argues that Cologuard product is not “co-extensive” with the claimed invention. Pet. at 67. However, nexus is presumed “when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘embodies the claimed features, and is coextensive with them.’” *Quanergy Sys. Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022)(citations omitted). Here, as described below, Cologuard practices at least claim 3, and the claimed invention is not a subcomponent of the entire product—it is Cologuard’s fundamental workflow. Moreover, even if the Cologuard product were not co-extensive with the challenged claims, nexus can be established where “the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’” *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023).

There can be no dispute that patient acceptance and ease of use are critical to any screening test. *See, e.g.*, EX1020 at 4 (“Population participation is essential for cancer detection.”). The method of at least Claim 3 of the ’746 patent is fundamental to use of the Cologuard test as described in detail in Exact Sciences’ product literature. EX2044 ¶¶199-213. The Cologuard Patient Guide provides detailed

instructions for the collection of a fecal sample that is shipped without freezing. EX2044 ¶201; EX1076 at 24-28, 30-31. The patient receives a Cologuard Collection Kit (the “Collection Kit”) that includes everything that the patient needs for at home collection of fecal sample, separation of the sample into two portions in separate sealable containers, and combination of the first portion with a stabilizing buffer and second portion with a solution that prevents denaturation or degradation of blood protein.

What Is Inside the Cologuard Collection Kit



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

EX1076 at 8; EX2044 ¶¶199-213.

The two separate portions are obtained by a lab where nucleic acid is extracted from the first portion and tested and where the second portion is tested for an amount of blood protein. EX1080 at 4; EX2044 ¶¶208-213.

Petitioner is incorrect that the patented invention is “a minor component” of the Cologuard product. Pet. at 67. Claim 3 of the '746 patent includes the convenient at-home collection method requiring at-home division of the stool sample into two containers with the specified buffers in each container; extracting nucleic acid from the first portion of the sample; testing the nucleic acid for an amount of human nucleic acid; and testing the second portion of the sample for an amount of blood protein. EX1001 at 45:57-65; 46:56-57; 46:63-47:16; EX2044 ¶¶199-213. The Cologuard fundamental workflow tracks Claim 3 of the '746 patent. EX2044 ¶¶199-213.

Petitioner tries to break the nexus by arguing that various “[d]istinct components” of Cologuard are covered by other patents. Pet. at 67-68. This argument turns the traditional nexus analysis on its head. *See Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1361 (Fed. Cir. 2021) (It is “unsound” to require that “presumption of nexus does not apply if any unclaimed feature materially affects the functioning of the product that is alleged to be coextensive” as “virtually every innovative product inevitably has some unclaimed feature that

materially affects its functionality.”). Nexus is presumed where, as here, the product embodies the claimed features and is coextensive with them. *Polaris Indus., Inc. v. Arctic Cat Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018). A patentee must show more only “if the patented invention is only a component of a commercially successful machine or process.” *Id.* (citations omitted). That is not the case here. The other Exact Sciences patents to which Petitioner refers are not at issue here, and Petitioner’s declarant offered no opinion as to whether, or how, any of those other patents contributed to uptake or accuracy of Cologuard. EX1002 ¶¶344-345; EX2051 at 61:18-62:3. Moreover, by Petitioner’s own description, unlike the ’746 patent, those patents each concern “[d]istinct components,” and not the entire method. *See* Pet. at 67.

Petitioner tries to defeat the nexus between Cologuard’s commercial success and the claimed invention by pointing to other Exact Sciences patents, including statements during prosecution of U.S. Patent No. 9,163,278, titled “isolation of nucleic acids.” Pet. at 68-69; EX1028. Petitioner mischaracterizes these statements as “attribut[ing] Cologuard’s success ... to the later-invented particular combination of markers and methods for extracting the maker DNA from stool.” Pet. at 68. In reality, these statements address the long-felt need for a method of “isolat[ing] DNA from stool samples” and the success of Cologuard’s methods for extracting marker DNA to satisfy that need, rather than any blanket attribution of Cologuard’s

commercial success to another invention. EX1029 at 8-9. Moreover, extracting nucleic acid from the fecal sample is one of the multiple steps in the fundamental Cologuard workflow that is captured in Claim 3 of the '746 patent. Whether a later-improved means of extracting nucleic acids has also contributed to Cologuard's success does not change that (1) CRC screening with Cologuard involves more than just extracting nucleic acids, and (2) CRC screening with Cologuard follows every element of at least claim 3 of the '746 patent. EX2044 ¶196. Petitioner's cursory argument is insufficient to rebut the presumption of nexus where, as here, the Cologuard product embodies "the full scope of the claimed invention" and "the claimed invention is not merely a subcomponent of" Cologuard. *See Quanergy*, 24 F.4th at 1418.

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

More than 14 million Cologuard tests have been performed since its launch in 2014. EX2019 ¶38. Cologuard remained Exact Sciences' only product for the years 2014 through 2018, and Exact Sciences' revenue for those years reflects the product's success: \$1,798,000 in 2014; \$39,437,000 in 2015; \$99,376,000 in 2016; \$265,989,000 in 2017; and \$454,462,000 million in 2018. EX2019 ¶¶36-37. Petitioner's own presentation supports the ever-increasing commercial success of

Cologuard, showing the “rapid growth” of Cologuard sales to almost 4 million tests in 2023. EX2021 at 11.

Cologuard would not have achieved commercial success if it did not satisfy two critical aspects of screening tests: diagnostic accuracy and uptake. EX2044 ¶216. The claimed invention of the '746 patent is essential to both. *Id.* The addition of buffers to each of the first and second portions of the sample and testing for both nucleic acids and fecal occult blood all contribute to the test's diagnostic performance. *Id.* The Cologuard test kit itself, using the '746 patented method, allows convenient, at-home collection that patients have accepted. *Id.*

Exact Sciences has achieved this success with Cologuard notwithstanding patient reluctance, existing biases, and negative perceptions of earlier CRC screening mechanisms. EX2044 ¶¶217-221; EX2019 ¶¶29-31. A 2005 article observed that “[n]egative attitudes toward the tests themselves are also prevalent. Fecal occult blood testing (FOBT) is widely perceived as embarrassing or distasteful.” EX2036⁵ at 1; EX2044 ¶218. 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; EX2044 ¶219.

⁵ Exhibit 2036 is a true and correct copy of Schroy. EX2007 ¶¶60-63.

Itzkowitz further stated the obvious, that “[i]nherent in the success of any screening test is patient acceptance.” EX1006 at 6; EX2044 ¶219.

When Cologuard was launched in 2014, it faced a commercial environment where doctors and patients had to be educated concerning the test to overcome existing negative attitudes. EX2044 ¶¶218-221; EX2019 ¶¶29-31. Exact Sciences has expended substantial resources on this education effort with marketing focused on the availability, advantages, and ease of use of Cologuard. EX2019 ¶¶31-32. Exact Sciences’ efforts have contributed to increased compliance by individuals who previously had not been screened. *Id.* ¶39; EX2029 at 5; EX2039 at 4-5.

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

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

By 2009, it had long been recognized that early screening and detection reduced CRC mortality. EX2044 ¶¶29-31. Petitioner’s references demonstrate the extensive and differing failed attempts to develop CRC screening tests that could effectively and realistically screen large portions of the population. The technologies

that existed at the time of the invention, such as colonoscopy and noninvasive tests including gFOBT and iFOBT, each had their own limitations and had not adequately reduced the numbers of unscreened individuals. *Id.* ¶¶32-37.

Although colonoscopy was considered the gold standard for testing as of 2009, it has significant drawbacks. EX2044 ¶¶35-39, 225. It is an invasive procedure that carries a risk, although low, of complications including perforation that would require surgery. *Id.* ¶37. It also requires preparation through colonic purge. *Id.* ¶38. In addition, colonoscopy must be performed at a medical facility which requires patient time, potential travel, and availability of trained medical personnel. *Id.* ¶39.

gFOBT, iFOBT, and previous nucleic acid-based tests also failed to satisfy the need. EX2044 ¶226; EX1042 at 7-8. Fecal DNA analysis had also been explored. However, DNA analysis at the time offered only marginal increase in sensitivity for advanced neoplasia, including advanced adenomas and CRC, to 18.2%, the benefit of which was offset by increased cost per test. EX2044 ¶227; EX1042 at 7-8.

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

gFOBT, the overall sensitivity for invasive cancers plus adenomas was a disappointing 40.8%. EX1042 at 1; EX2044 ¶228.

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

As of the February 2009 priority date of the '746 patent, a high proportion of individuals within the group for whom guidelines recommended screening still had not undergone CRC screening and there remained a longstanding, unmet need for effective, efficient, non-invasive CRC screening tests. EX2044 ¶230.

These low screening levels of individuals within the recommended screening group persisted until the introduction of Cologuard, 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. EX2044 ¶231. 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. EX2044 ¶231; *see also* EX2019 ¶¶37, 39.

Various publications have credited Cologuard 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. EX2037⁶ at 2; EX2044 ¶233. Another study described better adherence from patients using Cologuard 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. EX2038⁷ at 10; EX2044 ¶234.

Other studies further confirm that Cologuard is being used by a patient population whose needs were previously unmet by then-available screening options. A study published in 2020 found 24% of patients with a positive Cologuard test who subsequently had a screening colonoscopy were over 10 years overdue for screening. EX2039⁸ at 4-5; EX2044 ¶235. Moreover, internal studies by Exact Sciences have shown approximately 40% of surveyed Cologuard users were previously unscreened for CRC. EX2019 ¶39; EX2029 at 5. The volume of Cologuard sales, increased screening rates overall, and number of Cologuard test users who were never previously screened all demonstrate that Cologuard is meeting the previously unmet need.

⁶ Exhibit 2037 is a true and correct copy of Miller-Wilson. EX2007 ¶¶64-67.

⁷ Exhibit 2038 is a true and correct copy of Kisiel. EX2007 ¶¶68-70.

⁸ Exhibit 2039 is a true and correct copy of Eckmann. EX2007 ¶¶71-74.

D. Cologuard Has Received Industry Praise and Recognition

Cologuard has received significant recognition and numerous awards. For example, for its groundbreaking innovation, Cologuard won the prestigious Prix Galien USA Award for best medical technology product in 2016. EX2031⁹; EX2019 ¶21. In 2014, the year Cologuard received FDA approval, Cologuard won a “Best of What’s New” award from Popular Science. EX2032; EX2019 ¶22.

In January 2015, Cologuard won an Everyday Health Award for Innovation, which recognizes services and technologies “dedicated to improving overall health and wellbeing.” Everyday Health’s then-Vice President and Chief Operating Officer Paul Slavin stated “these awards continue to bring the most inventive and creative digital health technologies and services to the forefront,” and “[e]ach of the winners demonstrated an incredible understanding about where the digital health marketplace is going and how we can propel it forward.” EX2033¹⁰; EX2019 ¶23. Cologuard was also awarded a Wisconsin Innovation Award (WIA) in the “Healthcare/Health IT” category in 2015. EX2034; EX2019 ¶24.

⁹ Exhibits 2031-2032, 2034-2035 are true and correct copies of press releases that are accessible at Exact Sciences’ website, <https://www.exactsciences.com/newsroom/press-releases>. EX2019 ¶¶21-22, 24-25; EX2007 ¶¶45-50, 54-59.

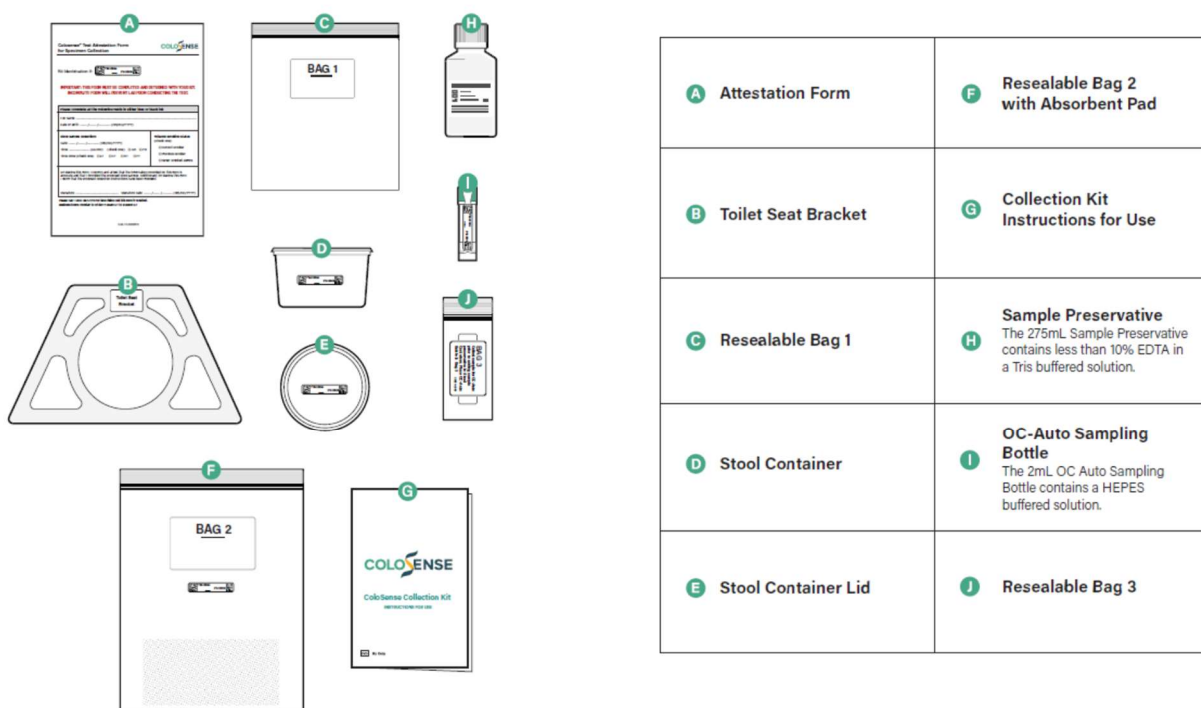
¹⁰ Exhibit 2033 is a true and correct copy of a press release by Everyday Health. EX2019 ¶23; EX2007 ¶¶51-53.

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

E. Petitioner's Recently Approved "ColoSense" Copies the Claimed Invention

Despite the variety of past and present approaches to CRC screening, Petitioner's ColoSense test copies the '746 patented invention. To begin, the ColoSense Collection Kit contains the same elements as Exact Sciences' successful Cologuard Collection Kit. EX2044 ¶¶238-246; EX2040.

ColoSense Collection Kit Contents



EX2044 ¶239; EX2040 at 34.

Petitioner's Product Information describes the method. EX2044 ¶¶238-246; EX2040. And, as with Cologuard, after collection with a ColoSense collection kit a lab obtains the two containers with the first and second portions and tests the second portion for a blood protein. EX2044 ¶246; EX2040 at 56. Nucleic acid is extracted from the first portion and the nucleic acid is tested for an amount of nucleic acid. EX2044 ¶246; EX2040 at 54-55.

IX. CONCLUSION

For the foregoing reasons, the Board should affirm patentability of all challenged claims of the '746 patent.

Date: May 30, 2025

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

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 13,889 words and thus complies with the applicable word limit.

Date: May 30, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on May 30, 2025 the foregoing Response from Patent Owner was served via email on the following counsel of record for the Petitioner:

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