UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

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

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

Page

I. INTRODUCTION 1

II. BACKGROUND OF THE COLOGUARD TEST AND '781 PATENT 2

A. CRC Screening Techniques Prior to the Cologuard Test 2

B. The Invention of the '781 Patent 4

III. GENEOSCOPY'S PRIOR (AND FAILED) ATTEMPT TO INVALIDATE THE '781 PATENT 5

IV. PROSECUTION HISTORY 8

A. The '607 Parent Application Issued Over Substantially Similar Rejections as the Petition Art and Arguments 8

B. Similar Claims in the '945 Application Were Recently Allowed Over all References Cited in the Petition 10

C. The Petition References are the Same as, or Substantially Overlap with, References Considered During Examination of the '335 Application that Resulted in the '781 Patent 11

V. OVERVIEW OF REFERENCES CITED IN GROUNDS 12

1. Lenhard (Ex. 1004) – Describes Laboratory Collection and Comparison of gFOBT with a Specific Methylation Marker Tested from Frozen Samples 12

2. Vilkin (Ex. 1005) – Limited to a Specific iFOBT Device Compared to gFOBT 14

3. Itzkowitz (Ex. 1006) – Limited to Specific DNA-Based Testing 15

4. Shuber (Ex. 1009) – Limited to Nucleic-Acid Based Testing 17

VI. THE BOARD SHOULD EXERCISE DISCRETION AND DENY INSTITUTION UNDER § 325(d) 18

A. Ground 1 – Lenhard in view of Itzkowitz and Vilkin is the same as, or cumulative of, previously cited art and arguments 21

1. *Becton Dickinson* Factors (a) and (b) - Lenhard in view of Itzkowitz and Vilkin is the same or substantially the same as previously presented art 22

2. *Becton Dickinson* Factors (d) - the Petitioner's arguments substantially overlap the previous reexamination arguments and the Examiner's arguments 32

B. Ground IV – Shuber in combination with Vilkin is the same as, or cumulative of, previously cited art and arguments – *Becton Dickinson* Factors (a), (b), and (d) 34

C. All Grounds - *Becton Dickinson* Factors (c), (e), and (f) – Petitioner's failure to allege "material error" weighs heavily in favor of denial 36

VII. THE BOARD SHOULD EXERCISE DISCRETION AND DENY INSTITUTION UNDER § 314(a) 38

A. Factor 1: "whether the same petitioner previously filed a petition directed to the same claims of the same patent." 41

B. Factor 2: "whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it." 41

C. Factor 3: "whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition." 42

D. Factor 4: "the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition." 44

E. Factor 5: "whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent." 44

F. Factor 6: the finite resources of the Board. 44

G. Factor 7: the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review. 45

VIII. CLAIM CONSTRUCTION IS NOT NECESSARY TO DENY INSTITUTION 46

IX. THE PETITIONER'S GROUNDS INDEPENDENTLY FAIL ON THE MERITS 46
A. Level of Ordinary Skill in the Art 46
B. The Lenhard, Vilkin, and Itzkowitz Combination Does Not Teach or Suggest the Claimed Invention 48
C. The Shuber and Vilkin Combination Does Not Teach or Suggest the Claimed Invention 55
D. Petitioner's Second, Third, Fifth, and Sixth Grounds Also Fail 60
X. CONCLUSION 61

TABLE OF AUTHORITIES

Page

Cases

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH,
2020 WL 740292 (P.T.A.B. Feb. 13, 2020) (precedential, designated March 24, 2020).....19, 36

Becton, Dickinson & Co. v. B. Braun Melsungen AG,
IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017).....20

Biocon Pharma Ltd. v. Novartis Pharmaceuticals Corp.,
2021 WL 608300 (P.T.A.B. Feb. 16, 2021) 19, 29

Ecofasten Solar, LLC v. Unirac, Inc.,
2022 WL 443369 (P.T.A.B. Feb. 8, 2022) 20, 38

General Plastic Indus. Co., Ltd. v. Kaisha,
2017 WL 3917706 (P.T.A.B. Sept. 6, 2017) 40, 42, 43, 44

Google LLC v. Valtrus Innovations,
IPR2022-01197, Paper 18 (P.T.A.B. June 13, 2023).....28, 37, 38

Illumina Inc. v. Ravgen, Inc.,
IPR2021-01271, Paper 12 (P.T.A.B. Jan. 26, 2022).....39

NVIDIA Corp. v. Samsung Elec. Co.,
IPR2016–00134 (P.T.A.B. May 4, 2016) 40

Realtime Data, LLC v. Iancu,
912 F.3d 1368 (Fed. Cir. 2019).....46

Samsung Elec. Co. Ltd. v. Rembrandt Wireless Techs., LP,
IPR2015-00114, Paper 14 (P.T.A.B. Jan. 28, 2015).....40, 45

Samsung Elecs. Co., Ltd. v. Netlist, Inc.,
2022 WL 22412095 (P.T.A.B. Oct. 19, 2022).....39

Toyota Motor Corp. v. Cellport Systems, Inc.,
IPR2015-01423, Paper No. 7 (P.T.A.B. Oct. 28, 2015) 45

Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.,
200 F.3d 795 (Fed. Cir. 1999).....46

In re Vivint
14 F.4th 1342 (Fed. Cir. 2021) 39

Statutes

35 U.S.C. § 103 35

35 U.S.C. § 314 2

35 U.S.C. § 314(a) 38, 39, 45

35 U.S.C. § 316(a)(11) 45

35 U.S.C. § 316(b) 44

35 U.S.C. § 325(d) 2, 18, 19, 20, 30, 36, 38

Other Authorities

H.R. Rep. No. 112-98, pt.1 (2011) 40

EXHIBIT LIST

No.	Exhibit
2001	Declaration of Vadim Backman, Ph.D.
2002	*Curriculum vitae* of Vadim Backman, Ph.D.
2003	Prosecution file history for application number 15/634,607, issued as patent number 11,845,991
2004	Prosecution file history for application number 17/936,335, issued as patent number 11,634,781
2005	Prosecution file history for application number 18/179,945, issued as patent number 11,970,746
2006	European Patent Application Publication No. EP1266715A1 to DeLuca et al. ("DeLuca")
2007	Zohar Levi et al., *A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test*, 23(9) Aliment Pharmacol Ther., 1359, 1359–1364 (2006) ("Levi")
2008	Thomas F. Imperiale et al., *Multitarget Stool DNA Testing for Colorectal-Cancer Screening*, 370(14) N. Eng. J. Med., 1287, 1287–1297 (2014)
2009	Sidney J. Winawer and Ann G. Zauber, *The Advanced Adenomas as the Primary Target of Screening*, 12(1) Gastrointestinal Endosc. Clin. N. Am. 1, 1–9 (2002)
2010	Daniel C. Chung, *The Genetic Basis of Colorectal Cancer: Insights Into Critical Pathways of Tumorigenesis*, 119 Gastroenterology 854, 854–865 (2000)
2011	Hermann Brenner et al., *Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840 149 screening colonoscopies*, 56(11) Gut 1585, 1585–1589 (2007)
2012	David L. Zack et al., *Colorectal Cancer Screening Compliance by Medicine Residents: Perceived and Actual*, 96(10) Am. J. Gastroenterology 3004, 3004–3008 (2001)
2013	Amnon Sonnenberg and Fabiola Delcò, *Cost-effectiveness of a Single Colonoscopy in Screening for Colorectal Cancer*, 162(2) Arch Intern Med. 163, 163–168 (2002)

2014	Peter B. Cotton et al., *Computed Tomographic Colonography (Virtual Colonoscopy): A Multicenter Comparison With Standard Colonoscopy for Detection of Colorectal Neoplasia*, 291(14) JAMA 1713, 1713–1719 (2004)
2015	Nathalie Schoofs, et al., *A. PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study*. Endoscopy 38, 971-977 (2006)
2016	Exact Sciences, "Cologuard™ Patient Guide" (2014)
2017	Exact Sciences, "FDA Approves Exact Sciences' Cologuard®; First and Only Stool DNA Noninvasive Colorectal Cancer Screening Test," https://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2014/FDA-Approves-Exact-Sciences-Cologuard-First-and-Only-Stool-DNA-Noninvasive-Colorectal-Cancer-Screening-Test/default.aspx (August 12, 2014)
2018	Exact Sciences, "Get Off the Bench: Hoops Themed Campaign Urges Colorectal Cancer Screening," https://www.exactsciences.com/newsroom/news-and-stories/get-off-the-bench-hoops-themed-campaign-urges-colorectal-cancer-screening-#:~:text=March%2007%2C%202024-,Get%20Off%20the%20Bench%3A%20Hoops%2DThemed%20Campaign%20Urges%20Colorectal%20Cancer,'&text=Shortly%20after%20basketball%20star%20Jamal,he%20got%20some%20tough%20news (March 07, 2024)
2019	Geneoscopy, "Geneoscopy Submits Premarket Approval Application to U.S. food and Drug Administration for its Noninvasive Colorectal Cancer RNA Biomarker Screening Test," https://www.geneoscopy.com/geneoscopy-submits-premarket-approval-application-to-fda-for-its-noninvasive-colorectal-cancer-rna-biomarker-screening-test/ (January 24, 2023)
2020	United States Department of Health and Human Services, "Increase the proportion of adults who get screened for colorectal cancer — C-07," https://health.gov/healthypeople/objectives-and-data/browse-objectives/cancer/increase-proportion-adults-who-get-screened-colorectal-cancer-c-07

I. INTRODUCTION

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

Petitioner Geneoscopy is attempting to bring its own competing product to market. Geneoscopy already failed at its first attempt to challenge the '781 patent – a 280-page *ex parte* reexamination request with 14 proposed rejections (2 anticipatory and 12 obviousness based) that applied 8 different references – which resulted in the CRU confirming all claims as patentable. Geneoscopy is trying again here, but this Petition is entirely duplicative of what the PTO has already considered. Indeed, this Petition relies on art that is substantively the same as the reexamination art as well as art raised in initial prosecution. The Petition likewise raises arguments here that are substantively identical to those raised in the reexamination. Yet nowhere does the Petition explain how the art raised here is any different than the art already considered, and thus fails to establish under the first prong of the *Becton Dickinson* analysis that the art or arguments are in any way different than those already considered. The Petition likewise fails the second

prong of the *Becton Dickinson* test, as Petitioner fails to allege ***any*** material error—even for art that was undisputedly considered during prosecution. These failures warrant discretionary denial under 35 U.S.C. § 325(d).

Denial is also appropriate here under 35 U.S.C. § 314. Geneoscopy's serial challenges to the '781 patent are unnecessary, waste the Board's time, and impose undue burden on the Patent Owner. And while section 314 has been applied to serial IPRs, the underlying rationale applies equally here, in some respects more so, considering the broader standard for claim interpretation and unlimited pages available to Petitioner in the reexamination.

Finally, even if the Board finds discretionary denial is not appropriate, the Petition should nevertheless be denied on the merits. Petitioner improperly relies on hindsight to pick and choose features from multiple references, and there is no teaching or reason that would have motivated a person of ordinary skill in the art to choose the various, isolated elements of different references and combine them to arrive at the claimed invention.

II. BACKGROUND OF THE COLOGUARD TEST AND '781 PATENT

A. CRC Screening Techniques Prior to the Cologuard Test

CRC is a leading cause of cancer-related deaths worldwide. Ex. 1001 at 1:41-43. By the '781 patent's priority date, colonoscopy had become the primary screening test for CRC because of its high sensitivity and specificity, and because

polyps can be removed during the procedure. *Id.* at 1:65-67. However, while both sensitive and specific, colonoscopy is also "invasive, costly, has limited availability and includes certain risks." *Id.* at 2:1-3. There was therefore a need for effective, efficient screening tests. *See* Ex. 2001 ¶¶31-32, 34. To be useful, any such tests would need (i) to have sufficient sensitivity to detect indications of cancer and precursor lesions, (ii) to have sufficient specificity to minimize false positives that result in unnecessary colonoscopies, and (iii) to be both accessible to, and acceptable to, patients. *See id.*

By 2009, various approaches for screening for CRC that were less invasive than colonoscopy, including fecal occult blood tests ("FOBT") and nucleic acid screening tests, were also being used and further developed. *See* Ex. 1001 at 2:4-3:40. Each of the less invasive tests had limitations, including limited sensitivity, specificity, patient acceptability, or a combination of all three. *See id.* Those working in the field sought to balance the goals of both sensitivity and specificity in a test that could be made widely available. Ex. 2001 ¶¶31-32, 34. Further, those working in the field recognized that precancer indications, such as adenomas, should be a target of screening because detection and removal of adenomas provides an opportunity to prevent CRC. Ex. 2009 at 1; Ex. 2001 ¶¶23, 31-32.

B. The Invention of the ’781 Patent

The Cologuard test using the ’781 patented technology accomplished these goals. Indeed, use of the Cologuard test achieved 92.3% sensitivity and 86.6% specificity. Ex. 2008 at 1. The Cologuard test revolutionized home CRC screening. Under the ’781 patent’s novel and innovative approach, a fecal sample for both nucleic acid and blood testing can be conveniently collected at the same time, in the privacy of a patient’s own home, and shipped without freezing from virtually anywhere. Ex. 2016 at 13-31. The Cologuard test using the ’781 patent’s invention enables many patients to get screened for CRC, patients who would otherwise go unscreened. Ex. 2001 ¶32.

More specifically, the invention of the ’781 patent, as embodied in the Cologuard product, provides a patient-friendly, effective means of collecting and processing fecal samples for screening. Under the patented method, a patient collects a fecal sample by direct defecation into a convenient container in the privacy of their own home, and then removes a portion of the sample to a separate sealable container. Ex. 2016 at 17-21. That separate sealable container contains a buffer that prevents denaturation or degradation of blood proteins. *Id.* at 8. The patient also adds a stabilizing buffer to the remaining sample in the first container. *Id.* at 8, 22. The containers are both sealed and shipped to a lab at room temperature – they are not ever frozen. *Id.* at 21, 23, 30. The portion in one

container is then tested for a blood protein and the portion in the other container is tested for nucleic acid. *Id.* at 8. The Cologuard test was the first, and is still the only, FDA-approved commercially available multitarget stool-based blood and nucleic acid test for CRC screening. Ex. 2017. It has been used by millions since it received FDA approval in 2014. *See* Ex. 2018.

III. GENEOSCOPY'S PRIOR (AND FAILED) ATTEMPT TO INVALIDATE THE '781 PATENT

Geneoscopy is seeking FDA approval for its own CRC screening test known as ColoSense. Ex. 2019. Geneoscopy filed a request for *ex parte* reexamination of the '781 patent on May 22, 2023, less than a month after it issued. Ex. 1021. Geneoscopy's 282-page request relied upon multiple references and combinations and asserted six separate bases for purported substantial new questions of patentability ("SNQ") for claim 1 alone. *Id.* at 2, 14. Geneoscopy also asserted at least four separate bases for purported SNQs for each of the '781 patent's twenty claims. *Id.* at 10-13. The proceeding confirmed the patentability of all claims of the '781 patent.

As discussed in more detail below, the art cited here is substantively the same as the art cited during the reexamination. In many cases, art cited here, such as Lenhard and Itzkowitz, are substantively no different than the reexamination prior art reference Ahlquist. Further, while Petitioner argues that it does not rely on

any of the same references as the reexamination, Petitioner fails to inform the Board that, although not named in (VI)(B) References in Grounds, Petitioner nonetheless relies on a key reexamination reference in the arguments submitted. The Olson reference examining fecal DNA stabilizing buffers was used in twelve of the fourteen proposed reexamination rejections. *See* Ex. 1021 at 2. Here, the Petitioner instead cites Itzkowitz, but points to Itzkowitz's citation of Olson, then to Olson itself, to inform its discussion. *See* Pet. at 24-25. Indeed, there is almost complete overlap in how Olson was used in the reexamination, and how it is repackaged in the Petition. *Compare* Ex. 1021 at 97, *with* Pet. at 24-25.

Petitioner's arguments in support of purported motivations to combine likewise mirror the reexamination, where Petitioner unsuccessfully argued that generalized goals of improved performance and patient convenience provided adequate motivation. Those arguments are repeated here.

The CRU granted the request for reexamination as to all claims. Ex. 1022. In doing so, the CRU agreed that consideration of the combination of Ahlquist with DeLuca[1] and Olson raised an SNQ as to claims 1-6 and 15. *Id.* at 8. The CRU found that Ahlquist teaches at home collection of a fecal sample; that after collection, the patient separated the sample by smearing stool onto cards; and that

[1] DeLuca is not included in the dozens of references that Petitioner chose to submit with the Petition. *See* Pet. at viii-xvi.

the patient then shipped the smeared cards and sealed bucket containing the remaining portion of the stool sample for testing. *Id.* The CRU found that DeLuca teaches separating a portion of a fecal sample into a sealable tube and adding a buffer to the sample. *Id.* at 7. The CRU found that Olson discusses the use of buffers to stabilize DNA in stool samples stored at room temperature. *Id.*

The Patent Owner did not file a statement under 37 C.F.R. § 1.530. Ex. 1023 at 4. Without input from the Patent Owner, the CRU confirmed patentability of all twenty claims. *Id.* at 5. As the CRU explained, "[n]one of the references of record reasonably suggest collection at home with each of the fecal portions sealed in separate containers, each with a buffer therein as required by independent claim 1." *Id.* at 4.

Notably, although Petitioner asserts that the arguments and combinations of art in the Grounds are substantively different from the multiple SNQs presented in the reexamination proceedings, Petitioner makes no attempt to explain how they purportedly differ. Pet. at 10, 67. If anything, the Grounds are even weaker than the failed reexamination arguments. Just like the references in the reexamination, none of the references in the Grounds "reasonably suggest collection at home with each of the fecal portions sealed in separate containers, each with a buffer therein as required by independent claim 1." Ex. 1023 at 4.

IV. PROSECUTION HISTORY

The ’781 patent issued on April 25, 2023, from Application No. 17/936,335. 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.

Petitioner suggests that the ’781 patent issued without significant prosecution history. Pet. at 10. This largely ignores the history of office actions during prosecution of the ’607 parent application, in which the Patent Owner overcame rejections based on Petitioner’s primary Shuber reference and on the subject matter of Petitioner’s primary Lenhard reference. Pet. at 9-10, 67. The ’781 patent is subject to terminal disclaimer over the ’607 application. Ex. 2004 at 157.

Moreover, since the Petition was filed, a notice of allowance has issued for another patent application (18/179,945) in the same family. That notice of allowance issued after Patent Owner reopened examination to submit the current Petition arguments, expert declaration, and references to the Examiner. That patent, which issued on April 30, 2024, is subject to terminal disclaimer over the ’781 patent. Ex. 2005 at 1, 560.

A. The ’607 Parent Application Issued Over Substantially Similar Rejections as the Petition Art and Arguments

Petitioner acknowledges that the Shuber reference (the primary reference in Grounds 4-6) was the basis of an obviousness rejection in the ’607 parent

application. Pet. at 67.[2] It attempts to side-step this fact, however, arguing that the rejection was based on different secondary references and arguments. *Id.* However, the Examiner expressly cited Shuber for its discussion of stabilizing biological samples, including fecal samples, with a nucleic acid stabilizing solution. Ex. 2003 at 358. This is the primary purpose for which Petitioner relies on Shuber here. Pet. at 19-20.

After Patent Owner overcame the rejection over the Shuber combination, the Examiner rejected the pending claims in the parent '607 application on other grounds. Ex. 2003 at 640-643. Once again, the cited art and the Examiner's reasoning substantially overlapped with Petitioner's arguments. *See id.* Among other references, the Examiner relied on Kutzner. Ex. 2003 at 643; Ex. 1012. In particular, the Examiner asserted that Kutzner describes a "method for the detection of colorectal tumors using a combination of tests – one of which looks for a component of blood, and one of which is based on nucleic acid analysis, e.g., PCR." Ex. 2003 at 643. This is the same purpose for which Petitioner now relies on Lenhard. Pet. at 13.

[2] Petitioner relies on International Patent Application Publication Number WO2005/113769 as "Shuber." Ex. 1009. Petitioner acknowledges that cited reference US 2008/0124714 A1 (Shuber et al.) is the same reference. Pet. at 67. Patent Owner refers to both interchangeably herein as "Shuber."

Patent Owner also overcame the rejection over the Kutzner combination. After an Advisory Action from the Office (Ex. 2003 at 687), Patent Owner filed a Pre-Appeal Brief Request for Review in which it explained the deficiencies in the Examiner's rejection over Wang in view of Liang, Olek, and Kutzner. *Id.* at 719-723. The previous rejection was then withdrawn. *Id.* at 727. A notice of allowance issued on December 2, 2022. *Id.* at 740-747. Prosecution of the parent application continued after requests for continued examination, including to allow consideration of the materials submitted in the request for reexamination of the '781 patent. *Id.* at 884. The '607 application issued as U.S. Patent No. 11,845,991 (the "'991 patent") on December 19, 2023. Ex. 2003 at 1.

B. Similar Claims in the '945 Application Were Recently Allowed Over all References Cited in the Petition

Patent Owner is continuing to prosecute applications in the same family, including continuation application No. 18/179,945 (the "'945 application"), filed on March 7, 2023. Ex. 2005 at 6. The claims of the '945 application are similar to the claims challenged here – Patent Owner in fact filed a terminal disclaimer over the '781 patent on October 6, 2023. *Id.* at 560. Of importance to this proceeding, Patent Owner withdrew the '945 application from issuance in order to file an IDS disclosing the Petition and materials cited in support of the Petition. *Id.* at 27-33, 87-88. The '945 application claims have been re-allowed over all of these

references. *Id.* at 17-20. The ’945 application issued as U.S. Patent 11,970,746 on April 30, 2024. *Id.* at 1.

C. The Petition References are the Same as, or Substantially Overlap with, References Considered During Examination of the ’335 Application that Resulted in the ’781 Patent

The ’781 patent issued on April 25, 2023, from a continuation of the ’607 application. Ex. 1001. Applicant disclosed references in information disclosure statements (“IDS”) during examination, and the Examiner indicated on the IDS that all references were considered, except if they were lined through. Ex. 2004 at 140-143, 242-243, 256. Petitioner concedes that both of its primary references, Shuber and Lenhard, were listed in an IDS. Pet. at 67. The numerous other listed, and considered, references included Itzkowitz 2008 and Levi. Ex. 2004 at 140-143. As discussed below, the Itzkowitz reference on which Petitioner relies is substantially the same as the cited Itzkowitz 2008 reference. Compare Ex. 1006, *with* Ex. 1055. Likewise, the Vilkin reference on which Petitioner relies is substantially the same as the cited Levi[3] reference – disclosing essentially the same work by a largely overlapping group of authors. Compare Ex. 1005, *with* Ex. 2007.

[3] Levi is not included in the dozens of references that Petitioner chose to submit with the Petition. *See* Pet. at viii-xvi.

Thus, the exact same or substantially the same references as cited in Grounds I and IV were considered during prosecution of the '781 patent.[4]

V. OVERVIEW OF REFERENCES CITED IN GROUNDS

None of the references in the Grounds address the CRU's explanation for confirming all claims as patentable in the reexamination. In particular, none of the Grounds "reasonably suggest collection at home with each of the fecal portions sealed in separate containers, each with a buffer therein as required by independent claim 1." *See* Ex. 1023 at 4.

1. Lenhard (Ex. 1004) – Describes Laboratory Collection and Comparison of gFOBT with a Specific Methylation Marker Tested from Frozen Samples

Lenhard does not describe at home collection of samples. Lenhard also does not describe the separation of the fecal portions sealed in separate containers, with a buffer in each container. Lenhard also does not describe processing without freezing. In fact, far from describing at home collection for processing without freezing, Lenhard describes that the samples "were received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80°C." Ex. 1004 at 2; Ex.

[4] Petitioner relies on the remaining two references, Derks and Kanaoka only for its arguments concerning the additional limitations of claims 10, 12 and 13, Grounds II-III and V-VI. Pet. at 12. Patent Owner reserves its rights to raise additional arguments for other claims should the Board institute *inter partes* review.

2001 ¶47. Lenhard also does not teach use of stabilizing buffers in stool samples. Ex. 2001 ¶48.

Lenhard focuses on comparison of a single epigenetic marker with a guaiac-based FOBT test card ("gFOBT") for purposes of distinguishing between patients with CRCs and those without. *Id.* Among other things, Lenhard observes that the combination of the specific "HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs." Ex. 1004 at 6. However, there was no increase in the sensitivity for adenomas with the combination. *Id.*; Ex. 2001 ¶¶49, 73-74.

Lenhard also discusses other methylation markers found in stool, including SFRP2, which detected 77%-90% of CRCs – more than the 65% detected by HIC1 methylation analysis combined with gFOBT. Ex. 1004 at 2; Ex. 2001 ¶¶50, 75. The specificity of SFRP2 methylation was quite poor, though, at 77%. Ex. 1004 at 2; Ex. 2001 ¶¶50, 75.

Lenhard concludes that the study shows "HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 ***with a few additional sensitive and specific methylation markers*** may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas." Ex. 1004 at 7 (emphasis added); Ex. 2001 ¶76. Thus, Lenhard itself concludes that the logical next path to explore would be combining different methylation markers,

not combining nucleic acid-based testing with fecal occult blood testing as Petitioner asserts. Ex. 2001 ¶¶51-52, 76.

2. Vilkin (Ex. 1005) – Limited to a Specific iFOBT Device Compared to gFOBT

Vilkin is limited to FOBT. Specifically, Vilkin discusses testing of a particular desktop immunochemistry-based FOBT ("iFOBT") that demonstrated a "high sensitivity of 76.5% for all colorectal neoplasia and acceptable specificity of 95.3%." Ex. 1005 at 7; Ex. 2001 ¶¶53, 78. Vilkin does not disclose any combination of tests. Ex. 2001 ¶78. Vilkin does not teach or suggest any of (a) collection at home by defecation directly into a sealable collection vessel, (b) removing a portion of the sample to produce both a removed portion and a remaining portion, or (c) combining the remaining portion in the sealable collection vessel with a buffer. *See* Ex. 1005.

With respect to sample handling, 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." Ex. 1005 at 4; Ex. 2001 ¶¶54, 79. Vilkin concludes that "[r]efrigerated OC-Sensor samples are stable for 21 days." Ex. 1005 at 3 (Conclusions); Ex. 2001 ¶54. 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. Ex. 1005 at 4; Ex. 2001

¶54. Accordingly, although the Vilkin sample is not frozen, the Vilkin refrigeration requirement mandates similarly inconvenient and restrictive sample-handling.

Vilkin also required that the subject prepared three consecutive daily samples. Ex. 1005 at 1 (Methods); *Id.* at 4. According to Vilkin the "best results were obtained when all three tests were performed and utilized for the analysis." *Id.* at 6; Ex. 2001 ¶55.

Vilkin discloses essentially the same work, by a substantially overlapping group of authors, as the Levi reference cited during prosecution. Compare Ex. 1005, with Ex. 2007. Like Vilkin, Levi compares gFOBT with a specific desktop iFOBT. Levi concludes that the tested iFOBT "maintains the high sensitivity" of the tested gFOBT "but can significantly reduce the colonoscopy burden and expenses resulting from a guaiac FOBT-based screening program." *Id.* at 5. Levi cites Vilkin, including for the statement that the tested iFOBT "has been described by us . . ." *Id.* at 3, 6 n. 25.

3. Itzkowitz (Ex. 1006) – Limited to Specific DNA-Based Testing

Itzkowitz is limited to DNA-based testing. Ex. 2001 ¶81. In particular, Itzkowitz describes testing version 2 of Exact Sciences' fecal DNA test for CRC, with "improved DNA stabilization / isolation techniques and a new promoter methylation marker." Ex. 1006 at 1; Ex. 2001 ¶¶58, 81. Itzkowitz does not disclose

any combination of tests. Ex. 2001 ¶81. Itzkowitz does not teach or suggest any of (a) removing a portion of the sample to produce both a removed portion and a remaining portion, or (b) combining the removed portion of the sample with a buffer in a sealable container.

Itzkowitz is cited in Itzkowitz 2008, and Itzkowitz 2008 was cited during prosecution. Ex. 1055 at 8, n. 12; Ex. 1001 (Other Publications). Itzkowitz 2008 is a validation study of the sDNA test published in Itzkowitz, performed using methods identical to those published in Itzkowitz. Like Itzkowitz, Itzkowitz 2008 describes direct defecation into a stool collection kit followed by addition of a DNA-stabilizing buffer. Ex. 1055 at 3. Itzkowitz 2008 also describes that the addition of the DNA-stabilizing buffer "prevents DNA degradation during transport for several days and enhances performance of DIA." *Id.* at 2; Ex. 2001 ¶60. Further, like Itzkowitz, Itzkowitz 2008 cites Olson for use of DNA-stabilizing buffer. Ex. 1006 at 6; Ex. 1055 at 2. Itzkowitz 2008 concludes that the study "provides validation of a simplified, improved sDNA test that incorporates only two markers that demonstrate high sensitivity (83%) and specificity (82%) for CRC…The use of only two markers will make the test easier to perform, reduce the cost, and facilitate distribution to local laboratories." Ex. 1055 at 1.

4. Shuber (Ex. 1009) – Limited to Nucleic-Acid Based Testing

Shuber is a patent application with two named inventors, Anthony Shuber and Duncan Whitney. Ex. 1009. Although Mr. Shuber submitted a declaration in support of Petitioner's reexamination request, Petitioner did not rely on this reference in the reexamination.

Shuber is limited to nucleic acid-based testing, and more particularly, to preparing samples for use in nucleic acid-based testing. *Id.* at 2 (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 2:5-10; Ex. 2001 ¶70. 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."). Ex. 1009 at 28:23-27. Each of these is a nucleic acid-based test. Ex. 2001 ¶70. Shuber does not disclose any combination of nucleic acid-based tests with any other form of test. *Id.* ¶90. Shuber also does not teach or suggest any of (a) removing a portion of the sample to produce both a removed portion and a remaining portion, or (b) combining the removed portion of the sample with a buffer in a sealable container.

Mr. Shuber is also a named inventor on two of Petitioner's primary references from the reexamination, Lapidus '178 and Lapidus '650, both of which also concern preparing stool-samples for CRC screening. Ex. 1021 at 14; Ex. 1027, Ex. 1028. Mr. Shuber is also the final author on the Olson reference, a reference that Petitioner used in twelve of the fourteen SNQs in the reexamination (Ex. 1021 at 2, 14-17), and on which Petitioner relies here for its discussion of the use of stabilizing buffers to preserve DNA in stool. Pet. at 24-25.

Shuber was considered during prosecution of the '781 patent, and was discussed during prosecution of the '607 parent application, as to which the '781 patent is subject to terminal disclaimer. Ex. 2004 at 157, 256; Ex. 2003 at 358.

VI. THE BOARD SHOULD EXERCISE DISCRETION AND DENY INSTITUTION UNDER § 325(d)

The Board should exercise its discretion to deny institution under 35 U.S.C. § 325(d). First, the cited art and arguments are substantially the same as the references and arguments in the reexamination request. Second, each of Petitioner's primary references was considered during prosecution. The only references used in Grounds I and IV that were not expressly considered (Itzkowitz and Vilkin), are substantially the same as the cited Itzkowitz 2008 and Levi references. Moreover, Patent Owner overcame substantially the same art and arguments during prosecution of the '607 parent application that Petitioner raises

here. Finally, and perhaps most importantly, the Petition includes ***no explanation*** as to why (i) the references in the Petition are non-cumulative of the art considered in the reexamination or prosecution or (ii) the Office or the Examiner erred in any way.

Section 325(d) allows discretionary denial where the "same or substantially the same" art or arguments were considered during prosecution. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, 2020 WL 740292, at *3 (P.T.A.B. Feb. 13, 2020) (precedential, designated March 24, 2020). There is no dispute that both of Petitioner's primary references, Lenhard and Shuber, appeared in an IDS during prosecution of the '781 patent. Pet. at 66. These disclosures alone are sufficient to establish that the same art was previously presented. *Biocon Pharma Ltd. v. Novartis Pharmaceuticals Corp.*, 2021 WL 608300, at *4 (P.T.A.B. Feb. 16, 2021) (accepting that the examiner considered a reference that was "listed on the IDS and the Examiner signed the IDS with the statement 'all references considered except where lined through.'").

In *Advanced Bionics*, the Board set forth a two-part framework: "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied,

whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." 2020 WL 740292, at *3.

In applying this two-part framework, the Board considers a number of nonexclusive factors (the "Becton, Dickinson factors"), which include:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017). The burden is on the Petitioner to persuade the Board why any newly cited reference is "not the same or substantially the same as the prior art raised during the original prosecution or reexamination." *Ecofasten Solar, LLC v. Unirac, Inc.*, 2022 WL 443369, at *16 (P.T.A.B. Feb. 8, 2022). Petitioner made no attempt to satisfy its burden. Although not Patent Owner's burden, Patent Owner describes below why the art and arguments in the Grounds are substantially the same as art and arguments considered during reexamination

and prosecution. As discussed below, the *Becton Dickinson* factors support discretionary denial under 35 U.S.C. § 325(d).

A. Ground 1 – Lenhard in view of Itzkowitz and Vilkin is the same as, or cumulative of, previously cited art and arguments

Each of the Ground I references – Lenard, Itzkowitz and Vilkin – include substantially the same disclosure as previously-presented references. Specifically, Petitioner relied primarily on a ***single*** reference in the reexamination – Ahlquist – for many of the claim limitations. Here, Petitioner relies on ***two*** references – Lenhard and Itzkowitz – for those ***same*** limitations. Yet other than mapping those limitations to two different references, there is no substantive difference between Ahlquist from the reexamination and Lenhard/Itzkowitz here. Likewise, Petitioner relied on DeLuca in the reexamination for claim 1's "removing" a portion and combining that portion with a buffer limitations, and relies on substantively the same disclosure in Vilkin for the same limitations here. Even more egregiously, here Petitioner relies on Olson as a basis to establish its motivation to combine – but fails to inform the Board that it relied on Olson for the same disclosures in the reexamination. Petitioner attempts to hide that fact by not listing Olson in the combination here (as it did in the reexamination), but its omission is form over substance: the reexamination and the Petition both rely on Olson for the same

disclosures concerning use of stabilizing buffers to improve performance of DNA-based tests.

1. *Becton Dickinson* Factors (a) and (b) - Lenhard in view of Itzkowitz and Vilkin is the same or substantially the same as previously presented art

(a) Lenhard in view of Vilkin and Itzkowitz is substantially the same as Ahlquist in view of DeLuca and Olson

Grounds I-III are based primarily on Lenhard, Vilkin, and Itzkowitz. This combination is substantively the same as, and adds nothing relevant to, the Petitioner's previous reexamination arguments. In particular, Ground I is duplicative of at least the reexamination SNQ based on Ahlquist, DeLuca and Olson.

Ahlquist discloses everything for which Petitioner relies on Lenhard, and more, and yet was insufficient to invalidate any claims of the '781 patent in the reexamination. Petitioner argues that Lenhard discloses "a method of processing a fecal sample that includes collecting a fecal sample from the subject, removing a portion of it to test for blood proteins and then testing the remaining portion for cancer-specific DNA." Pet. at 21; *see also* Pet. at 13-14. Petitioner argued in the reexamination that Ahlquist discloses testing stool samples from the same patient using both DNA and gFOBT tests. Ex. 1021 at 19. The CRU agreed, finding that Ahlquist teaches collection of stool sample in one container, separation of a portion that was smeared on gFOBT test cards, and then sending the portions for fecal

occult blood and DNA-testing. Ex. 1022 at 8; *see also* Ex. 1044 at 2-3. Other than that Petitioner now resorts to combinations where it previously relied on Ahlquist alone, there are no substantive differences between Ahlquist's disclosure and what Petitioner contends Lenhard discloses on these points. Nor does Petitioner offer any explanation on these limitations. Critically, the CRU found that Ahlquist ***discloses*** these limitations, yet still confirmed patentability. Ex. 1022 at 8; Ex. 1023. Lenhard is thus, at best, cumulative of Ahlquist.

The Preamble: Lenhard does not disclose processing a freshly-collected sample, without freezing. The '781 patent describes a method of processing a freshly collected fecal sample, without freezing. Petitioner argues that the preamble is "rendered obvious" when Lenhard is combined with Vilkin and Itzkowitz. Pet. at 26-27. In the reexamination, Petitioner relied on Ahlquist alone for fresh collection and shipment, without freezing. Ex. 1021 at 89-90.

Limitation 1a: Ahlquist discloses home sample collection for which Petitioner now relies on Itzkowitz. Petitioner's primary reference in Ground I, Lenhard, does not describe at home sample collection. Instead, Petitioner turns to its combination references, arguing that a POSA would combine Lenhard with direct defecation into a sealable container, as described in Itzkowitz. Pet. at 24. In the reexamination proceeding, no such combination was necessary because Ahlquist describes at home collection, including direct defecation into a bucket

attached to a toilet seat. Ex. 1044 at 2; Ex. 1022 at 8. The bucket of Ahlquist was then sealed for shipping. Ex. 1044 at 2-3; Ex. 1022 at 8. Thus, not only is Itzkowitz's disclosure on this point cumulative of Alquist, it is a step backwards, as the Petition relies on two references for this limitation while the reexamination relied upon a single reference.

Limitations 1(b): Ahlquist/DeLuca discloses the same information for which Petitioner relies on Lenhard/Vilkin for the "removed" "remaining" and "separate sealable container" elements. Petitioner argues that Lenhard describes removing a portion of a patient's stool sample for testing using gFOBT, after which the rest of the sample is used for DNA-based testing. Pet. at 28. In the reexamination, Geneoscopy argued, and the CRU agreed, that Ahlquist disclosed removing a portion of sample from the collection bucket to smear sample on gFOBT cards. Ex. 1021 at 91; Ex. 1022 at 8.

Petitioner concedes that Lenhard "does not expressly state that the removed portion of the sample was removed to a separate sealable container," as required by claim limitation 1b. Pet. at 29. Petitioner relies on Vilkin for the separate sealable container limitation, arguing that a POSA would have replaced Lenhard's gFOBT with iFOBT and chosen selected elements of the iFOBT test described in Vilkin. Pet. at 14-15, 28-30. The Petition further relies on the iFOBT sample collection device of Vilkin, which Petitioner describes as a small test tube with a probe,

where the probe is inserted into the sample then returned to the tube that contains a buffer. Pet. at 29. But this is substantively indistinguishable from the DeLuca reference, on which Petitioner relied during the reexamination. DeLuca similarly discloses a sealable tube for collecting a test portion of a fecal sample to be used in iFOBT tests, where buffer is introduced into the tube. Ex. 1022 at 7; Ex. 2006 at Abstract, [0005] [0019]. Thus, there is no substantive difference between the disclosure relied upon in either the Petition's Vilkin or the reexamination's DeLuca.

Further, this is another example of where Geneoscopy relied on the primary reexamination reference, Ahlquist, for more than it can extract from Lenhard. In the reexamination, Geneoscopy argued that Ahlquist itself provides a motivation to replace the gFOBT with iFOBT because of iFOBT's superiority, "improved detection of adenomas," over gFOBT. Ex. 1021 at 93, 95. In the Petition, Petitioner similarly relies generally on advantages of iFOBT over gFOBT for motivation, citing to Vilkin and what was "known in the art" as support. Pet. at 29. Accordingly, not only is this argument also cumulative, but it is once again a step backward from the reexamination arguments.

Limitations 1(c): DeLuca discloses a sealable container with a buffer for iFOBT, for which Petitioner now relies on Vilkin. As discussed above, Petitioner argues that a POSA would have replaced Lenhard's gFOBT (which does not

require a buffer) with Vilkin's iFOBT (which does) and chosen selected elements of the iFOBT test described in Vilkin. Pet. at 14-15, 28-30. The Petition then relies on the iFOBT sample collection device of Vilkin, which contains a buffer. Pet. at 30. As discussed above, this is substantively indistinguishable from the DeLuca reference, which discloses a sealable tube for collecting a test portion of a fecal sample to be used in iFOBT tests, where buffer is introduced into the tube. Ex. 1022 at 7; Ex. 2006 at Abstract, [0005] [0019]. Thus, there is no substantive difference between the disclosure relied upon in either the Petition's Vilkin or the reexamination's DeLuca.

Limitation 1(d): Olson and Ahlquist both disclose use of DNA stabilization buffer, for which Petitioner now relies on Itzkowitz as informed by Olson.

Petitioner relies on Itzkowitz for aspects of the collection kit, discussed above, and the addition of a buffer to the collection container to improve fecal DNA screening. Pet. at 17, 24. The reexamination relied on Olson for this same limitation. But there is no substantive difference between Olson's disclosure of a buffer and Itzkowitz's. Indeed, the Petition ***relies*** on Olson. In fact, the Petition relies on the ***very same*** disclosure in Olson as the reexamination to argue that "the advantages of using DNA stabilizing buffer were well known." Pet. at 24-25. This is precisely how Olson was used in the reexamination, where the CRU described Olson as showing that the use of stabilization buffers for samples stored at room

temperature counteracted potential sample compromise and degradation. Ex. 1022 at 7.

Moreover, this is another example of where Geneoscopy relied on a primary reexamination reference, Ahlquist, for elements for which it now relies only on combinations. Specifically, for this element Geneoscopy argued in the reexamination that "Ahlquist states that its authors and other researchers 'have shown that adding a preservative to stool at the time of defecation can prevent degradation of long DNA.'" Ex. 1021 at 96, *citing* Ex. 1044 at 8. Moreover, as discussed above, Ahlquist discloses a sealable collection vessel (*see* Ex. 1022 at 8), whereas Petitioner argues here that a POSA "would understand" that the collection vessel would be sealed. Pet. at 31-32. Thus, this is another example of where Petitioner's argument is not only cumulative, but a step backward from the reexamination arguments.

Petitioner's Lenhard, Vilkin, Itzkowitz combination is substantially the same as its earlier combination of Ahlquist, DeLuca and Olson in the reexamination. To the extent there are differences, those differences show that Lenhard as a primary reference is even further removed from the claimed invention than Ahlquist.

(b) The Ground I references are substantially similar to prior art considered during the initial prosecution of the '781 patent.

Not only is the Ground I art substantially the same as art considered in the reexamination, it is also substantially the same as art cited during initial prosecution.

Lenhard was cited and considered during initial prosecution: There is no dispute that Lenhard was considered during initial prosecution – Petitioner concedes that it was properly cited on an IDS. Pet. at 66. Petitioner argues – incorrectly—that Lenhard's citation during prosecution is irrelevant because "neither the Examiner nor the Applicant discussed or otherwise cited either one during prosecution or reexamination." *Id.* As discussed below, however, this is not the standard. It is Petitioner's burden to explain why allowance over cited references was material error. *Google LLC v. Valtrus Innovations, Inc.,* IPR2022-01197, Paper 18 (P.T.A.B. June 23, 2023). It has failed to do so, and the unrebutted evidence here is that Lenhard was considered during prosecution.

Vilkin and Itzkowitz are substantively the same as the Levi and Itzkowitz 2008 references cited during initial prosecution: Vilkin and Itzkowitz, respectively, are substantially the same as the related Levi and Itzkowitz 2008 references. Compare Exs. 1005 and 1006, *with* Exs. 1055 and 2007. Both Levi and Itzkowitz 2008 were cited during initial prosecution. Ex. 2004 at 142-143. Indeed,

the cited Levi reference covers the same body of work as the Petition's Vilkin. This should come as no surprise, as Levi is a later publication covering essentially the ***same work*** by the ***same group*** as Vilkin. Compare Ex. 2007 at 1 with Ex. 1005. Like Vilkin, Levi describes an automated iFOBT that was more efficient than existing gFOBTs. *Id.* at 5. Similarly, Itzkowitz 2008 discusses the same at home sample collection for DNA tests for which Petitioner relies on Itzkowitz. Compare Ex. 1055 at 3 with Ex. 1006. Itzkowitz 2008 also recognizes the improvements that had been made in Exact Sciences' DNA assay, including that "the addition of a DNA-stabilizing buffer to the stool immediately upon defecation prevents DNA degradation during transport for several days and enhances the performance of DNA." Ex. 1055 at 2. In fact, the disclosures for which Petitioner relies on Itzkowitz (Pet. at 27, 31), can be found almost verbatim in Itzkowitz 2008. Ex. 1055 at 3. The Petition addresses neither the similarity between these references nor the fact that they issued from the same working group on the same subject matter.

The Examiner considered these references when they were cited in an IDS. Ex. 2004 at 142-143. *Biocon Pharma*, 2021 WL 608300, at *4.

(c) The Ground I references are substantially similar to references discussed during prosecution of the '607 parent application

The '607 application is the immediate parent application to the '781 patent. The '781 patent is subject to terminal disclaimer over the '607 application. Ex. 2004 at 157. Petitioner's Lenhard, Vilkin, Itzkowitz combination adds nothing relevant to additional references that were discussed in rejections during prosecution of the '607 patent application, including the Examiner's rejection over Wang in view of Liang, Olek, and Kutzner (the "Kutzner Combination"). Ex. 2003 at 640-643.

Kutzner discloses everything for which Petitioner relies on Lenhard, and more. Petitioner argues that Lenhard discloses "a method of processing a fecal sample that includes collecting a fecal sample from the subject, removing a portion of it to test for blood proteins and then testing the remaining portion for cancer-specific DNA." Pet. at 21; *see also* Pet. at 13-14. As Petitioner notes, the Examiner did not specifically discuss Lenhard in any rejection. Pet. at 66. However, the Examiner did discuss the Kutzner reference in rejections of the parent '607 application. With respect to Kutzner, the Examiner stated that it discloses a "method for the detection of colorectal tumors using a combination of tests – one which looks for a component of blood, and one which is based on nucleic acid

analysis, e.g., PCR." Ex. 2003 at 643. The Examiner found that Kutzner "teaches performing different types of assays on the fecal samples." *Id.*

The cited and discussed references also include numerous references that fill the role for which Petitioner uses Vilkin. For example, in the Kutzner Combination, the Examiner relied on cited references Wang and Liang. *Id.* at 640. The Examiner described Wang as teaching a device that can be used to collect a sample, mixing the sample with a 'preserving fluid,' and shipping the sample unfrozen to a testing lab. *Id.* The Examiner described Liang as teaching a device and method for collecting fecal samples, which included a sampling wand that is inserted into a test apparatus that contains a buffer. *Id.* at 641. The device of Liang could be used for FOBT. *Id.* at 642.

Further, the Kutzner Combination include Olek for its disclosure of DNA methylation analysis. *Id.* Moreover, other cited references fill the role for which Petitioner relies on Itzkowitz. Most notably, as discussed above, Itzkowitz 2008 discusses the same Exact Sciences' DNA-based tests for which Petitioner relies on Itzkowitz. Ex. 1055 at 2.

The fact that the Examiner did not base any rejection on Lenhard as a primary reference does not change that the Examiner considered cumulative references, such as Kutzner, and that the '607 parent application was allowed over those references.

2. *Becton Dickinson* Factors (d) - the Petitioner's arguments substantially overlap the previous reexamination arguments and the Examiner's arguments

Petitioner makes effectively the same argument in its Petition as it made during reexamination. At its core, Petitioner's argument is that at least one reference discloses one or more of (i) testing samples from the same patient with more than one type of test, (ii) home stool collection kits (iii) iFOBT tests that include buffers, (iv) DNA stabilization buffers, and (v) that samples could be shipped at room temperature. Petitioner simply rearranges how it pulls each of these pieces from the various references then cobbles them together using the '781 patent claims as a roadmap.

Indeed, Petitioner's arguments to combine the references are indistinguishable to the arguments raised in the reexamination. Specifically, Petitioner argued in the reexamination that a POSA would have been motivated to combine Ahlquist, DeLuca, and Olson for "improved diagnostic power." Ex. 1021 at 24. Petitioner similarly argues here that a POSA would be motivated to combine the reference to "improve" Lenhard. Pet. at 21-24. More specifically, Petitioner argued in the reexamination that DeLuca and Olson taught advantages of using stabilizing buffers to improve diagnostic testing. Ex. 1021 at 20. Similarly here, Petitioner argues that Vilkin and Itzkowitz teach use of stabilization buffers as superior alternatives to improve testing. Pet. at 22, 24. Petitioner's arguments also

rely on advantages of iFOBT over gFOBT as a purported motivation to combine. In the reexamination, Petitioner pointed to Ahlquist as motivating substitution of iFOBT for gFOBT because of performance superiority, particularly improved detection of adenomas. Ex. 1021 at 93, 95. The Petition relies on Vilkin and "general knowledge in the art" for argument concerning advantages of iFOBT, including performance superiority. Pet. at 22-23.

Petitioner's arguments also substantially overlap with the bases for rejection during prosecution of the '607 parent application, including the Examiner's rejection over Wang in view of Liang, Olek, and Kutzner. Ex. 2003 at 640. All of the rejections were overcome successfully, and thus Petitioner's virtually identical arguments simply retread old ground with no explanation concerning any purported error by the Examiner. As Patent Owner explained, the art cited by the Examiner failed to disclose the specific arrangements of the claimed invention, including that, "after the human subject has collected a fecal sample in the sealable collection vessel, a **removed portion** is taken from the collected fecal sample and combined with buffer" "in a separate container" and "the remaining portion of the fecal sample in the sealable collection vessel" is "combined with buffer." *Id.* at 720. Like the references cited in the reexamination and during prosecution, none of the references in the Petition suggest at-home portioning of a single freshly-collected fecal sample into multiple separate samples or portions, with addition of

separate buffers to each. Further, none of the cited references disclose or suggest using both an iFOBT test and nucleic acid-based test in combination.

Moreover, an Examiner has now considered the Petition in a related prosecution. The Petition itself and all cited materials were submitted during continued prosecution of the ’945 application, which is subject to terminal disclaimer over the ’781 patent. Ex. 2005 at 560. The ’945 application claims were re-allowed over all of these materials and arguments. Ex. 2005 at 17-21. The application issued as U.S. Patent 11,970,746 on April 30, 2024. Ex. 2005 at 1.

B. Ground IV – Shuber in combination with Vilkin is the same as, or cumulative of, previously cited art and arguments – *Becton Dickinson* Factors (a), (b), and (d)

Petitioner’s combination of Shuber with Vilkin is likewise substantially similar to the art relied upon in the reexamination. In fact, the primary reference for Ground IV – Shuber – describes earlier work in the field at Exact Sciences. The reexamination relied on Olson – which also describes Exact Sciences’ work, and on which Mr. Shuber is the senior author. Ex. 1025. Moreover, the Ahlquist reference used in the reexamination describes a study of the earlier Exact Sciences DNA-based tests. Ex. 1044. Further, not only was the Petition’s Shuber reference cited during prosecution of the ’781 patent, it was used as a rejecting reference during prosecution of the parent to the ’781 patent. Ex. 2003 at 358. This alone

demonstrates that the Office was aware of and considered Shuber during the '781 prosecution, and simply considered it irrelevant.

Petitioner asserts that "Shuber is a 2005 patent application filed by Exact that describes a method for preparing a fecal sample using nucleic acid stabilizing buffer." Pet. at 19. Petitioner also asserts that Shuber "touts that the disclosed methods 'do not require refrigeration or freezing'" which could be useful when samples are collected at remote locations and describes a variety of DNA-based tests for which the methods of Shuber could be used. *Id.* at 19-20. Finally, Petitioner characterizes the sample collection method of Shuber as directly depositing the sample into a sealable container to which a stabilizing solution can be added before the container is sealed and shipped. *Id.* at 20.

As discussed above, the Ahlquist and Olson references discussed during the reexamination described testing of Exact Sciences' earlier DNA-based test and Exact Sciences' earlier work – the same work that Petitioner asserts is disclosed in Shuber. As is also discussed above, Vilkin adds nothing that Petitioner had not previously asserted was disclosed by Ahlquist itself and/or DeLuca.

Moreover, Shuber itself was considered, and was used in 35 U.S.C. § 103 rejections, during prosecution of the parent application. Ex. 2003 at 353-359; *see also id.* at 497-502. Further, as discussed above, numerous cited references,

including Levi and Liang, contain information substantially similar to the portions of Vilkin on which Petitioner relies.

The Shuber and Vilkin combination is another repackaging of Petitioner's multiple attempts to piece together elements of Exact Sciences' earlier work on DNA-based tests with unrelated references describing specific iFOBT collection procedures.

C. All Grounds - *Becton Dickinson* Factors (c), (e), and (f) – Petitioner's failure to allege "material error" weighs heavily in favor of denial

Factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office. *Advanced Bionics*, 2020 WL 740292, *3.

As discussed above, the same or substantially the same references and arguments have been considered by the Office during prosecution and in the reexamination. Petitioner has made no attempt to point out any examiner error at any time. Petitioner's section 325(d) argument consists of just under two pages in which Petitioner asserts that none of the specific Itzkowitz, Vilkin, Derks, and Kanaoka references were before the Examiner. Pet. at 66-67. Petitioner further asserts that, although "Lenhard and Shuber were listed in an IDS, neither the Examiner nor the applicant discussed or otherwise cited either reference during prosecution of the '781 patent." Pet. at 67. Petitioner then asserts, without detail, that "[a]though Shuber was cited as a secondary reference" in the parent

application, "that rejection was based on different secondary references and different arguments than the grounds presented in this petition." *Id.*

Petitioner's arguments however, should be flatly rejected. The Board's decision in *Google v. Valtrus* is instructive. *Google LLC v. Valtrus Innovations,* IPR2022-01197, Paper 18. In that case, Petitioner argued, as Geneoscopy argues here, that an EP reference was not "considered" during prosecution, and thus no material error need be established, simply because it was not the subject of a rejecting reference. In that case, just as in this Petition, the disputed reference was cited on a form PTO-1449 filed with an IDS that was initialed by the Examiner. *Id*. at 15. The Board expressly found that citing a reference on an IDS ***was sufficient to satisfy*** prong 1, and thus, Petitioner was required to establish "material error" at the PTO:

> Our precedent holds that providing a document to the Office in an Information Disclosure Statement is sufficient to satisfy prong one of the *Advanced Bionics* analysis as long as that "previously presented" art is "the same or substantially the same" as that presented in the Petition. . . . ***The Examiner need not have substantively discussed [the disputed reference] in a rejection*** for prong one of *Advanced Bionics* to be satisfied…Because the [disputed reference] was 'considered' by the Examiner during prosecution, we find that the asserted art in this proceeding ***was evaluated to some extent.***

Id. at 15, 17-18, 19 (emphasis added).

Indeed, just as in *Google,* Petitioner here "provides no analysis whatsoever of the Office's previous consideration" of the disputed references, and "does not

even assert that the Office erred" on that basis. *Id.* at 19. In *Google*, the Board's decision to deny institution based on 325(d) was based ***heavily*** on the Petitioner's failure to point to any error at the board. *Id.* at 24 ("because Petitioner in this case has failed to [point out material error,] this factor weighs heavily in favor of us exercising discretion to deny institution.")

Thus, Petitioner's complete lack of "any evidence or argument to persuade" the Board that the references used in the Petition "are not substantially the same as the prior art raised during the original prosecution or reexamination" weighs ***heavily*** in favor of the Board exercising its discretion to deny institution. *See Ecofasten Solar*, 2022 WL 443369, at *16 .

VII. THE BOARD SHOULD EXERCISE DISCRETION AND DENY INSTITUTION UNDER § 314(a)

This Petition presents a unique situation where a challenger has already sought reexamination of the claims before petitioning for *inter partes* review. While 314(a) has been applied against serial IPR petitions on the same patent, the rationale underlying 314(a) applies equally to an IPR filed after a failed reexamination request.

The Board has addressed in other, significantly different factual contexts, the discretionary denial of an IPR that followed a reexamination request. But this case presents a unique situation that merits denial under 314(a) because here, the

previous reexamination request was made by ***same party,*** and involved ***substantially the same*** arguments and prior art. Other similar requests of the Board did not. For example, in *Samsung Elecs. Co., Ltd. v. Netlist, Inc.*, a non-precedential opinion, Petitioner requested discretionary denial of an IPR petition that followed an *inter partes* reexamination request. 2022 WL 22412095 (P.T.A.B. Oct. 19, 2022). The Board denied that request, but in that case, the previous reexam was requested by a ***different party*** that was not in privity with the petitioner. *Id.* at *8-9. The Board also found in that case that, unlike here, the subsequent IPR involved different prior art, and for the sole overlapping reference, the Patent Owner did explain how the PTO erred. *Id.* at *10-11. Other requests have likewise relied on similar facts. *See, e.g., Illumina Inc. v. Ravgen, Inc.*, IPR2021-01271, Paper 12 at 18 (P.T.A.B. Jan. 26, 2022) (finding that previous reexamination request brought by a party without "significant relationship" with petitioner did not weigh in favor of discretionary denial).[5]

Thus, this case presents a perfect match with the rationale underlying 314(a), and merits denial on that basis. The Board has repeatedly recognized the post-grant

[5] The Board has found in other contexts that its rationale on discretionary denial applies to reexam requests. In *in re Vivint*, for example, the Board applied 325(d) to discretionarily deny a reexamination request that followed an IPR request, and included some of the same arguments and art. 14 F.4th 1342, 1353–54 (Fed. Cir. 2021).

review process bears a risk of abuse through "repeated attacks on patents." *General Plastic Indus. Co., Ltd. v. Kaisha*, 2017 WL 3917706, at *7 (P.T.A.B. Sept. 6, 2017); *NVIDIA Corp. v. Samsung Elec. Co*., Case IPR2016–00134, Paper 9 (P.T.A.B. May 4, 2016); *see also* Consolidated Trial Practice Guide at 58 ("multiple petitions by a petitioner are not necessary in the vast majority of cases. To date, a substantial majority of patents have been challenged with a single petition."). As noted in the legislative history, AIA proceedings "are not to be used as tools for harassment or a means to prevent market entry through repeated litigation and administrative attacks on the validity of a patent." *See* H.R. Rep. No. 112-98, pt.1, at 48 (2011). Rather, "it is more efficient for the parties and the Board to address a matter once rather than twice." *Samsung Elec. Co. v. Rembrandt Wireless Techs., LP*, IPR2015-00114, Paper 14 at 6 (P.T.A.B. Jan. 28, 2015).

The Board has thus routinely declined to institute unjustified serial petitions against the same patent. In determining whether to institute, the Board applies the seven-factor test set forth in *General Plastic.* That rationale applies just as strongly here, especially given that the Petition lacks any explanation as to how the Petition art differs from the reexamination art or arguments. Nor does the Petition assert that Petitioner was unaware of any of the Petition art when it submitted the request for reexamination. As detailed below, the *General Plastic* factors weigh heavily in favor of denial.

A. Factor 1: "whether the same petitioner previously filed a petition directed to the same claims of the same patent."

Petitioner challenged the same 20 claims of the '781 patent in both the request for reexamination and in the Petition. *See* Ex. 1021 at 10-13; Pet. at 12. This factor weighs in favor of discretionary denial.

B. Factor 2: "whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it."

Petitioner does not assert that it was unaware of the references cited in the Petition when it filed the request for reexamination. Indeed, Petitioner's two primary references, Shuber and Lenhard, were both cited in an IDS during the initial prosecution of the '781 patent. Pet. at 66. Moreover, Petitioner's declarant for the reexamination, Mr. Shuber, was likely aware of the Petition references when he submitted his reexamination declaration. Indeed, Mr. Shuber is a former Exact Sciences employee and a named inventor on the very same Shuber reference that the Petition applies in grounds 4-6. Ex. 1009. Mr. Shuber is also the final author of the Petition's Itzkowitz reference. Ex. 1006. Vilkin, a Petition reference used in all of the Grounds, concerns essentially the same work by the same group as the Levi reference that was cited during prosecution. Ex. 1005; Ex. 2007. Vilkin was also published in the same journal, the *Am. Journal of Gastroenterology*, as several references cited on the face of the '781 patent. Compare Ex. 1005, *with* Ex. 1001 (Other References). Petitioner therefore knew, or should have known, of each

of these references when it filed the reexamination request. This factor weighs in favor of discretionary denial.

C. Factor 3: "whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition."

The rationale underlying this factor is to prevent a Petitioner an unfair advantage. Allowing Petitioner to file repeated follow-on proceedings without restriction would allow petitioners the "opportunity to strategically stage their prior art and arguments in multiple petitions, using our decisions as a roadmap, until a ground is found that results in the grant of review." *General Plastic*, 2017 WL 3917706 at *7. That stated rationale, while in the context of multiple IPR proceedings, applies equally here. When it filed the Petition in January 2024, Petitioner already knew of the decision in the reexamination proceeding and that the CRU had confirmed patentability of all claims. The CRU's notice stating its reasons for patentability of all challenged claims is dated October 18, 2023. Ex. 1023. Petitioner refers to that notice in the Petition. Pet. at 10.

Here, as in *General Plastic*, there is reason to be "concerned by the shifts in the prior art asserted and the related arguments in follow-on petitions." *General Plastic*, 2017 WL 3917706 at *7.

Petitioner asserted ***fourteen*** SNQs during the reexamination that applied ***eight*** prior art references. Ex. 1021 at 10-13. Having failed on all SNQs in the reexamination, Petitioner chose a different (yet substantively identical) set of references for the Petition. Pet. at 10. This is precisely the "staging" issue the Board warned of in *General Plastic.* As already discussed, Petitioner was aware of the art cited in this Petition when it filed the reexamination. Nothing prevented Petitioner from raising those references in the reexamination where there are no page limits. Yet Petitioner instead chose to allow that proceeding to play out, hold the Petition prior art in reserve, and file this IPR as a second attempt to invalidate the '781 patent. Petitioner launched this second challenge with the full benefit of the CRU's decision as a roadmap, and yet Petitioner has not identified any substantive difference between the references it chose for the Petition and the references cited in the reexamination. Indeed, as discussed in detail above, this second attempt relies on art that is even further removed from the patented invention than the failed reexamination art. Even with the CRU's decision for guidance, Petitioner has not cured any deficiencies in their previous arguments because they cannot. Granting the Petition under these circumstances would be an invitation for serial challenges that would tax the Office's and the Board's resources and would prejudice patentees. This factor weighs in favor of discretionary denial.

D. Factor 4: "the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition."

As discussed in connection with Factor 2, Petitioner knew or should have known of all of the prior art on which it bases the Grounds at least by the time of the reexamination request. This factor weighs in favor of discretionary denial.

E. Factor 5: "whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent."

This factor, along with factors 2 and 4, allows the Board "to assess and weigh whether a petitioner should have or could have raised the new challenges earlier." *General Plastic*, 2017 WL 3917706 at *7. Petitioner provides no explanation as to why it did not assert the known references during the reexamination proceedings or why it waited to assert certain references in a second challenge to the same claims. The lack of explanation particularly stands out where two of the references now asserted in the Petition concern Patent Owner's earlier work and where Mr. Shuber, who submitted a declaration on behalf of Petitioner in the reexamination proceeding, is a named inventor or author on those references. This factor weighs in favor of discretionary denial.

F. Factor 6: the finite resources of the Board.

Efficiency and timely administration of proceedings are critical considerations in the *inter partes* review system. *See* 35 U.S.C. § 316(b) ("In

prescribing regulations under this section, the Director shall consider the effect of any such regulation on the economy, the integrity of the patent system, the efficient administration of the Office, and the ability of the Office to timely complete proceedings instituted under this chapter."). Serial challenges to the same patent, particularly where there is no argument that any new information has come to light in the interim, wastes the Board's limited resources. *See e.g. Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-01423, Paper 7 at 7-8 (P.T.A.B. Oct. 28, 2015); *Rembrandt Wireless*, IPR2015-00118, Paper 14 at 6. This factor weighs in favor of discretionary denial.

G. Factor 7: the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

To the extent that this factor has any impact here, it weighs in favor of discretionary denial. If review were instituted, it would impose an obligation on the Board to resolve challenges to the '781 patent that could have been resolved in the earlier reexamination proceedings.

The factors considered in assessing whether to institute review based on a serial petition overwhelmingly weigh against institution here. The fact that Geneoscopy first filed a reexamination instead of an earlier petition does not affect the reasoning. The Board should exercise its discretion under 35 U.S.C. § 314(a) and deny institution.

VIII. CLAIM CONSTRUCTION IS NOT NECESSARY TO DENY INSTITUTION

Petitioner proposes no claim constructions. Patent Owner does not believe that the Board must construe any claim terms in order to deny institution. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) ("The Board is required to construe 'only those terms...that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Patent Owner reserves the right to assert claim construction positions should the Board institute IPR.

IX. THE PETITIONER'S GROUNDS INDEPENDENTLY FAIL ON THE MERITS

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

A. Level of Ordinary Skill in the Art

In its two separate challenges to the '781 patent, the Petitioner has offered two, significantly different, proposed levels of skill for the person of ordinary skill. Ex. 2003 ¶¶40-42. Citing to Mr. Shuber's opinion, Geneoscopy asserted in its reexamination request that a person of ordinary skill in the art ("POSA") in the relevant field of the invention of the '781 patent:

> would have had at least a Bachelor of Science degree in Biology (or a similar major) and several years of experience in the processing of biological samples, such as fecal samples from a human. Such a person would have been well-acquainted with methods of collecting

> fecal samples, preserving proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, and subsequently evaluating the fecal samples for proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, as of February 3, 2009.

Ex. 1021 at 7. In the Petition, Petitioner contends that a "POSA relevant to the '781 Patent would have a Ph.D. in chemistry, biochemistry, biology, or a related field and at least five years of experience designing and performing diagnostic assays on fecal samples." Pet. at 12.

Patent Owner disagrees with both of Petitioner's proposals. Although Petitioner's proposed level of skill in the reexamination touches on the breadth of potentially relevant topic areas, the education level of a Bachelor's of Science degree is less than is typical for individuals of ordinary skill in this field. Ex. 2001 ¶42. On the other hand, the level of skill set forth in the Petition requires an extraordinary level of skill within an overly narrow focus. *Id.* The proper level of ordinary skill in somewhere between the two and takes into consideration the full scope of the claimed invention. Specifically, a POSA would have a doctoral degree in medicine, chemistry, biochemistry, biology, or a related field and 1-2 years of experience in the processing and analysis of biological samples, including fecal samples. *Id.* ¶43. Such a person could have been an individual or a member of a team of scientists addressing fecal sample processing and analysis. *Id.*

Patent Owner has submitted with this POPR the declaration of Dr. Vadim Backman in support of this section of the POPR. Ex. 2001. No matter which of the three different levels of skill is applied, Dr. Backman is a person of at least ordinary skill, and it does not change that the claims of the '781 patent would not have been obvious to a person of ordinary skill as of the Priority Date. *Id.* ¶¶44-45.

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

Petitioner's first primary reference, Lenhard, is far removed from the claimed invention. Petitioner asserts that Lenhard discloses "a method of processing a fecal sample that includes collecting a fecal sample from the subject, removing a portion of it to test for blood proteins and then testing the remaining portion of cancer-specific DNA." Pet. at 21. Petitioner largely ignores the fact that the method of claim 1 requires, among other things, processing "without freezing," and collection "at home." Ex. 1001 at Claim 1. Lenhard does not describe at-home collection, or separation into separate sealed containers, or the addition of stabilizing buffers, or processing of the samples without freezing. Ex. 1004; Ex. 2001 ¶¶47-52.

Notably, although Petitioner submitted the Petition with the advantage of the Examiner's reasoning from the reexamination, Petitioner's reliance on Lenhard does not address the CRU's reasons for confirming patentability of all claims. Like

the references cited during the reexamination, Lenhard fails "to reasonably teach or suggest a method of collecting a fresh fecal sample without freezing wherein a sample is collected at home in a sealable collection vessel, a portion of the sample is removed to a separate sealable container, combining the removed portion of fecal sample with a buffer that prevents degradation of blood proteins and sealing the sealable container, and combining the remaining portion with a stabilizing buffer and sealing the collection vessel." Ex. 1023 at 4-5; Ex. 2001 ¶47. Lenhard also does not "reasonably suggest collection at home with each of the fecal portions sealed in separate containers, each with a buffer therein as required by independent claim 1." Ex. 1023 at 5; Ex. 2001 ¶47.

Petitioner's combination of Lenhard with Vilkin and Itzkowitz does not solve the many deficiencies. Vilkin focuses on FOBTs and compares gFOBT with a specific iFOBT device. Ex. 1005; Ex. 2001 ¶¶53, 78. Vilkin does not suggest the collection processes of the claims, a process that involves, among other things, at home separation of the sample and addition of buffer to each of the removed and remaining portions in separate sealable containers. In addition, Vilkin teaches that refrigeration was necessary for sample preservation. Ex. 1005 at 4 ("samples are kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development."); Ex. 1005 at 3 (Conclusions) ("[r]efrigerated OC-Sensor samples are stable for 21 days."); Ex. 2001 ¶¶54, 79. Vilkin also does

not suggest testing a single sample using both iFOBT and nucleic acid-based tests. *See* Ex. 2001 ¶57.

Just as Vilkin discusses only FOBT, Itzkowitz discusses only fecal DNA tests. Ex. 1006; Ex. 2001 ¶¶58, 81. Itzkowitz also does not suggest the home collection processes of the claims, let alone testing a single sample using both FOBT and DNA tests. None of these references "reasonably suggest collection at home with each of the fecal portions sealed in separate containers, each with a buffer therein as required by independent claim 1." Ex. 1023 at 3.

Petitioner's combination of specific aspects of the Vilkin iFOBT with the DNA-test of Itzkowitz to arrive at the particular features of the claims reflects classic hindsight. Even if there were a motivation to combine stool nucleic acid-based CRC tests with iFOBT as of the Priority Date, which there was not, the combination would not have resulted in the specific at home collection method of the claims.

Petitioner also does not satisfy its burden of showing any motivation to combine Lenhard with Vilkin and Itzkowitz.

Petitioner relies on Lenhard's disclosure of 65% sensitivity with the combination of a single DNA methylation marker and gFOBT to argue that a POSA would have been motivated to combine iFOBT with nucleic acid-based testing. Pet. at 21. Petitioner ignores that increased sensitivity of that one, specific

combination in Lenhard came with a reduction in specificity. Ex. 2001 ¶¶50, 73. This would have discouraged a POSA from making any such combination. *Id.* In addition, the one specific combination, as discussed in Lenhard, was not as sensitive as DNA-only testing that is also disclosed in Lenhard. *Id.* For example, Lenhard discloses that SFRP2 was "found to be the most sensitive fecal methylation marker, detecting 77%-90% of CRCs. However, specificity of SFRP2 methylation was quite poor, at 77%. Ex. 1004 at 2; Ex. 2001 ¶71. Lenhard concludes that the study shows "HIC1 as a sensitive and specific marker well suited for stool-based CRC screening. Combination of HIC1 ***with a few additional sensitive and specific methylation markers*** may allow for the highly sensitive and specific stool-based detection of CRCs and adenomas." Ex. 1004 at 7 (emphasis added). Thus, Lenhard expressly suggests multiple methylation markers, not combining methylation marker testing with any other forms of testing. Ex. 2001 ¶¶51, 75.

Neither Vilkin nor Itzkowitz supplies the missing motivation to combine iFOBT with nucleic acid-based tests, particularly not with the specific claim elements. Vilkin concludes that a particular iFOBT test is highly sensitive and specific: "we have found this desktop, automated-developed and quantified Hb version of the immunochemical fecal occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with an acceptable specificity and

consequent high negative predicative value." Ex. 1005 at 8. The results of Vilkin 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.* Using an iFOBT "threshold of 100 ng Hb/mL" allowed the Vilkin authors to achieve sensitivity of 76.5% with "acceptable specificity" of 95.3%. *Id.* Thus Vilkin taught improved iFOBT with no suggestion that iFOBT could or should be used in combination with another type of CRC screening. Ex. 2001 ¶78.

Itzkowitz described an increase in sensitivity from 52% to 72.5% in version 1 of Exact Sciences' DNA-only based test attributed to the improved methods of stabilization and extraction. Ex. 1006 at 6. Itzkowitz noted that this improvement in version 1 was achieved at a "relatively minor decrease in specificity from 94.4% to 89.3%." *Id.* With the version 2 panel that was the focus of Itzkowitz, "[t]he combination of vimentin plus DIA-DY resulted in an optimal sensitivity of 85.5% (95% CI, 73.9%-94.5%). This optimal combination detected most cancers, including early stage (stage I) lesions, regardless of their location in the colon." *Id.* The Itzkowitz "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 described a series of improvements in DNA-based testing and concluded that a combination of DNA-based markers could achieve acceptable sensitivity with reduced complexity. Ex. 2001 ¶81.

Itzkowitz also taught away from use of FOBT. Itzkowitz noted that "[i]nherent in the success of any screening test is patient acceptance. Our preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirms a very high degree of patient satisfaction." *Id.* at 6-7. "These findings support results from the previous multicenter study in which ***subjects preferred fecal DNA testing to both the fecal occult blood test*** and colonoscopy." *Id.* at 7 (emphasis added); Ex. 2001 ¶82. A POSA would not have been motivated to combine the patient-preferred, improved DNA-based tests of Itzkowitz with FOBT. Ex. 2001 ¶82.

Vilkin and Itzkowitz demonstrate that a POSA at the time would have known that the limited combination in Lenhard was not as sensitive or specific as either iFOBT alone or other fecal nucleic acid-based tests. In light of the individual advancements and the express teachings, there would have been no reason for a POSA to add the cost and complexity of combining two differing types of tests. Ex. 2001 ¶83. Separating a single fecal sample into different containers with different buffers, and shipping the sealed containers for different analyses, adds

cost and complexity for both the patient and test provider, and would have discouraged any such combination. Ex. 2001 ¶82-83. In addition, patient preference for fecal DNA testing over FOBT would have further taught away from any combination of the two types of tests in this area where patient acceptance is critical to success. *Id.* ¶82.

Finally, even if Lenhard could be viewed as a suggestion to combine different types of tests, Lenhard described a specific combination of a gFOBT with one particular methylation marker. *Id.* ¶72. A POSA at the time would have understood that there was no way to predict without testing whether a combination of different tests would result in improved performance. *Id.* ¶84. In fact, it was known by the Priority Date that combining types of diagnostics can result in reduced performance. *Id.* Thus, a POSA would not have been motivated to combine iFOBT with nucleic acid-based tests, even if Petitioner were otherwise correct about Lenhard.

None of the Lenhard, Vilkin, or Itzkowitz references suggest the combination of FOBTs with nucleic acid-based tests, particularly not in the specific configuration of the at home collection method of the claims, and a POSA would not have been motivated to combine the two types of tests at all, let alone in the manner claimed in the specific invention of the ’781 patent. Ex. 2001 ¶86.

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

Petitioner's argument with respect to Shuber is, at its core, that nucleic acid-based stool kits existed, and iFOBT stool kits existed, and that a POSA would have been motivated, not only to combine those two types of tests, but to combine them into the exact home collection method of the claims, including separate sealable containers and two buffers. The art as of February 3, 2009, did not provide motivation to combine nucleic acid-based tests with iFOBT with any reasonable expectation of success, and even if such motivation were found, nothing in Shuber, Vilkin, or the other references on which Petitioner relies suggests specific configuration of the claimed invention.

Petitioner asserts that Shuber "describes the possibility of using multiple tests in combination to improve the test's sensitivity for detection of CRC." Pet. at 20. In purported support of that assertion, Petitioner quotes from the portion of Shuber that states "[i]n one embodiment, the invention may be useful to avoid or reduce the number of false negative results in a screen of a population of individuals for one or more 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**.") Pet. at 20, quoting and adding emphasis to Ex. 1009 at 28:18-27. On its face, Shuber suggests combination of nucleic acid-based tests.

Nothing in Shuber discloses or suggests combining any of DNA integrity assay, a multiple mutation assay, or a hypermethylation assay with any FOBT. Ex. 2001 ¶¶87-89

In an attempt to justify the proposed combination, Petitioner incorrectly asserts that "the advantages of combining such stool DNA and blood protein assays were well understood in the art" by the Priority Date. Pet. at 48. Petitioner relies on various quotes out of context, none of which would have motivated the combination of FOBT tests with nucleic acid-based tests as of February 3, 2009, and particularly not to arrive at the elements of the claimed invention. Ex. 2001 ¶¶91-97.

Petitioner first relies on a closing sentence from the 2002 Nishikawa reference. Pet. at 48, citing Ex. 1011. 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." Ex 1011 at 6. The statement in this 2002 reference is pure speculation without reference to any data or support. Notably, seven years passed between Nishikawa and the invention of the '781 patent without anyone else

arriving at the combination before Exact Sciences' claimed invention. Ex. 2001 ¶92.

Petitioner next cites to Lenhard. Pet. at 49. However, as discussed above, consideration of the complete Lenhard reference, and not just the isolated portions on which Petitioner relies, would have discouraged even the disclosed, specific use of gFOBT and a single marker. Ex. 2001 ¶92. As 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." Ex. 1004 at 6 (emphasis added). There is no teaching, suggestion, or motivation to combine in Lenhard. Lenhard itself concludes that HIC1 should be combined with additional methylation markers, ***not*** with the gFOBT test that it used to compare HIC1. *Id.* ¶93.

Petitioner also cites to the Kutzner reference that was considered during prosecution. 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." Ex. 1012 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). Kutzner was discussing gFOBT (which does not require a buffer), not iFOBT (which uses a buffer in the separate references identified by Petitioner). More importantly, by posing the question, Kutzner reveals that the answer was not obvious, and that it would not have been obvious to a POSA to combine nucleic acid-based testing with any form of FOBT with any reasonable expectation of success. *Id.* ¶94.

Levin also does nothing more than pose a question for potential investigation. Pet. at 49. Levin posits that "[a]nother question worthy of consideration is ***whether or not*** including a sensitive gFOBT or FIT at the time of [sDNA] testing would improve sensitivity without adversely affecting specificity." Ex. 1013 at 9 (emphasis added). Levin goes on to cite Kutzner, further supporting that Kutzner does nothing more than raise a question, without providing motivation or any reasonable expectation of success. *Id.*; Ex. 2001 ¶95.

Petitioner also argues that Example 1 of Kanaoka provides further motivation to combine. Pet. at 63. Petitioner is again incorrect. Analysis of the data in Example 1 shows that testing for COX-2 and using an iFOBT test resulted in one additional positive test from the iFOBT what was not identified with the COX-2 test. Ex. 1007 at [0067]. However, the iFOBT test also had three positives among

the control cases (specificity 86.3%), where the COX-2 test had no positives in the control cases (specificity 100%). Ex. 1007 at [0066]; *id.* at [0065]; Ex. 2001 ¶95. Based on the small sample size in Kanaoka, the combination resulted in an insignificant increase in sensitivity, with a more significant decrease in specificity. *Id.* As with Lenhard, analysis of the full picture in Kanaoka would have taught away from a combination of nucleic acid-based and FOBT tests. Ex. 2001 ¶96.

Contrary to Petitioner's conclusions, a POSA at the time seeking to "improve the sensitivity of CRC diagnosis" would have focused on improving either DNA-based analysis or FOBT analysis. Multiple references, including Lenhard, Vilkin, and Itzkowitz, each drew conclusions about improving a particular type of test. Ex. 2001 ¶97. They did not suggest combining nucleic acid-based tests with FOBT tests. Ex. 2001 ¶¶76-83.

Even had the art suggested combining iFOBT with nucleic acid-based analysis, which it did not, the POSA would not have had a reasonable expectation of success. Ex. 2001 ¶¶84, 97. A POSA at the time would have understood that there was no way to predict without testing whether a combination of different tests would result in improved performance. *Id.* ¶84. In fact, it was known by the Priority Date that combining types of diagnostics can result in reduced performance. *Id.* This is revealed by the very references on which Petitioner relies.

Moreover, even if there had been a suggestion to combine some specific nucleic acid biomarker with some specific blood protein test, which there was not, there is no teaching or suggestion in the references to provide an at-home test, unfrozen, with a removed sample and sample remaining in the collection vessel, each with their own container and each with their own buffer, as opposed to using the lab-collected testing of frozen samples and/or samples separately collected for blood tests. Petitioner's arguments can only be designed by impermissible hindsight knowledge of the claims and, as noted above, still fail to teach or suggest all of the claimed elements as arranged in the claims

Further, nothing in the references on which Petitioner relies discloses or suggests the configuration disclosed in the claims. This is evidenced by the fact that (i) the claims issued in the face of all art cited in prosecution, (ii) patentability of all claims was confirmed in reexamination, and (iii) similar claims issued in the related '945 application where the Petition itself was considered.

D. Petitioner's Second, Third, Fifth, and Sixth Grounds Also Fail

Petitioner's Grounds II and V address only dependent claims 12 and 13. Those Grounds fail for the same reasons Grounds I and IV fail. Petitioner's Grounds III and VI address only dependent claim 10. Those Grounds also fail for the same reasons Grounds I and IV fail.

X. CONCLUSION

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

Date: April 30, 2024

/s/ James Glass

James M. Glass (Reg. No. 46,729)
Quinn Emanuel Urquhart
& Sullivan LLP
51 Madison Ave, 22nd Floor
New York, New York 10010
Email: jimglass@quinnemanuel.com
Tel.: (212) 849-7142
Fax (212) 849-7100

Counsel for Patent Owner
Exact Sciences Corporation

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 13,918 words and thus complies with the applicable word limit.

Date: April 30, 2024

/s/ James Glass

James M. Glass (Reg. No. 46,729)
Quinn Emanuel Urquhart
& Sullivan LLP
51 Madison Ave, 22nd Floor
New York, New York 10010
Email: jimglass@quinnemanuel.com
Tel.: (212) 849-7142
Fax (212) 849-7100

Counsel for Patent Owner
Exact Sciences Corporation

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on April 30, 2024 the foregoing Preliminary Response from Patent Owner was served via email on the following counsel of record for the Petitioner:

Brendan Jones
(Reg. No. 65,077)
bjones@foleyhoag.com
Foley Hoag LLP
155 Seaport Blvd # 1600
Boston, MA 02210
Phone: (617) 832-1267

David Shore
(Reg. No. 75,183)
dshore@foleyhoag.com
Foley Hoag LLP
155 Seaport Blvd # 1600
Boston, MA 02210
Phone: (617) 832-1714

Donald R. Ware
(*pro hac vice* admission to be requested)
dware@foleyhoag.com
Foley Hoag LLP
155 Seaport Blvd # 1600
Boston, MA 02210
Phone: (617) 832-1167

Sarah Burg
(*pro hac vice* admission to be requested)
sburg@foleyhoag.com
Foley Hoag LLP
155 Seaport Blvd # 1600
Boston, MA 02210
Phone: (617) 832-1249

Date: April 30, 2024

/s/ James Glass

James M. Glass (Reg. No. 46,729)
Quinn Emanuel Urquhart
& Sullivan LLP
51 Madison Ave, 22nd Floor
New York, New York 10010
Email: jimglass@quinnemanuel.com
Tel.: (212) 849-7142
Fax (212) 849-7100

Counsel for Patent Owner
Exact Sciences Corporation