

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

IPR2024-01330
Patent 11,970,746 B2

Before TINA E. HULSE, DAVID COTTA, and JAMIE T. WISZ,
Administrative Patent Judges.

HULSE, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Geneoscopy, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–4 and 12–19 of U.S. Patent No. 11,970,746 B2 (Ex. 1001, “the ’746 Patent”). Paper 1 (“Pet.”). Exact Sciences Corporation (“Patent Owner”) filed a Preliminary Response to the Petition, including notice that Patent Owner disclaimed claims 1 and 2. Paper 9 (“Prelim. Resp.”), 2. Therefore, only claims 3, 4, and 12–19 of the ’746 Patent are at issue in this *inter partes* review.

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon considering the arguments and evidence presented in the papers, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition, and we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d). Accordingly, we institute an *inter partes* review of the challenged claims of the ’746 Patent.

A. *Real Parties-in-Interest*

Petitioner identifies itself as the real party-in-interest. Pet. 3.

Patent Owner identifies itself as the real party-in-interest. Paper 4, 2.

B. *Related Matters*

The parties identify *Exact Sciences Corp. v. Geneoscopy, Inc.*, No. 24-cv-00583-MN (D. Del.), as involving the ’746 Patent, which was consolidated with case No. 23-cv-1319-MN (D. Del.). Pet. 3–4; Paper 4, 2.

Petitioner also filed a petition for *inter partes* review of U.S. Patent No. 11,634,781 B2 (“the ’781 Patent”), which is the parent of the ’746

Patent. IPR2024-00459 (“the -459 IPR”), Paper 1. The Board instituted the -459 IPR on July 26, 2024. IPR2024-00459, Paper 9 (“-459 IPR Dec. Inst.”).

C. The ’746 Patent

The ’746 Patent, entitled “Fecal Sample Processing and Analysis Comprising Detection of Blood,” was filed as U.S. Patent Application No. 18/179,945 on March 7, 2023, and claims priority to a series of continuation applications, including U.S. Patent Application No. 17/936,335, which issued as the ’781 Patent, and U.S. Provisional Application No. 61/149,581, which was filed on February 3, 2009. Ex. 1001, codes (54), (21), (22), (63), (60), 1:8–19. Thus, the earliest possible effective filing date of the ’746 Patent is February 3, 2009, which we apply to our analysis in this Decision.

The ’746 Patent relates to methods and kits for analysis of fecal samples. *Id.* at 1:31–32. According to the Specification, colorectal cancer (“CRC”) is a leading cause of cancer-related deaths worldwide. *Id.* at 1:41–43. Most colon cancers arise from adenomatous polyps, which are usually asymptomatic. *Id.* at 1:46–52. Because of this, mass screening of asymptomatic patients is the cornerstone for detecting and eliminating these precursor lesions to reduce the risk of CRC. *Id.* at 1:51–55.

Colonoscopy is the primary screening test for CRC because of its high sensitivity and specificity and the ability to remove polyps, if found. *Id.* at 1:65–67. The procedure, however, is invasive, costly, and has certain risks, such as infection and perforation of the bowel. *Id.* at 2:1–3. Fecal occult blood testing (“FOBT”), which tests for blood in the stool, is commonly used and less invasive and less expensive than colonoscopy. *Id.* at 2:4–12. But because occult blood in stool can be indicative of different gastrointestinal disorders, further testing is necessary to detect CRC. *Id.* at

2:9–12. There are two types of FOBT: guaiac FOBT (“gFOBT”), which detects peroxidase activity of hemoglobin in fecal blood, and immunochemical FOBT (“iFOBT” or “FIT”), which uses anti-human hemoglobin antibodies to detect fecal blood. *Id.* at 2:13–34. Although the immunochemical procedure is more complicated and more expensive, iFOBT is more sensitive than gFOBT. *Id.* at 2:25–40.

The Specification also explains that recent developments in testing look specifically for mutations in DNA characteristic of colorectal neoplasia that are detectable in exfoliated epithelial cells in the stool. *Id.* at 2:44–47. The Specification explains that increased DNA methylation is an epigenetic alteration that is common in human cancers. *Id.* at 3:5–7. Aberrantly methylated DNA has also been proposed as a potential tumor marker for CRC detection. *Id.* at 3:7–9.

The ’746 Patent further explains that, although combined assays for detecting CRC have been described, their approach targets either multiple protein markers or multiple DNA alterations. *Id.* at 3:41–43. According to the Specification, “[t]o date, immunochemical tests and DNA tests for CRC detection have been evaluated and compared on a separate basis only.” *Id.* at 3:43–45.

The ’746 Patent states that the invention “aims to improve the positive and negative predictive value and also the sensitivity and specificity of detection of colorectal cancer through non-invasive means.” *Id.* at 6:52–55. Accordingly, the invention is based upon a combination of tests for detecting proteins and epigenetic modification markers in the same fecal sample. *Id.* at 6:59–62.

D. Illustrative Claim

Petitioner challenges claims 3, 4, and 12–19 of the '746 Patent.

Claim 3 is illustrative and depends from claim 1, the only independent claim of the '746 Patent. Claims 1 and 3 are reproduced below:

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:
 - a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
 - b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and
 - c) in a sealable container, combining the second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

3. A method of processing a fecal sample, the method comprising:
 - a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and
 - ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample,wherein the pair of portions are obtained by the method of claim 1;
 - b) extracting nucleic acid from the first portion of the fecal sample;
 - c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and
 - d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample.

Ex. 1001, 45:56–67, 46:56–57, 46:64–47:15.

Claims 4 and 12–19 depend, either directly or indirectly, from claim 3. Claims 4, 12, and 13 recite further limitations for testing nucleic acid, and claims 14–19 recite further limitations for testing for an amount of a blood protein. *Id.* at 47:17–18, 48:6–36.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 3, 4, and 12–19 of the ’746 Patent would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §¹	Reference(s)/Basis
3, 4, 14–19	103	Lenhard, ² Vilkin, ³ Itzkowitz ⁴
12, 13	103	Lenhard, Vilkin, Itzkowitz, Kanaoka ⁵
3, 4, 14–19	103	Shuber, ⁶ Vilkin
12, 13	103	Shuber, Vilkin, Kanaoka
3, 4, 14–19	103	Inbar, ⁷ Vilkin, Shuber
12, 13	103	Inbar, Vilkin, Shuber, Kanaoka

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the ’781 Patent has an effective filing date before March 16, 2013, the pre-AIA version of § 103 applies. Our decision, however, would be the same under either version.

² Lenhard et al., *Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer*, 3 CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 142–49 (2005) (Ex. 1004, “Lenhard”).

³ Vilkin et al., *Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical, Fecal Occult Blood Screening Test*, 100 AM. J. GASTROENTEROL. 2519–25 (2005) (Ex. 1005, “Vilkin”).

⁴ Itzkowitz et al., *Improved Fecal DNA Test for Colorectal Cancer Screening*, 5 CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 111–17 (2007) (Ex. 1006, “Itzkowitz”).

⁵ S. Kanaoka, US2006/0216714 A1, published Sept. 28, 2006 (Ex. 1007, “Kanaoka”).

⁶ Shuber et al., WO2005/113769 A1, published Dec. 1, 2005 (Ex. 1008, “Shuber”).

⁷ Inbar et al., WO97/25925, published Jul. 24, 1995 (Ex. 1009, “Inbar”).

Petitioner also relies on the Declaration of Duncan Whitney, Ph.D.
Ex. 1002. Patent Owner relies on the Declaration of Vadim Backman, Ph.D.
Ex. 2001.

II. ANALYSIS

A. *Person of Ordinary Skill in the Art*

Petitioner contends that a person of ordinary skill in the art at the time of the invention (“POSA”) would have had “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. 12 (citing Ex. 1002 ¶¶ 9–13).

Patent Owner disagrees. Prelim. Resp. 20–21. According to Patent Owner, a POSA would have had “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.* at 21 (citing Ex. 2001 ¶ 51). Patent Owner also indicates that 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 notes that Petitioner’s proposal in the Petition is significantly different from the proposal in its *ex parte* reexamination request of the ’781 Patent, which merely required a bachelor’s degree and several years of experience processing biological samples. *Id.* at 21; Ex. 2042, 7.⁸ Patent Owner also contends that the level of skill proposed in the Petition requires an extraordinary level of skill within an overly narrow focus. Prelim. Resp. 21. Regardless, Patent Owner states that its expert, Dr. Backman, is a person of

⁸ We cite to the page numbers of the exhibit for prosecution histories such as Exhibit 2003 and Exhibit 2042. Unless stated otherwise, we cite to the page numbers of the reference for all other exhibits.

at least ordinary skill, and the claims of the '746 Patent would not have been obvious under any of the parties' proposed definitions of the level of ordinary skill in the art. *Id.* at 21–22.

As explained in the -459 IPR, we do not discern much of a substantive difference between the parties' respective definitions in this proceeding beyond the number of years of experience after obtaining a doctoral degree. *Compare* Pet. 12, *with* Prelim. Resp. 21. For purposes of this Decision, we adopt Patent Owner's definition as it appears to be reasonable and falls between Petitioner's definitions asserted in the Petition and in its request for reexamination of the '781 Patent. *See* Ex. 2001 ¶ 51. Moreover, Patent Owner's definition appears consistent with the prior art's demonstration of the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))). To the extent the parties continue to disagree on the level of ordinary skill in the art, they should brief the issue further during trial.

B. Claim Construction

In an *inter partes* review, the Board applies the same claim construction standard that would be used to construe claims in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Petitioner does not explicitly address claim construction in the Petition. *See generally* Pet.

Patent Owner states that it “does not believe that the Board must construe any claim terms in order to deny institution” and “reserves the right to assert claim construction positions should the Board institute IPR.” Prelim. Resp. 20.

At this stage of the proceeding, we agree with the parties that no construction of any claim term is necessary for purposes of our Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘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))).

C. Asserted Obviousness Grounds over Lenhard

Petitioner contends that claims 3, 4, and 14–19, would have been unpatentable as obvious over Lenhard, Vilkin, and Itzkowitz (Ground I). Pet. 19–34. Petitioner also argues that claims 12 and 13 would have been unpatentable over Lenhard, Itzkowitz, Vilkin, and Kanaoka (Ground II). Pet. 35–37. Patent Owner opposes. Prelim. Resp. 24–39, 49–50.

Having considered the arguments and evidence presented by the parties, we determine that Petitioner has shown a reasonable likelihood of prevailing on its assertion that the challenged claims would have been unpatentable as obvious over the cited references.⁹

⁹ We note that we address Patent Owner’s evidence of secondary considerations to Petitioner’s obviousness grounds in Section II.F below.

1. *Lenhard (Ex. 1004)*

Lenhard is a journal article entitled “Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer” that appears to have been published in the journal *Clinical Gastroenterology and Hepatology* in 2005 and is therefore prior art under 35 U.S.C. § 102(b). Ex. 1004, 142. Patent Owner does not challenge the prior art status of Lenhard at this stage of the proceeding. *See generally* Prelim. Resp.

According to Lenhard, the detection of tumor-derived genetic changes in stool is a promising new approach for CRC screening. *Id.* Lenhard describes a study involving the potential use of hypermethylated in cancer 1 (“HIC1”) promoter methylation as a stool-based DNA marker. *Id.* at 143. According to Lenhard, the promoter of HIC1 frequently is methylated in CRC, but not in normal or aging colonic tissue. *Id.* Lenhard states that it has shown that “HIC1 promoter methylation can be detected frequently and with high specificity in stool samples from patients with CRCs.” *Id.* Moreover, Lenhard states “[t]he combination of HIC1 methylation analysis with FOBT allowed for detection of two thirds of CRCs.” *Id.* at 147. According to Lenhard, “[t]he combination of both assays resulted in increased detection rates for CRCs.” *Id.*; *see also id.* at 146 (Table 4) (providing data for positivity rates of HIC1 assay, FOBT assay, and combination of the tests). Lenhard further states that “[a]lthough the combined test detected all localized cancers, no increase in sensitivity for adenoma was seen.” *Id.*

Lenhard states that stool samples were collected preoperatively from patients with verified CRCs and before colonoscopy for patients with adenomas larger than one centimeter. *Id.* Samples were received within ten

hours after defecation at the laboratory, subjected to gFOBT immediately on receipt, and then stored at -80°C until analyzed for methylated DNA. *Id.* at 143, 145.

2. *Itzkowitz (Ex. 1006)*

Itzkowitz is a journal article entitled “Improved Fecal DNA Test for Colorectal Cancer Screening” that appears to have been published in the journal *Clinical Gastroenterology and Hepatology* in 2007 and is therefore prior art under 35 U.S.C. § 102(b). Ex. 1006. Patent Owner does not challenge the prior art status of Itzkowitz at this stage of the proceeding. *See generally* Prelim. Resp.

Itzkowitz explains that several studies have shown the feasibility of detecting colon tumor-specific products in stool. *Id.* at 111. The markers in these studies represent alterations of various genes. *Id.* Itzkowitz teaches that pilot studies have shown that several technical and conceptual advances could improve fecal DNA testing. *Id.* For example, adding a DNA-stabilizing buffer to the stool immediately on defecation was shown to prevent DNA degradation for several days and enhance the performance of a DNA integrity assay (“DIA”). *Id.* Also, promoter methylation has become recognized as a key pathway by which colon cancers develop. *Id.*

Itzkowitz describes a two-phase study. *Id.* at 112. Phase 1 involved analyzing stool samples from approximately 50 patients with CRC and 200 patients with normal colonoscopy to define suitable DIA cut-off values and to determine optimal markers for the new assay. *Id.* Phase 2, which is ongoing, was designed as a validation set in which an additional 125 patients with CRC and 200 patients with normal colonoscopy will be analyzed using the optimal marker panel from phase 1. *Id.*

Itzkowitz explains that subjects were given a special stool collection kit that is mounted on the toilet bowl. *Id.* Immediately after defecation, the subject added 250 ml of a DNA-stabilizing buffer to the stool specimen and then shipped the specimen at room temperature overnight to a laboratory for processing and analyzing. *Id.*

3. *Vilkin (Ex. 1005)*

Vilkin is a journal article entitled “Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical, Fecal Occult Blood Screening Test” that appears to have been published in the *American Journal of Gastroenterology* in 2005 and is therefore prior art under 35 U.S.C. § 102(b). Ex. 1005. Patent Owner does not challenge the prior art status of Vilkin at this stage of the proceeding. *See generally* Prelim. Resp.

Vilkin explains that the standard guaiac fecal occult blood test (“gFOBT”) is faulted for its low sensitivity for significant colorectal neoplasia (i.e., CRC and advanced adenomatous polyps) and low specificity due to nonspecificity for human hemoglobin (“Hb”). *Id.* at 2519. Vilkin explains that the introduction of central laboratory and office-developed, immunochemical fecal occult blood tests (“iFOBT”) specific for human Hb improved specificity. *Id.* Vilkin describes a colonoscopy-controlled study that allowed for a detailed evaluation of an automated desktop instrument for quantitative, immunochemical determination of fecal occult blood. *Id.* at 2523.

Vilkin describes a fecal test sampling device shaped like a small test tube with a fecal probe that is inserted into the stool and then pushed back into the tube through a membrane into a sample cup that includes a Hb stabilizing buffer. *Id.* at 2520. Vilkin explains that the samples are double-

closed in ziplock bags and kept in the refrigerator until returned to the laboratory where they are kept at 4°C until development. *Id.*

4. *Kanaoka (Ex. 1007)*

Kanaoka is a United States patent application entitled “Method of Detecting Colon Cancer Marker,” which was filed on September 19, 2003, and published on September 28, 2006. Ex. 1007, codes (54), (22), (43). Kanaoka is therefore prior art under 35 U.S.C. § 102(e) and (b). Ex. 1007. Patent Owner does not challenge the prior art status of Kanaoka at this stage of the proceeding. *See generally* Prelim. Resp.

Kanaoka relates to a method for detecting tumor markers for diagnosing colon cancer comprising collecting a biological sample, homogenizing the sample in the presence of an RNase inhibitor to give a suspension, extracting RNA from the suspension, subjecting the extracted RNA to reverse transcription to give cDNA, amplifying the cDNA and then detecting the amplified cDNA. Ex. 1007, Abstract. Kanaoka states that the biological samples are preferably human feces and “can be used as they are, or, in some cases, after frozen.” *Id.* ¶¶ 40, 41. Kanaoka also states that one of the tumor markers used is COX-2. Example 1 describes using the method to detect COX-2 among colon cancer cases. *Id.* ¶¶ 55–68. Example 1 states “for comparison and reference, human hemoglobin (Hb) in the feces of each sample was measured by immunological fecal occult blood test.” *Id.* ¶ 57.

5. *Legal Background*

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406

(2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, Petitioner must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

6. *Analysis of Claim 3*

Petitioner asserts that the combination of Lenhard, Vilkin, and Itzkowitz teaches each limitation of claim 3 (including claim 1 from which it depends). Pet. 19–31. Patent Owner opposes, asserting that the combination does not teach or suggest the claimed invention. Prelim. Resp. 25–27.

On this record, we find Petitioner has shown sufficiently that the combination teaches each limitation of the claim. For example, regarding claim 1, Lenhard teaches an assay in which a first portion of a stool sample

is tested for tumor-derived DNA and a second portion is tested for fecal blood using gFOBT. Ex. 1004, 143–45. Vilkin and Itzkowitz teach at-home fecal sample collection by a human subject without freezing. Ex. 1005, 2520; Ex. 1006, 112. Itzkowitz teaches adding DNA stabilizing buffer to the stool specimen that was shipped to the laboratory, which a POSA would have understood to have been sealed so that the stabilizing buffer and sample are contained. Ex. 1006, 112; Ex. 1002 ¶ 185. Vilkin teaches a method of using iFOBT where a patient uses a “fecal test device” to remove a portion of a fecal sample, combine the sample with hemoglobin stabilizing buffer, and seal the sample and buffer in the sealable container. Ex. 1005, 2520–21.

Regarding claim 3, we find Petitioner has shown sufficiently that Lenhard and Itzkowitz additionally teach extracting and testing nucleic acid from the first portion of the fecal sample. Ex. 1004, 143–44; Ex. 1006, 112. And Petitioner has shown sufficiently that Lenhard and Vilkin teach testing the second portion of the fecal sample for blood protein. Ex. 1005, 2519, 2522. Thus, we are persuaded that Petitioner has shown sufficiently that the combination of Lenhard, Itzkowitz, and Vilkin teaches each limitation of claim 3. *See* Ex. 1002 ¶¶ 169–190, 194–207.

At this stage of the proceeding, we are not persuaded by Patent Owner’s arguments to the contrary. Patent Owner criticizes each reference individually, but does not identify any specific claim limitation that is not taught by at least one of the three references. *See id.* “A finding of obviousness . . . cannot be overcome by ‘attacking references individually where the rejection is based upon the teachings of a combination of references.’” *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1050 (Fed. Cir. 2019) (quoting *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986)).

To the extent Patent Owner is arguing that the combination does not teach or suggest the claimed invention because there is no motivation to combine the references, we address those arguments next. *See* Prelim. Resp. 25 (arguing that a POSA would not have modified Lenhard to combine with Itzkowitz and Vilkin).

a) Reason to combine Lenhard, Itzkowitz, and Vilkin with a reasonable likelihood of success

Petitioner asserts that it would have been obvious for a POSA to use the iFOBT of Vilkin and the fecal collection and DNA stabilization process of Itzkowitz in the screening method of Lenhard to arrive at the claimed method. Pet. 19–21. Specifically, Petitioner argues that Lenhard provides the reason to combine the references because it teaches that “[t]he **combination** of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs” and that combining the tests “increased detection rates for CRCs” and “detected all localized cancers.” *Id.* at 19 (citing Ex. 1004, 143, 147).

Although Lenhard does not expressly disclose the use of the claimed buffers, Petitioner asserts it would have been obvious to replace the gFOBT in Lenhard with the iFOBT of Vilkin, which stabilized the stool sample in a buffer to prevent blood protein degradation. Pet. 20 (citing Ex. 1005, 2519–20). According to Petitioner, a POSA would have had a reason to modify Lenhard’s assay to use Vilkin’s iFOBT because Vilkin teaches numerous advantages of iFOBT over gFOBT, which were known in the art, including iFOBT’s higher sensitivity and its ability to quantify the blood proteins so a physician could choose the Hb threshold level for a patient. *Id.* (citing Ex. 1005, 2519, 2524; Ex. 1002 ¶¶ 149–153).

As for combining Itzkowitz, Petitioner asserts that a POSA would have had a reason to improve Lenhard's assay by combining a portion of an at-home collected stool sample with a DNA stabilizing buffer in a sealable container before shipping the sample to a laboratory, as was done in Itzkowitz. Pet. 22 (citing Ex. 1002 ¶¶ 154–168; Ex. 1006, 112). Petitioner asserts that by the priority date, the advantages of using DNA stabilizing buffer were well known. *Id.* (citing Ex. 1002 ¶¶ 160–162). According to Petitioner, a POSA would have been motivated to use the stool collection and DNA stabilization methods of Itzkowitz in Lenhard's assay to maintain DNA integrity in a portion of the fecal sample, allowing it to be collected at home and shipped to a diagnostic laboratory without freezing. *Id.* at 23 (citing Ex. 1002 ¶¶ 159–164).

Thus, Petitioner asserts that a POSA would have had a reasonable expectation of successfully combining the references to reach the claimed invention because “it amounts to the routine performance, in combination, of two well-established prior art tests that already had been shown to work on fecal samples.” *Id.* at 24 (citing Ex. 1002 ¶ 167).

Patent Owner disagrees, asserting that Petitioner has failed to set forth any rationale for how a POSA in 2009 would have chosen the specific elements of the '746 Patent from three different references to the exclusion of other teachings of those references to reach the claimed invention. Prelim. Resp. 28. For example, Patent Owner argues that nothing in the art would have motivated a POSA to develop a test requiring at-home interaction with the sample to combine two separate portions of the sample with different media. *Id.* at 22–24 (citing Ex. 2001 ¶¶ 122–124). Patent Owner further notes that Lenhard concludes that combining HIC1 with a few additional methylation markers is preferred as it may be highly sensitive and

specific for detection of CRCs and adenomas. *Id.* at 28–30 (citing Ex. 1004, 148). Moreover, Patent Owner argues that a POSA would have been dissuaded from combining iFOBT with nucleic acid-based testing because the increased sensitivity came with a reduction in specificity. Prelim. Resp. 32–34 (citing Ex. 2001 ¶¶ 110–124). Patent Owner also argues that a POSA would have been dissuaded from combining Lenhard with Vilkin because Vilkin requires that the subject collect three consecutive daily fecal samples and store the samples in the refrigerator, which subjects are reluctant to do. *Id.* at 34–36. Patent Owner further asserts that a POSA would not have been motivated to pursue a test with increased cost and complexity “unless there was a significant likelihood of substantial performance gains that could not be achieved otherwise.” *Id.* at 36–39.

At this stage of the proceeding and on this record, we are persuaded that Petitioner has shown sufficiently that a POSA would have had a reason to modify the assay of Lenhard to combine Vilkin’s iFOBT and Itzkowitz’s collection process and DNA stabilization buffer with a reasonable expectation of success. Lenhard expressly states that “[t]he combination of [HIC1 methylation analysis with gFOBT] resulted in increased detection rates for CRCs” and includes data that supports this statement. *See* Ex. 1004, 147, 146 (Table 4); *see also id.* at 143 (“The combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.”). We find these positive statements and supporting data in Lenhard are sufficient to provide a “rational underpinning” to combine the gFOBT and DNA test at this stage of the proceeding. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Moreover, we are persuaded on this record that Vilkin’s explanation of the benefits of iFOBT over gFOBT provide a reason to replace Lenhard’s gFOBT with Vilkin’s iFOBT assay. *See*

Ex. 1005, 2519. And we agree at this stage of the proceeding that a POSA would have had a reason to improve Lenhard's assay by requiring a patient to defecate into a sealable container and add a stabilization buffer to the sample so it could be shipped to a laboratory without freezing, as described in Itzkowitz. *See* Ex. 1002 ¶¶ 154–166.

On this record, we are not persuaded by Patent Owner's arguments to the contrary. Although Lenhard concluded that combining different nucleic acid tests may allow for more sensitive and specific detection of CRCs and adenomas, that does not teach away from combining FOBT and DNA tests. The Federal Circuit instructs that the reason to combine need not coincide with the preferred or most desirable combination described in the prior art to provide motivation for the invention. *See Gen. Elec. Co. v. Raytheon Techs. Corp.*, 983 F.3d 1334, 1351 (Fed. Cir. 2020) (holding the Board erred in finding no motivation to combine where the art merely suggested a preference for a different engine and did not teach away from the claimed invention) (citing *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (“[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.”)).

Moreover, even if the specificity of the combined tests in Lenhard were lower than either Vilkin's iFOBT alone or other fecal nucleic acid tests, the claims do not require a particular level of sensitivity or specificity. *See* Ex. 1001, 45:20–47:4. Regardless, we note Dr. Backman states that a POSA “would have sought to balance sensitivity and specificity.” Ex. 2001 ¶ 39. Moreover, we note Dr. Whitney's testimony that “[h]aving a high sensitivity is particularly important in fecal CRC tests, where the consequence of false-negative results is that CRC patients do not receive

needed cancer treatment, leading to a worse prognosis and potentially death.” Ex. 1002 ¶ 29. Thus, on this record, we find a POSA would have considered any decrease in specificity—on balance—to be outweighed by the increase sensitivity of the combined tests in Lenhard in addition to the advantages of using Vilkin’s iFOBT over gFOBT, such as the lack of diet restrictions and the ability for Hb quantification. *See* Ex. 1005, 2519; *see also* Ex. 1002 ¶¶ 143–147. Thus, we do not limit our finding to a “single parameter,” as Patent Owner suggests. Prelim. Resp. 32–33.

Similarly, we are not persuaded on this record that a POSA would have been dissuaded from modifying Lenhard according to Vilkin and Itzkowitz due to alleged increased costs and complexity. *See id.* 34–39. For example, Patent Owner argues that the Vilkin method teaches collecting three consecutive daily fecal samples, which would complicate the assay. *See id.* at 34–35. But Petitioner relies on the use of Vilkin’s “fecal test device” to teach the limitations of the claims, rather than the number of fecal samples taken. *See* Ex. 1002 ¶¶ 187–188. Moreover, Patent Owner’s expert Dr. Backman offers conclusory testimony that a POSA would not have combined the tests because of the increase in cost and complexity, particularly given “the likelihood of improved diagnostic performance from a combination was unpredictable.” *See* Ex. 2001 ¶ 121. But Dr. Backman provides no objective evidence supporting his opinion and ignores the data provided by Lenhard that the combination DNA/FBOT test increases the sensitivity of detecting CRCs. *See* Ex. 1004, 147. Thus, at this stage of the proceeding, we are not persuaded by Patent Owner’s arguments.

We, therefore, find on this record that Petitioner has shown sufficiently for purposes of institution that the combination of Lenhard, Vilkin, and Itzkowitz teaches each limitation of claim 3 and a POSA would

have had a reason to combine the teachings with a reasonable expectation of success to reach the claimed invention.

7. *Analysis of Remaining Claims 4 and 12–19*

Petitioner asserts that the combination of Lenhard, Itzkowitz, and Vilkin teaches each limitation of claims 4 and 14–19 and that the combination of Lenhard, Itzkowitz, Vilkin, and Kanaoka teaches each limitation of claims 12 and 13. Pet. 28–37.

We have considered the arguments and evidence presented by the parties and find Petitioner has shown sufficiently that the combination of the cited references teaches each limitation of the claims and that a POSA would have had a reason to combine the references according to the claimed invention with a reasonable expectation of success for the reasons stated by Petitioner, which we adopt for purposes of this Decision. *See* Pet. 28–37; Ex. 1002 ¶¶ 208–226. Patent Owner argues that a POSA would not have had a reason to combine Kanaoka with Lenhard, Itzkowitz, and Vilkin because Kanaoka teaches that combining the iFOBT test with the test for COX-2 resulted in an insignificant increase in sensitivity with a more significant decrease in specificity. Prelim. Resp. 49–50 (citing Ex. 1007 ¶¶ 65–67; Ex. 2001 ¶ 144). As explained above, we note that a POSA would balance the sensitivity and specificity of a combination nucleic acid/FOBT test and likely favor an increase in sensitivity over specificity, given the detrimental impact of a false negative. *See* Ex. 1002 ¶ 29; Ex. 2001 ¶ 39. Thus, at this stage of the proceeding, we find Petitioner has shown sufficiently that a POSA would have had a reason to combine the method of Lenhard with the fecal collection and testing of Itzkowitz, Vilkin, and Kanaoka to reach the claimed invention with a reasonable expectation of

success. But we encourage the parties to address the issue further during trial.

D. Asserted Obviousness Grounds over Shuber

Petitioner contends that claims 3, 4, and 14–19, would have been obvious over Shuber and Vilkin (Ground III). Pet. 37–48. Petitioner also asserts that claims 12 and 13 would have been obvious over Shuber, Vilkin, and Kanaoka (Ground IV). Pet. 48–49. Patent Owner opposes. Prelim. Resp. 39–50.

Having considered the arguments and evidence presented by the parties, we determine that Petitioner has shown a reasonable likelihood of prevailing on its assertion that the challenged claims would have been unpatentable as obvious over the cited references.

We incorporate our analysis and findings regarding Vilkin and Kanaoka here.

1. Shuber (Ex. 1008)

Shuber is a PCT application entitled “Method for Stabilizing Biological Samples for Nucleic Acid Analysis,” which was published on December 1, 2005, and is therefore prior art under 35 U.S.C. § 102(b). Ex. 1008, codes (43), (54). Patent Owner does not challenge the prior art status of Shuber at this stage of the proceeding. *See generally* Prelim. Resp.

Shuber relates to methods for preparing nucleic acid-containing biological samples for an assay to detect nucleic acid markers indicative of cancer. *Id.* at 1:11–13. According to Shuber, contacting a patient sample with a stabilization solution stabilizes the DNA so that intact nucleic acids indicative of diseased cells are more effectively detected in a nucleic acid integrity assay. *Id.* at 2:7–9. Shuber explains that a stabilization solution “may be particularly useful when samples are not refrigerated or frozen” and

if a sample “is obtained at a remote location and mailed or delivered to a testing center.” *Id.* at 10:10–14. In one aspect of the invention, a stool sample may be directly deposited into a sealable container and a stabilization solution may be added to the container, after which the container may be sealed for storage/shipping. *Id.* at 29:8–19.

2. *Analysis*

Petitioner asserts that the combination of Shuber and Vilkin teaches each limitation of claims 3, 4, and 14–19 and that it would have been obvious for a POSA to combine the fecal DNA assay of Shuber with the iFOBT assay of Vilkin to arrive at the claimed methods with a reasonable expectation of success. Pet. 37–48. Petitioner also asserts that Kanaoka further teaches the limitations of claims 12 and 13 and that a POSA would have had a reason to combine Kanaoka’s RNA detection assay with Shuber and Vilkin for the same reasons discussed above. Pet. 48–49; *see supra* Section II.C.7.

Unlike Lenhard, Shuber does not expressly combine FOBT and nucleic acid tests or suggest that combining the tests may result in increased sensitivity of detecting CRC. Instead, Petitioner relies on the statements discussed above in Lenhard—along with other prior art—to argue that the benefits of combining stool DNA and blood protein assays were well understood in the art. Pet. 38–41 (citing, e.g., Ex. 1004, 143, 147, Table 4;

Ex. 1011,¹⁰ 112; Ex. 1012,¹¹ 34, 40; Ex. 1002 ¶¶ 233–236). Petitioner also asserts that successfully combining the assays of Shuber and Vilkin “requires no more than the use of routine methods to perform [] a pair of well-established assays on separate portions of a fecal sample.” *Id.* at 41 (citing Ex. 1002 ¶ 238).

We find on this record that Petitioner has shown sufficiently for purposes of institution that the combination of Shuber and Vilkin teaches or suggests each limitation of claims 3, 4, and 14–19 and that the combination of Shuber, Vilkin, and Kanaoka teaches or suggests each limitation of claims 12 and 13 for the reasons stated by Petitioner, which we adopt for purposes of our Decision. Pet. 41–49; Ex. 1002 ¶¶ 240–277. Patent Owner disagrees, asserting that Petitioner’s arguments to arrive at the claimed invention suffer from impermissible hindsight. Prelim. Resp. 41. For example, Patent Owner argues that neither reference teaches or suggests that the subject separate one stool sample such that there is a first and second portion, each in a separate container, where the first portion is tested for nucleic acid and the second for blood protein. *Id.* We are not persuaded because, once again, Patent Owner attacks the references individually. Petitioner relies on the combination of references to suggest this limitation of the claims; that is, when the fecal DNA test of Shuber and the iFOBT of Vilkin are combined and performed on a stool sample, first and second portions of the fecal

¹⁰ Nishikawa et al., *A simple method of detecting K-ras point mutations in stool samples for colorectal cancer screening using one-step polymerase chain reaction/restriction fragment length polymorphism analysis*, 318 CLINICA CHIMICA ACTA 107–12 (2002) (Ex. 1011, “Nishikawa”).

¹¹ Kutzner et al., *Non-invasive detection of colorectal tumours by the combined application of molecular diagnosis and the faecal occult blood test*, 229 CANCER LETTERS 33–41 (2005) (Ex. 1012, “Kutzner”).

sample are obtained, as required by the claims. Pet. 43 (citing Ex. 1002 ¶¶ 247–250).

Patent Owner further asserts that the art did not provide a reason to combine DNA and iFOBT tests with a reasonable expectation of success and asserts that nothing in the art suggests combining DNA and iFOBT tests to improve the sensitivity of CRC diagnosis. Prelim. Resp. 42. We find on this record that a POSA would have had a reason to combine the DNA assay of Shuber with the iFOBT of Vilkin in view of Lenhard’s finding that combining the DNA and FOBT tests increased detection rates for CRCs and in view of the various suggestions in the art to combine fecal DNA assays with FOBT assays. *See* Ex. 1004, 147 (stating that “[t]he combination of [HIC1 methylation analysis with gFOBT] resulted in increased detection rates for CRCs.”); Ex. 1011, 112 (stating its fecal DNA assay “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. 1012, 40 (“The combined applications of [the fecal DNA test and FOBT] together led to a significantly higher sensitivity than the application of any of the methods alone.”).

On this record, we are not persuaded by Patent Owner’s argument that the statements from Nishikawa (Ex. 1011) and Kutzner (Ex. 1012) are taken out of context and insufficient to provide a reason to combine fecal DNA tests with FOBT tests. Prelim. Resp. 43–45. Both references suggest a benefit in combining the two types of tests, which is sufficient at this stage of the proceeding. *See Outdry Techs. Corp. v. Geox S.p.A.*, 859 F.3d 1364, 1370–71 (Fed. Cir. 2017) (“Any motivation to combine references, whether articulated in the references themselves or supported by evidence of the

knowledge of a skilled artisan, is sufficient to combine those references to arrive at the claimed process.”). As for the reasonable expectation of success, on this record, we agree with Petitioner that combining the two tests according to the claimed methods amounts to no “more than the predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417.

Patent Owner also argues that a POSA would not have been motivated to improve Shuber in light of its already high sensitivity of detecting adenomas at greater than 95%. Prelim. Resp. 46 (citing Ex. 1008, 14:15–16; Ex. 2001 ¶¶ 118–121, 125–131). But, as Patent Owner’s expert notes, Shuber discloses detecting adenomas with “60%, 74%, and 90% sensitivity,” as well. Ex. 2001 ¶ 128 (citing Ex. 1008, 14:1–16). Finally, as with Ground I, Patent Owner argues that a POSA would not have been motivated to combine Vilkin with Shuber given the increase in cost and complexity. Prelim. Resp. 46–47. For the same reasons stated above, we are not persuaded by Patent Owner’s argument on this record at this stage of the proceeding. *See supra*.

Thus, having considered the parties’ respective arguments and evidence, we are persuaded that Petitioner has shown sufficiently for purposes of institution that the asserted combinations of Shuber, Vilkin, and Kanaoka teach each limitation of the challenged claims and a POSA would have had a reason to combine the teachings with a reasonable expectation of success to reach the claimed invention.

E. Asserted Obviousness Grounds over Inbar

Petitioner asserts that claims 3, 4, and 14–19, would have been obvious over Inbar, Vilkin, and Shuber (Ground VI¹²). Pet. 56–65. Petitioner also asserts that claims 12 and 13 would have been obvious over Inbar, Vilkin, Shuber, and Kanaoka (Ground VII). Pet. 65–66. Patent Owner opposes. Prelim. Resp. 48–50.

Having considered the arguments and evidence presented by the parties, we determine that Petitioner has shown a reasonable likelihood of prevailing on its assertion that the challenged claims would have been unpatentable as obvious over the cited references.

We incorporate our analysis and findings regarding Vilkin, Shuber, and Kanaoka here.

1. Inbar (Ex. 1009)

Inbar is a PCT application entitled “Collection and Transportation of a Pasty Material Sample,” which was published on July 24, 1997, and is therefore prior art under 35 U.S.C. § 102(b). Ex. 1009, codes (43), (54). Patent Owner does not challenge the prior art status of Inbar at this stage of the proceeding. *See generally* Prelim. Resp.

Inbar relates to a system for collecting, storing, and transporting material, such as stool. *Id.*, Abstract. Inbar discloses a system that allows for multiple separate sealable containers, which each contain unique preservation media corresponding to different laboratory assays. *Id.* at Abstract, 3:3–8, 4:13–22, Figures 1–4. Inbar allows for the specimen to be preserved and sealed within each separate container to allow for shipment to

¹² Ground V is no longer at issue in light of Patent Owner’s disclaimer of claims 1 and 2.

a laboratory so necessary assays can be performed. *Id.* Inbar explains this system comprises at least one sealable container that holds preservation medium to store samples for an extended period of time before testing. *Id.* at 3:18–4:12. To achieve different assays of the same sample material, which likely requires different media, Inbar describes having at least two containers each holding a different preservation medium corresponding to each assay. *Id.* at 4:13–18.

2. *Analysis*

Petitioner asserts that the combination of Inbar, Shuber, and Vilkin teaches each limitation of claims 3, 4, and 14–19 and that it would have been obvious for a POSA to combine the fecal specimen testing preparation system of Inbar with the DNA and blood protein assays of Shuber and Vilkin, respectively, to arrive at the claimed methods with a reasonable expectation of success. Pet. 56–65 (citing Ex. 1002 ¶¶ 306–329). Petitioner also asserts that Kanaoka further teaches the limitations of claims 12 and 13 and that a POSA would have had a reason to combine Kanaoka’s RNA detection assay with Inbar, Shuber and Vilkin for the same reasons discussed above. *Id.* at 65–66 (citing Ex. 1002 ¶¶ 330–331); *see supra* Section. II.C.7.

Petitioner asserts that a POSA would have understood that the Inbar system would incorporate the appropriate stabilizing buffers when used to collect specimens for a DNA test and an iFOBT and would have been motivated to do so. *Id.* at 57 (citing Ex. 1002 ¶¶ 307–308; Ex. 1008, 7:19–21; Ex. 1005, 2520; Ex. 1009, 4:16–18). Petitioner also asserts that a POSA would have had a reasonable expectation of successfully combining the assays because doing so “amounts to using the Inbar system for its intended purpose to facilitate performance of a pair of well-established assays on separate portions of a fecal sample.” *Id.* (citing Ex. 1002 ¶ 309).

We find on this record that Petitioner has shown sufficiently that the combination of Inbar, Shuber, and Vilkin teaches or suggests each limitation of claims 3, 4, and 14–19 and that the combination of Inbar, Shuber, Vilkin, and Kanaoka teaches or suggests each limitation of claims 12 and 13 for the reasons stated by Petitioner, which we adopt for purposes of our Decision. Pet. 56–66; Ex. 1002 ¶¶ 311–331.

Patent Owner disagrees, arguing that Inbar does not teach at-home sample collection, does not “require” different media, and does not disclose a solution that prevents degradation of blood protein or preserving nucleic acid in fecal samples. Prelim. Resp. 48–49. Once again, Patent Owner attacks Inbar individually, where Petitioner relies on the combination of the references for those teachings of the claims.

Patent Owner also argues that there was no motivation to combine the references, asserting the addition of Inbar does not cure the lack of motivation with respect to Shuber and Vilkin. *Id.* at 48 (citing Ex. 2001 ¶ 142). For the same reasons explained above with respect to the reason to combine Shuber and Vilkin, we find on this record that Petitioner has shown sufficiently that a POSA would have had a reason to combine the specimen collection system of Inbar to collect specimens for the DNA assay of Shuber and the iFOBT of Vilkin. On this record, we find Petitioner has shown sufficiently that a POSA would have recognized the Inbar system as a practical and convenient system to preserve and transport a stool specimen for DNA and iFOBT analysis in a laboratory. *See* Ex. 1002 ¶¶ 307–309.

Thus, having considered the parties’ respective arguments and evidence, we are persuaded that Petitioner has shown sufficiently for purposes of institution that the asserted combinations of Inbar, Shuber, Vilkin, and Kanaoka teach each limitation of the challenged claims and a

POSA would have had a reason to combine the teachings with a reasonable expectation of success to reach the claimed invention.

We now consider Patent Owner’s proffered evidence of objective indicia of nonobviousness.

F. Objective Indicia of Nonobviousness

Relying on its Cologuard product, Patent Owner argues that evidence of commercial success, long-felt need, industry praise, and copying support the nonobviousness of the ’746 Patent claims. Prelim. Resp. 50–61. In the Petition, Petitioner preemptively asserts that there is no nexus between any such evidence and Cologuard, arguing that Cologuard is not coextensive with the challenged claims. Pet. 66–69 (citing *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019)).

At this stage of the proceeding, we find Patent Owner has the better position that a presumption of a nexus exists between Patent Owner’s evidence related to Cologuard and the ’746 Patent claims. We find the Federal Circuit’s discussion in *Teva Pharmaceuticals Int’l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349 (Fed. Cir. 2021) to be instructive. The Federal Circuit rejected a bright-line rule that the presumption of nexus does not apply “if any unclaimed feature materially affects the functioning of a product that is alleged to be coextensive.” *Id.* at 1361. The court explained that “under such a rule the presumption of nexus would rarely, if ever, attach because virtually every innovative product inevitably has some unclaimed feature that materially affects its functionality.” *Id.* Petitioner argues that Cologuard is a complex multistep stool DNA test and the “claimed process of dividing a stool sample into two portions in separate buffers is, at most, a minor component of Cologuard.” Pet. 67. The challenged claims of the ’746 Patent, however, recite more than just a “process of dividing a stool

sample into two portions in separate buffers,” as Petitioner asserts. *Id.* The claims further include testing the nucleic acid and blood protein present in the two portions of the fecal sample. *See, e.g.,* Ex. 1001, claim 3. Thus, at this stage of the proceeding, we are persuaded that Cologuard “embodies the claimed features, and is coextensive with them” such that a presumption of nexus applies. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

Regardless, even assuming a nexus exists, Petitioner has not yet had an opportunity to respond to Patent Owner’s arguments and evidence of secondary considerations. Thus, although we have considered Patent Owner’s evidence of secondary considerations, we find the record is insufficiently developed at this stage of the proceeding to find that Patent Owner’s evidence of objective indicia of nonobviousness outweighs Petitioner’s obviousness challenge.

Thus, having considered the parties’ respective arguments and evidence, we find Petitioner has shown a reasonable likelihood of prevailing on its assertion that claims 3, 4, and 12–19 are unpatentable as obvious over the cited references.

III. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

We now address Patent Owner’s request that we exercise our discretion under 35 U.S.C. § 325(d) to deny institution. Prelim. Resp. 62–64. Petitioner opposes. Pet. 69–71. For the reasons discussed below, we decline to exercise our discretion to deny institution.

A. Legal Standards

Under § 325(d), we have discretion to deny a petition that presents the same or substantially the same prior art or arguments as previously presented to the Office. *See* 35 U.S.C. § 325(d).

In performing an analysis under § 325(d), the Board uses a two-part framework:

- (1) We consider 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 the first part of the framework is satisfied, we consider whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

To help us evaluate the *Advanced Bionics* framework, we consider a number of non-exclusive factors, as set forth in the decision in *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential) (“the *Becton, Dickinson* factors”):

- (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, IPR2017-01586, Paper 8 at 17–18.

According to *Advanced Bionics, Becton, Dickinson* factors (a), (b), and (d) relate to whether the same or substantially the same art or arguments previously were presented to the Office, and factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office.

Advanced Bionics, IPR2019-01469, Paper 6 at 9–11.

B. Analysis

1. Whether the same or substantially the same art was previously presented

Patent Owner asserts that each of Petitioner’s cited references and the -459 IPR Petition was submitted in an Information Disclosure Statement and considered by the Examiner during prosecution of the ’746 Patent Application. Prelim. Resp. 62 (citing Ex. 2005, 76–82). Petitioner does not dispute that assertion. Pet. 69. Accordingly, we find that the same art was previously presented to the Office during prosecution of the ’746 Patent Application. *See Advanced Bionics*, 7–8 (holding that “[p]reviously presented art includes . . . art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent”).

We next determine whether Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

2. *Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims*

Petitioner argues that the second prong of *Advanced Bionics* strongly favors institution, not denial. Pet. 69. Petitioner notes that the cited prior art was listed in an IDS but never substantively evaluated during examination and that the Board has repeatedly declined to discretionarily deny institution under such circumstances. *Id.* at 69–70 (citing *Satco Prods. Inc. v. Regents of the Univ. of Calif.*, IPR2021-00662, Paper 13 at 25 (PTAB Nov. 8, 2021)). Petitioner also asserts that because the scope of the currently challenged claims is broader than that of the claims of the '781 Patent, the decision to institute the -459 IPR over the same prior art applies equally to the currently challenged claims of the '746 Patent. *Id.* at 70.

Patent Owner argues that just because the Board instituted the -459 IPR does not establish that the Examiner erred during prosecution of the '746 Patent Application. Prelim. Resp. 63. Relying on *Advanced Bionics*, Patent Owner argues, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* (quoting *Advanced Bionics*, Paper 6 at 9). Patent Owner also asserts that we erred in finding a motivation to combine the references in the -459 IPR. *Id.* at 63–64.

We are not persuaded by Patent Owner’s arguments. Although the Examiner may have considered the -459 IPR Petition and the cited prior art, the Examiner did not have our Institution Decision when the '746 Patent issued on April 30, 2024. *See* Ex. 1001, code (45); -459 IPR Dec. Inst. (entered July 26, 2024). Moreover, *Advanced Bionics* explains that where the Office’s previous consideration of the art is silent under factor (c) (as it is here), “then a petitioner may show the Office erred by overlooking

something persuasive under factors (e) and (f).” *Advanced Bionics*, Paper 6 at 10. As set forth above, Petitioner has persuasively shown—here and in the -459 IPR—that the Office erred by overlooking the teachings of the cited prior art, including Lenhard’s express teaching that the combination of HIC1 methylation analysis with FOBT increased detection rates for CRC, thereby creating an express motivation for a POSA to combine the fecal collection and testing methods of Itzkowitz and Vilkin. *See* Ex. 1004, 147. On this record, we find that is sufficient basis to find Examiner error and for the Board to decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. CONCLUSION

For the foregoing reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one of the challenged claims of the ’746 Patent is unpatentable. Accordingly, we institute an *inter partes* review of claims 3, 4, and 12–19 of the ’746 Patent on each of the grounds raised in the Petition.

Our determination in this Decision is not a final determination on the construction of any claim term or the patentability of any challenged claim and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner’s contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that “there is a significant difference between a petitioner’s burden to establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)). Any argument not raised in a

timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived.

V. ORDER

In consideration of the foregoing, it is hereby

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 3, 4, and 12–19 of U.S. Patent No. 11,970,746 B2 is instituted with respect to all challenged claims and all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial, which will commence on the entry date of this decision.

IPR2024-01330
Patent 11,970,746 B2

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