

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN SCIENCES, LLC,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00027
Patent 11,725,241B2

Before DEBORAH KATZ, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background and Summary

Qiagen Sciences, LLC (“Petitioner”) filed a Petition requesting *inter partes* review of claims 1–16 of U.S. Patent No. 11,725,241 B2 (Ex. 1001, “the ’241 patent”). (Petition (“Pet.”), Paper 2.) Tecan Genomics, Inc. (“Patent Owner”) filed a Preliminary Response identifying itself as the owner of the ’241 patent. (Preliminary Response (“Prelim. Resp.”), Paper 6.)

The Director may not authorize an *inter partes* review “unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that 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). We determine whether to institute *inter partes* review on behalf of the Director. *See* 37 C.F.R. § 42.4(a).

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner.

For the reasons set forth below, we determine that Petitioner has demonstrated there is a reasonable likelihood that it would prevail in showing that at least one challenged claim is unpatentable. Accordingly, we institute *inter partes* review of all challenged claims on all asserted grounds. *See SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 362 (2018); 37 C.F.R. § 42.108(a).

B. Real Parties-in-Interest and Related Matters

Petitioner identifies QIAGEN Sciences, LLC, QIAGEN Gaithersburg, LLC f/k/a QIAGEN Gaithersburg, Inc., QIAGEN GmbH, and QIAGEN N.V., as its real parties-in-interest. (*See Pet.*, 2.) Patent Owner identifies Tecan Group AG (also known as Tecan Group Ltd.) as its real party-in-interest. (*See Paper 3*, 1.)

Both Petitioner and Patent Owner report that the litigation *Tecan Genomics, Inc. v. QIAGEN Sciences, LLC et al*, 1:23-cv-01115-GBW (D. Del.) and *Tecan Genomics, Inc. v. Invitae Corp. et al*, No. 23-cv-1114-GBW (D. Del.), in which Patent Owner has asserted the '241 patent and other patents, are related matters. (*See Pet.*, 2; *see Paper 3*, 1.) Furthermore, Petitioner and Patent Owner identify IPR2024-01506, which requests review of the '241 patent, as a related matter. (*See Paper 2*, 2–3; *Paper 3*, 1.)

In addition, IPR2024-01504 and IPR2025-00026, challenging Patent No. 11,098,357, IPR2025-00015 and IPR2025-00028, challenging Patent No. 10,036,012, and IPR2025-00016 and IPR2025-00029, challenging Patent No. 10,876,108, as well as IPR2024-01502, challenging Patent No. 9,546,399, are related matters. (*See Pet.*, 2; *Paper 3*, 1.)

C. The '241 Patent

The '241 patent is entitled “Compositions and Methods for Identification of a Duplicate Sequencing Read” issued on August 15, 2023, from application 17/381,888, which was filed on July 21, 2021. The '241 patent ultimately claims priority to provisional application 61/903,826, which was filed on November 13, 2013. (*See Ex. 1001.*)

The '241 patent provides methods for detecting duplicate sequencing reads in high-throughput sequencing reactions. (*See* Ex. 1001, 1:26–29.) The '241 patent explains that it can be difficult to know if two or more identical sequences represent unique cDNA molecules derived independently from different RNA molecules or if they are PCR duplicates derived from a single RNA molecule. (*See id.* at 1:36–41.) The '241 patent attempts to solve this problem with an “identifier” that can be included in an “adaptor” ligated to the nucleotide to be sequenced. (*See id.* at 2:20–32.)

The identifier is a nucleic acid sequence of random bases ligated to a DNA fragment prior to amplification and is unique to each fragment. The identifier allows duplications originating from the same DNA to be recognized because they have identical identifiers. (*See id.* at 14:18–29.) The '241 patent also provides for an “indexing site” and a “target sequence primer binding site” to be included in the adaptor. (*See id.* at 2:26–27.) The '241 patent explains that the ligated adaptor-nucleic acid fragment products can be amplified to generate a population of sequencing reads and that sequencing reads with a duplicate identifier site and target sequence can be detected from the population of sequencing reads. (*See id.* at 2:27–32.)

D. Illustrative Claim

Claim 1 of the '241 patent, the sole independent claim, recites:

[1p] A method for detecting duplicate sequencing reads, the method comprising:

[1a] obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor,

[1b] wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment;

[1c] sequencing the amplicons to generate sequence reads that include identifier and target sequences; and
[1d] identifying sequence reads with identical identifier and target sequences as duplicates.

(Ex. 1001, 25:33–43 (bracketed labels added that correspond with Petitioner’s notation of the claim (Pet. 7–8).)

E. Evidence and Asserted Grounds

Petitioner relies, *inter alia*, on the following references in its challenges.

Name	Number or Title	Publication Date	Exhibit
McCloskey	US2007/0020640 A1	January 25, 2007	1005
Porreca	US2012/0165202 A1	June 28, 2012	1006
Schmitt	WO2013/142389 A1	September 26, 2013	1007
Illumina 2008	“Multiplexed Sequencing with the Illumina Genome Analyzer”	December 26, 2008 ¹	1008
Li 2009	“The Sequence Alignment/Map format and SAMtools,” 25 BIOINFORMATICS 2078–2079 (2009)	2009	1011

Petitioner also relies on the testimony of Michael L. Metzker, Ph.D. (See Ex. 1003.)

¹ Illumina 2008 is dated December 2, 2008 and Petitioner asserts that it was available on Illumina’s website by December 26, 2010, as attested to by a Records Request Processor at the Internet Archive. (Pet. 16; see Ex. 1009 ¶¶ 2, 5.)

Petitioner asserts that claims 1–16 are unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. ² §	Reference(s)/Basis
I	1–3, 5–7, 9, 10, and 13–16	102(a)	McCloskey
II	1–3, 5–11, and 13–16	102(a)	Porreca
III	1–3, 5–12, 14, and 15	102(a)	Schmitt
IV	4	103	Porreca, Illumina 2008
V	4	103	Schmitt, Illumina 2008
VI	8	103	Porreca , Illumina 2008
VII	8	103	Schmitt, Illumina 2008
VIII	12	103	Porreca, Li 2009

II. ANALYSIS

A. Legal Standards

“A person shall be entitled to a patent unless— (1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the” 35 U.S.C. § 102(a). To be anticipated, each and every element of the claim must be found, either expressly or inherently, in a single prior art reference. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

² The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013, before the filing of the applications to which the ’241 patent claims priority. Therefore, we apply the AIA versions of Sections 102 and 103.

Under 35 U.S.C. § 103, a patent for a claimed invention may not be obtained,

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 said subject matter pertains.

Obviousness is determined by looking to the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966). “[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

B. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the “type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (quoting *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962, (Fed. Cir. 1986)). Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner asserts that a person of ordinary skill in the art would have either a Ph.D. or a Master's degree in molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field. (*See* Pet. 9 (citing Ex. 1003 ¶ 41).) Petitioner argues further that an ordinarily skilled artisan with a Ph.D. would also have at least two years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and sequencing experience, including but not limited to high-throughput sequencing technologies. (*See id.*) Petitioner argues that an ordinarily skilled artisan with a Master's degree would have at least four years of similar experience. (*See id.*)

Patent Owner asserts that Petitioner's definition requiring a Ph.D. or a Master's degree and several years of experience indicates higher than ordinary skill because by 2008 next generation sequencing was performed in laboratories according to published protocols and would have been accessible to experienced laboratory technicians and graduate students. (Prelim. Resp. 7–8.) Patent Owner proposes that, instead, the appropriate level of ordinary skill in the art was a Ph.D. in a field related to molecular biology, or a B.S. or M.S. degree with three to five years of experience working in a molecular biology lab. (*See id.*)

On this preliminary record, having considered Dr. Metzker's testimony and Patent Owner's reasoning, we agree that one of ordinary skill in the art would have had experience with next generation sequencing, but are not persuaded that this would only be possible in the field of molecular biology. For the purposes of this Decision, we find a person of ordinary skill would have had a Ph.D. in the field of chemistry, molecular biology, or

biochemistry or a B.S. or M.S. degree with three to five years of experience working in any of those fields. The person of ordinary skill would have had experience with next generation sequencing methods and a working knowledge of how those methods functioned. This definition of a person of ordinary skill is consistent with the skill level reflected in the disclosures of the '241 patent and prior art. We further note that neither aspect of the dispute over the skill level affects our decision to institute review.

C. Claim Construction

We construe each claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b) (2024). Under this standard, claim terms are generally given their plain and ordinary meaning as would have been understood by a person of ordinary skill in the art at the time of the invention and in the context of the entire patent disclosure. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). In some cases, the patentee may serve as its own lexicographer. *Grace Instrument Industries, LLC v. Chandler Instruments Co. LLC*, 57 F.4th 1001, 1010 (Fed. Cir. 2023) (*quoting Phillips*, 415 F.3d at 1316).

Petitioner argues that we should construe the claim term “adaptor” as “any oligonucleotide that is attached to the target sequence.” (*See* Pet. 10.) Petitioner cites the '241 patent as referring to an “adaptor” as “an oligonucleotide sequence, the ligation of which to a target polynucleotide or a target polynucleotide strand of interest enables the generation of amplification-ready products of the target polynucleotide or the target

polynucleotide strand of interest.” (Ex. 1001, 4:14–21; *see* Pet. 10.) According to Petitioner, this described function can be performed by any oligonucleotide. Petitioner also cites the Examiner’s reasoning during prosecution that “since any oligonucleotide can perform such function, any oligonucleotide is considered to anticipate this term.” (*See* Pet. 10 (citing Ex. 1013, 77).) Petitioner further cites the specification of the ’241 patent for its disclosure that “appending the adaptor to the nucleic acid fragments generated by methods described herein can be achieved using a ligation reaction or a priming reaction.” (Ex. 1001, 9:34–37; *see* Pet. 10.)

Patent Owner does not dispute this construction at this stage, arguing only that the term need not be construed beyond its plain and ordinary meaning and reserving the right to propose constructions and identify terms needing construction later in the proceeding. (*See* Prelim. Resp. 9.)

For the purposes of this decision, we adopt Petitioner’s construction of the term “adaptor,” although we note that it does not affect our decision to institute review.

D. Ground I – Anticipation by McCloskey

Petitioner challenges claims 1–3, 5–7, 9, 10, and 13–16 as being anticipated by McCloskey under 35 U.S.C. § 102(a). (*See* Pet. 18–30.)

1. McCloskey

McCloskey addresses the problem in PCR reactions of amplifying contaminant DNA, which can result in a skewed yield of PCR products such that there is a high degree of redundancy for a small portion of the original genomic sequences.” (Ex. 1005 ¶ 3.) McCloskey teaches:

In the practice of the present invention nucleic acid molecules (e.g., genomic DNA fragments) are labeled with distinct

sequence tags prior to PCR amplification. These sequence tags authenticate a nucleic acid sequence with information, Such as the date of the experiment, and the sample identity. Thus, the present invention permits identification of valid sequences, and distinguishes the valid sequences from contaminants and redundant sequences arising from template re-cloning. Contaminant sequences can be identified even when multiple control (no DNA) PCR samples are negative. Barcoding permits, for example, quantification of the relative abundance of genomic methylation patterns or polymorphic sequences by correcting for skewing that can arise from PCR amplification or the cloning of the products.

(*Id.* ¶ 5.) McCloskey provides examples of barcoding that reveal redundant sequences, as well as an example of determining and discounting redundant sequences with an “already seen bar-code.” (*Id.* ¶ 63.) McCloskey also provides for “batch-stamps” that are attached to target DNA to identify information such as the origin of the DNA. (*See id.* ¶ 16.)

McCloskey provides two embodiments of such adding an adaptor to a nucleic acid. In the first embodiment, as a hairpin linker is ligated to the nucleic acid to produce a bar-coded and batch-stamped nucleic acid. (*See id.* ¶¶ 92–98, Fig. 3.) In the second embodiment, an oligonucleotide annealed to nucleic acid and extended to produce a bar-coded and batch-stamped nucleic acid. (*See id.* ¶ 35, Fig. 2B and C.)

2. Analysis of Claim 1

a. Preamble [1p]: A method for detecting duplicate sequencing reads, the method

Petitioner argues that McCloskey teaches using “barcodes” to distinguish “valid sequences” from “redundant sequences,” which McCloskey explains are sequences with “identical barcodes.” (Ex. 1005 ¶¶

5, 16; *see* Pet. 18.) Petitioner cites to experiments disclosed by McCloskey that use barcodes where redundant sequences are observed. (*See* Pet. 18 (citing Ex. 1005 ¶¶ 63, 93, 103, 106).) For example, McCloskey teaches that “[e]ach genomic fragment is marked prior to amplification, allowing us to identify contaminant and redundant sequences and to quantify accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences.” (Ex. 1005 ¶ 93.) Petitioner cites Dr. Metzker’s testimony in support. (*See* Ex. 1003 ¶¶ 74–75.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding the preamble of claim 1 and McCloskey.³

b. Element [1a]: “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor,”

Petitioner argues that McCloskey teaches obtaining amplicons with an amplified fragment of a nucleic acid and an appended adaptor by disclosing a hairpin linker or an oligonucleotide containing a barcode and a batch-stamp added to a target nucleic acid sequence, and then amplified by PCR to produce amplicons. (*See* Pet. 19–20 (citing Ex. 1005 ¶¶ 13, 14, 35, 43–91–98, Figs. 2B, 2C, and 3).) Petitioner cites Dr. Metzker’s testimony in support. (*See* Ex. 1003 ¶¶ 76–77).)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this element of claim 1 and McCloskey.

³ Given the undisputed teachings of McCloskey and the arguments at this stage, we also need not decide whether the preamble is limiting.

c. Element [1b]: “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment;”

Petitioner argues that a barcode taught in McCloskey, which is incorporated into either the hairpin linker or oligonucleotide, is an identifier, as recited in claim 1. (See Pet. 20–21.) Petitioner argues that the barcode of McCloskey “refers to an arbitrary sequence that can uniquely identify a target nucleic acid in an experiment” and is of sufficient length to provide “a unique identity to each target nucleic acid molecule in the sample prior to amplification.” (Ex. 1005 ¶ 21.) Petitioner points to several examples provided in McCloskey of using a barcode to be amplified by PCR. (See Pet. 21 (citing Ex. 1005 ¶¶ 14–47, 57–60, 68–73, 76, 81–84, 95–98, 100–104, Figs. 2A–D, 3, 4).) Petitioner cites Dr. Metzker’s testimony in support. (See Ex. 1005 ¶¶ 78–80).)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this element of claim 1 and McCloskey.

d. Element [1c]: “sequencing the amplicons to generate sequence reads that include identifier and target sequences”

Petitioner argues that McCloskey discloses analyzing nucleic acid molecules by sequencing, in general, and that Example 6 shows amplification of nucleic acid products produced with a hairpin linker are sequenced. (See Pet. 21 (citing Ex. 1005 ¶¶ 98–107).) Petitioner cites further to Figures 4A–G of McCloskey, as well as the sequencing disclosed in Examples 1–3. (See *id.* at 21–22 (citing Ex. 1005 ¶¶ 43–77).) Petitioner quotes the teaching in McCloskey that “[t]he barcodes, batch-stamps, and

the annealing temperature of four exemplary bar-coded sequences are shown in TABLE 1.36 of the 46 were desirable and valid sequences, each of which had a unique barcode.” (Ex. 1003 ¶ 63.) Petitioner cites Dr. Metzker’s testimony in support. (See Ex. 1003 ¶¶ 81–86.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this element of claim 1 and McCloskey.

e. Element [1d]: “identifying sequence reads with identical identifier and target sequences as duplicates.”

Petitioner argues that McCloskey teaches that both the hairpin linker and the oligonucleotide allow identical sequence reads having the same barcode to be identified as redundant, that is, as duplicates. (See Pet. 22–23.) Petitioner cites Example 6 of McCloskey for its disclosure of observing “[r]edundant hypermethylated sequences with identical barcodes and methylation pattern” in Figures 4B and 4C and “redundant hypomethylated sequences with identical barcodes” in Figures 4E and 4F. (Ex. 1005 ¶ 103; see Pet. 23 (also citing Ex. 1005 ¶ 53 (“There were 22 sequences with a barcode that was identical to a sequence already obtained (i.e., redundant sequences).”).) Petitioner further cites the disclosure in Example 2 of McCloskey that “[a] redundant sequence was also recovered, meaning that a MLM1-positive sequence with an already seen bar-code was recovered.” (Ex. 1005 ¶ 63; see Pet. 23.) According to Petitioner, these disclosures show that the target sequence and the barcode were both used to determine which sequences were duplicates. (See Pet. 23.)

Petitioner cites Dr. Metzker’s testimony in support. (See Ex. 1003 ¶¶ 87–90.) Dr. Metzker testifies that the reference to “redundant

hypomethylated sequences” along with identical barcodes indicate that both the identical target sequence and the identical barcodes are used to determine which sequences were duplicates. (*See id.* ¶ 90.)

Patent Owner disputes this interpretation of McCloskey, arguing that McCloskey’s disclosure of “redundant hypermethylated sequences with identical barcodes and methylation patterns” and “redundant hypomethylated sequences with identical barcodes” provides no explanation regarding how either of these disclosures would render the claimed limitation anticipated. (*See Prelim. Resp.* 10.) Patent Owner argues that McCloskey fails to disclose a “process of detecting duplicates based on both an identifier site *and* at least a portion of the nucleic acid fragment.” (*Id.*) Patent Owner argues that Petitioner’s arguments about barcodes that were “identical to sequences already obtained” or “already seen” indicate that duplicates were identified based on the “barcode that was identical” or the “already seen barcode” alone, not on the use of a portion of the target sequence and barcode in combination. (*Id.* at 11 (quoting Ex. 1005 ¶ 53 (also citing Pet. 23; Ex. 1005 ¶ 63).))

We are not persuaded at this point in the proceeding by Patent Owner’s arguments because Dr. Metzker testifies that McCloskey refers to the redundant hypermethylated and hypomethylated sequences, which one of ordinary skill in the art would have understood to mean both the identical target sequence and the identical barcode to be used to identify duplicates. (*See Ex.* 1003 ¶ 90.) At this point in the proceeding, in the absence of contradictory evidence, we are persuaded that Petitioner has provided

sufficient evidence that McCloskey teaches “identifying sequence reads with identical identifier and target sequences as duplicates.”

On the record at this stage of the proceeding, Petitioner has demonstrated a reasonable likelihood that at least claim 1 of the ’241 patent is anticipated by McCloskey. Because we find a reasonable likelihood that Petitioner would prevail at trial as to at least one asserted claim (and because, as discussed below, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d)), we institute on all claims and all grounds asserted in the Petition. *See* 35 U.S.C. § 314(a); *SAS Inst.*, 584 U.S. at 362.

3. Dependent Claims

Petitioner presents arguments and evidence regarding anticipation of claims 2, 3, 5–7, 9, 10, and 13–16 by McCloskey. (*See* Pet. 23–30.) At this point in the proceeding, Patent Owner argues only that Petitioner’s challenges to the dependent claims fail because the challenge to claim 1 fails. (*See* Prelim. Resp. 12.)

As discussed above, we determine that Petitioner has shown that there is a reasonable likelihood that at least claim 1 is unpatentable under 35 U.S.C. § 102(a) over McCloskey and, accordingly, we institute review on all challenged claims. The parties will have additional opportunities to address the dependent claims after institution.

E. Ground II - Anticipation by Porreca

Petitioner challenges claims 1–3, 5–7, 9, 10, and 13–16 as being anticipated by Porreca under 35 U.S.C. § 102(a). (*See* Pet. 30–45.)

1. Porreca

Porreca is directed to methods of genotyping subjects and identifying and addressing different sources of ambiguity and error in genetic analyses. (*See* Ex. 1006 ¶¶ 6, 7.) In one method, Porreca teaches using “differentiator tag sequences,” which “uniquely tag individual nucleic acid molecules.” (*Id.* ¶ 23.) Porreca teaches that

[a]spects of the invention relate to providing sequence tags (referred to as differentiator tags) that are useful to determine whether target nucleic acid sequences identified in an assay are from independently isolated target nucleic acids or from multiple copies of the same target nucleic acid molecule (e.g., due to bias in a preparative step, for example, amplification).

(*Id.* ¶ 24.)

Porreca refers to combining or “collapsing” PCR duplicates into a single sequence. (*Id.* ¶ 298.) Specifically, Porreca explains:

For any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’ into a single read before consensus basecalls are determined. This will cancel the effect of bias on consensus basecall accuracy. FIG. 5 depicts a method for making diploid genotype calls in which repeat target:differentiator tag combination are collapsed.

(*Id.*) Figure 5 of Porreca is depicted below.

FIGURE 5

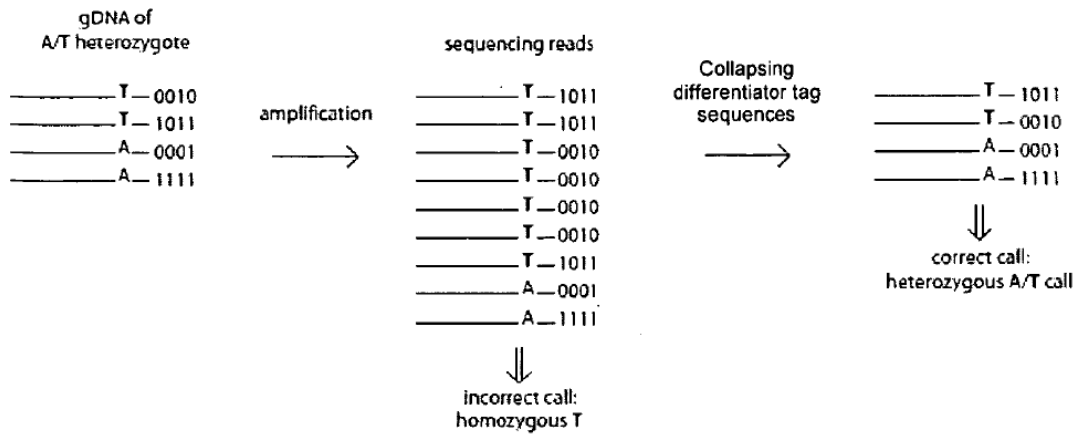


Figure 5 depicts a non-limiting method for genotyping based on target and differentiator tag sequences. (*See id.* ¶ 86.) Figure 5 uses four lines to indicate four different genomic DNAs (indicated by a single “T” or “A” base and labeled “gDNA of A/T heterozygote” as a group), with each line including a differentiator tag of 1s and 0s. In Figure 5, an arrow (labeled “amplification”) points from these four lines to nine lines, with repeats of the differentiator tags and the single “T” or “A” bases. Figure 5 includes another arrow (labeled “collapsing differentiator tag sequences”) pointing to four lines, each labeled with the original four differentiator tags and the original single “T” and “A” bases. Porreca explains that “[f]or any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’ into a single read before consensus basecalls are determined.” (*Id.* ¶ 298.)

Porreca states:

The skilled artisan will appreciate that as part of a MIP library preparation process, adapters may be ligated onto the ends of the molecules of interest. Adapters often contain PCR primer

sites (for amplification or emulsion PCR) and/or sequencing primer sites. In addition, barcodes may be included, for example, to uniquely identify individual samples (e.g., patient samples) that may be mixed together. (See, e.g., US PTO Publication Number US 2007 /0020640A1 (McCloskey et al.)

(*Id.* ¶ 149.)

2. Analysis of Claim 1

a. Preamble [1p]: A method for detecting duplicate sequencing reads”

Petitioner argues that Porreca teaches “the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules.” (Ex. 1006 ¶ 23; *see* Pet. 30.) Petitioner argues further that Porreca teaches that “[e]ach nucleic acid molecule may be tagged with a unique differentiator tag,” which allows for the determination of “whether target nucleic acid sequences identified in an assay are from independently isolated target nucleic acids or from multiple copies of the same target nucleic acid molecule (e.g., due to bias in a preparative step, for example, amplification).” (Ex. 1006 ¶¶ 24, 142; *see* Pet. 30.) Petitioner highlights the teachings in Porreca that differentiator tags are attached to nucleic acid fragments before amplification, allowing identical sequences bearing the same differentiator tag to be identified as PCR duplicates of each other. (*See* Pet. 30 (citing Ex. 1006, Fig. 5.)

In support of this argument, Petitioner cites the testimony of Dr. Metzker that Porreca teaches that a differentiator tag, which corresponds to the “identifier” recited in the claims of the ’241 patent, may be used to identify multiple copies of the same nucleic acid sequence, i.e., duplicate

sequences, by uniquely tagging individual nucleic acid molecules. (Ex. 1003 ¶¶ 114–115.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence about the preamble of claim 1 and Porreca.

b. Element [1a]: “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor,”

Petitioner argues that Porreca teaches ligating an adaptor comprising a differentiator tag sequence to a sequence of interest. (Pet. 31–32 (citing Ex. 1006 ¶ 150, Fig. 4C).) Petitioner cites the teaching in Porreca that “[t]he actual incorporation of the random differentiator tag sequences can be performed through various methods known in the art. For example, nucleic acids comprising differentiator tag sequences may be incorporated by ligation,” which is depicted in Figure 4C. (Ex. 1006 ¶ 150; *see id.* ¶ 85, Fig. 4C.) Figure 4C is reproduced below:

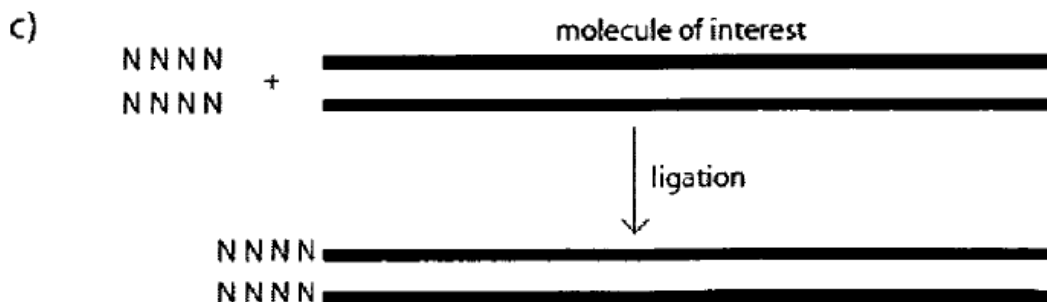


Figure 4C depicts a sequence “NNNN” and a “molecule of interest,” which is shown to be joined by “ligation.” Figure 4C is included in the description of Figure 4 as depicting “various non-limiting methods for combining differentiator tag sequence and target sequences (NNNN depicts a

differentiator tag sequence)[.]” (*Id.* ¶ 85.) Petitioner cites further to the disclosure in Porreca of a differentiator tag that can be included as part of a sequencing adaptor and the disclosure of the product resulting from the ligation of this adaptor being amplified by PCR to produce amplicons. (*See* Pet. 31–32 (citing Ex. 1006 ¶ 150).)

Petitioner cites to Dr. Metzker’s testimony that these portions of Porreca disclose ligating an adaptor to each of a plurality of nucleic acid fragments and amplifying the adaptor-ligated fragments into amplicons. (*See* Ex. 1003 ¶¶ 116–117.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this element of claim 1 and Porreca.

c. Element [1b]: “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment;”

Petitioner argues that Porreca discloses an adaptor comprising a unique identifier having from about 1 to about 8 nucleotides, as required in claim 1, because it teaches “differentiator tags” that “may be created by using degenerate, random-sequence polynucleotides of defined length,” and may be “up to 5 . . . up to 8 . . . up to 25, or more nucleotides in length.” (Ex. 1006 ¶¶ 141, 143; *see* Pet. 32–33.) Petitioner compares this disclosure to the differentiator tags provided in the ’241 patent, which are described as being “a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” (Ex. 1001, 4:45–47; *see* Pet. 32.) Petitioner argues that these differentiator tags are used to uniquely tag each nucleic acid. (*See* Pet. 33.) Petitioner cites to the discussion in Porreca of

preparing libraries wherein, “each nucleic acid molecule may be tagged with a unique differentiator tag sequence in a configuration that permits the differentiator tag sequence to be sequenced along with the target nucleic acid sequence of interest,” creating a large library of unique differentiator tag sequences is created. (Ex. 1006 ¶¶ 142, 143; *see* Pet. 33.)

Dr. Metzker testifies that these disclosures of Porreca teach a method using an identifier tag comprising random bases to identify duplicate sequencing reads, as required in claim 1, and that because Porreca teaches differentiator tag sequences having 25 nucleotides, it provides for 4^{25} or 1.125×10^{15} unique identifiers. (*See* Ex. 1003 ¶¶ 118–119 (citing Ex. 1006 ¶ 23).)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this element of claim 1 and Porreca.

d. Element [1c]: “sequencing the amplicons to generate sequence reads that include identifier and target sequences”

Petitioner argues that Porreca teaches sequencing amplicons to produce sequences reads that include the identifier and the target sequence because it teaches that the amplicons created with differentiator tags are sequenced and that the resulting sequence reads contain both differentiator and target sequences. (*See* Pet. 33–34 (citing Ex. 1006 ¶ 142).)

Specifically, Porreca teaches:

During a library preparation process, each nucleic acid molecule may be tagged with a unique differentiator tag sequence in a configuration that *permits the differentiator tag sequence to be sequenced along with the target nucleic acid*

sequence of interest (the nucleic acid sequence for which the library is being prepared, e.g., a polymorphic sequence).”

(Ex. 1006 ¶ 142 (emphasis added).) Petitioner cites Porreca for its teaching that “[i]n some embodiments, the differentiator tag sequence permits the detection of bias based on the frequency with which pairs of differentiator tag and target sequences are observed in a sequencing reaction” and that “[t]he sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence.” (*Id.* ¶¶ 138, 150; *see* Pet. 34.) Petitioner argues that Figure 5 of Porreca also shows this element by depicting a method for genotyping based on target and differentiator tag sequences. (Pet. 34 (citing Ex. 1006 ¶ 148).)

Dr. Metzker testifies that these portions of Porreca disclose “sequencing the amplicons to produce sequence reads that include identifier and target sequences,” as required in claim 1. (*See* Ex. 1003 ¶¶ 120–121.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence this element of claim 1 and Porreca.

e. Element [1d]: “identifying sequence reads with identical identifier and target sequences as duplicates.”

Petitioner argues that Porreca teaches identifying sequence reads with identical identifier and target sequences as duplicates because it teaches using differentiator tags to determine whether particular nucleic acid molecules are copies from PCR amplification and, thus, are duplicates. (*See* Pet. 34–35.) Petitioner cites to the teaching in Porreca that

sequence tags (referred to as differentiator tags) . . . are useful to determine whether target nucleic acid sequences identified in an assay are from independently isolated target nucleic acids or from multiple copies of the same target nucleic acid molecule

(e.g., due to bias in a preparative step, for example, amplification).

(Ex. 1006 ¶ 24; Pet. 34–35.) Petitioner cites further to Figure 5 and the description that it depicts “a non-limiting method for genotyping based on target and differentiator tag sequences, [wherein s]equencing reads of target and differentiator tags sequences are collapsed to make diploid genotype calls.” (Ex. 1006 ¶ 148; *see* Pet. 36.) According to Petitioner, one of ordinary skill in the art would have understood that the depiction of at “T” represents a single nucleotide of the target sequences show in Figure 5 and that, although not shown, the rest of the target sequence in the collapsed reads would have also been identical because collapsing a read means removing sequences having the same target and differentiator tag sequences. (*See* Pet. 36 (citing Ex. 1003 ¶¶ 122–124).)

Dr. Metzker testifies that Porreca discloses this element because it teaches that differentiator tags can be used to identify whether particular nucleic acid molecules are copies of the same molecule that result from the PCR amplification process (i.e., duplicates). (*See* Ex. 1003 ¶ 122.) He testifies further that one of ordinary skill in the art would have understood that in order to have “multiple copies of the same target nucleic acid molecule,” the target nucleic acid sequence must be identical and that Figure 5 of Porreca demonstrates that sequences having the same target nucleic acid sequence and differentiator tag are identified and collapsed. (*Id.* ¶ 123 (emphasis omitted).) Dr. Metzker testifies that in Figure 5, two sequences labeled “T-1011” are identified as duplicates and collapsed into a single read

and that three sequences labeled “T-0010” are identified as duplicates and collapsed into a single read. (*Id.* ¶ 124.) Dr. Metzker testifies further:

One of ordinary skill in the art would have known that the “T” represents a single nucleotide of the target sequence shown in Figure 5 of the ’202 Patent Pub. (Porreca). One of ordinary skill in the art would have further known that, while not shown, the rest of the target sequence in the collapsed reads is also identical, as collapsing a read means removing sequences having the same target and differentiator tag sequences.

(*Id.*) Dr. Metzker cites to the instructions, regarding Figure 5, in Porreca: “For any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’ into a single read before consensus basecalls are determined.” (Ex. 1006 ¶ 298; *see* Ex. 1003 ¶ 124.)

Patent Owner argues that the Petition fails to show that Porreca discloses identifying duplicate sequencing reads based on an identifier and at least a portion of the target sequence; according to Patent Owner, the Petition points to only “vague and ambiguous disclosures and gloss[es] over the gaps with conclusory expert testimony” instead. (*See* Prelim. Resp. 12.) Patent Owner argues further that Figure 5 of Porreca, which Petitioner cites, “does not disclose the process of the level of detail that Petitioner claims, nor does it disclose the required elements of the claim 1.” (*Id.* at 14.) According to Patent Owner, Figure 5 shows only a two-step process, wherein sequences are grouped based on an identifier site and then collapsed based on a single nucleotide. (*See id.*) Patent Owner also argues that Figure 5 does not provide further explanation of what is included in the disclosed “differentiator tag.” (*See id.*)

Patent Owner argues further that it is not clear from Figure 5 if both the identifier site and the portion of the target sequence are used in conjunction to identify duplicates, as Patent Owner asserts is required in claim 1 because Figure 5 does not illustrate any portion of the target sequence being used to identify duplicates. (*See id.* at 13–14.) According to Patent Owner, “[a]ll a [person of ordinary skill in the art] can glean from Figure 5 is that after being grouped based on identifier site, sequences with the same single nucleotide – not sequence with identical portions of the target sequence – are then collapsed.” (*See id.* at 15.)

Patent Owner disputes Petitioner’s argument that “[a] POSA would have further understood that, while not shown [in Figure 5 of Porreca], the rest of the target sequence in the collapsed reads is also identical, as collapsing a read means removing sequences having the same target and differentiator tag sequences.” (Pet. 36, *see* Prelim. Resp. 15.) According to Patent Owner, Dr. Metzker’s testimony cited by Petitioner in support is only conclusory and merely repeats the Petition verbatim, without any underlying reference. (*See* Prelim. Resp. 15.)

We are not persuaded at this stage by Patent Owner’s arguments. Dr. Metzker testifies that one of ordinary skill in the art would have known that in Figure 5 the “T” represents a single nucleotide of the target sequence, but that “[o]ne of ordinary skill in the art would have further known that, while not shown, the rest of the target sequence in the collapsed reads is also identical, as collapsing a read means removing sequences having the same target and differentiator tag sequences.” (Ex. 1003 ¶ 124.) Patent Owner argues that Dr. Metzker’s testimony is merely conclusory, but Patent Owner

does not substantively dispute it. At this point in the proceeding, we are persuaded that Petitioner has provided sufficient evidence that Porreca teaches the limitation of “identifying sequence reads with identical identifier and target sequences as duplicates.”

On the record at this stage of the proceeding, Petitioner has demonstrated a reasonable likelihood that at least claim 1 of the ’241 patent is anticipated by Porreca.

3. Dependent Claims

Petitioner presents arguments and evidence regarding anticipation of claims 2, 3, 5–11, and 13–16 by Porreca. (*See* Pet. 36–45.) At this point in the proceeding, Patent Owner argues only that Petitioner’s challenges to the dependent claims fail because the challenge to claim 1 fails. (*See* Prelim. Resp. 16.)

As discussed above, we determine that Petitioner has shown that there is a reasonable likelihood that at least claim 1 is unpatentable under 35 U.S.C. § 102(a) over Porreca and, accordingly, we institute review on all challenged claims. The parties will have additional opportunities to address the dependent claims after institution.

F. Ground III – Anticipation by Schmitt

Petitioner challenges claims 1–3, 5–12, 14, and 15 as being anticipated by Schmitt under 35 U.S.C. § 102(a). (*See* Pet. 45–63.)

1. Schmitt

Schmitt is directed to addressing errors in next generation sequencing techniques. (*See* Ex. 1007, abstr.) Schmitt teaches using a single molecule

identifier (“SMI”) adaptor molecule attached to a DNA fragment to provide a unique identifier. (*See id.* ¶ 9.) Schmitt states:

Because the use of SMI tags (or “double-stranded SMI sequences”) allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence. This approach would thereby minimize the loss of data by overcoming the intrinsic limitations of using shear points to identify PCR duplicates.

(*Id.* ¶ 85.) Schmitt further refers to steps in sequencing analyses to uniquely identify sequenced DNA fragments by including a step “to filter out PCR duplicates.” (*Id.*) To that end, Schmitt teaches that “[r]eads having common (i.e., identical) SMI sequences were grouped together, and were collapsed to generate a consensus read.” (*Id.* ¶ 96 (providing a data processing workflow, including the steps of “6. Group together reads which have identical 24 nt SMIs. 7. Collapse to SMI consensus reads, scoring only positions with 3 or more SMI duplicates and >90% sequence identity among the duplicates.”).)

2. Analysis of Claim 1

a. Preamble [1p]: A method for detecting duplicate sequencing reads, the method

Petitioner argues that Schmitt teaches that a single molecule identifier (SMI) “may be used in methods for unambiguous identification of PCR duplicates.” (Ex. 1007 ¶ 85; Pet. 45.) Schmitt teaches that “the SMI tags were used to group together PCR duplicates that arose from individual single-stranded DNA molecules and to create a consensus sequence from the family of duplicates” and that “[t]he improved sequence coverage arose

from use of the SMI to identify PCR duplicates” because of the limited use of other methods. (Ex. 1007 ¶ 104 (Example 1); Pet. 45.)

Dr. Metzker testifies that these portions of Schmitt disclose amplifying adaptor-ligated fragments into amplicons. (*See* Ex. 1003 ¶ 148.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding the preamble of claim 1 and Schmitt.

b. Element [1a]: “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor,”

Petitioner argues that Schmitt discloses amplifying adaptor-ligated fragments into amplicons in its teaching of a method that includes “ligating a double-stranded target nucleic acid molecule to at least one SMI adaptor molecule to form a double-stranded SMI-target nucleic acid complex; amplifying the double-stranded SMI-target nucleic acid complex, resulting in a set of amplified SMI-target nucleic acid products; and sequencing the amplified SMI-target nucleic acid products.” (Ex. 1007 ¶ 10; *see* Pet. 45–46.) Petitioner cites to another teaching in Schmitt of an embodiment wherein after ligating a double-stranded target nucleic acid molecule to an SMI adaptor molecule, “[t]he double-stranded target nucleic acid complex is then amplified by a method known in the art (e.g., a PCR or non-PCR method known in the art), resulting in a set of uniquely labeled, amplified SMI-target nucleic acid products.” (Ex. 1007 ¶ 74; *see* Pet. 46.) Petitioner argues further that Schmitt Example 1 also discloses the claimed amplicons. (*See* Pet. 46 (citing Ex. 1007 ¶¶ 89–95).)

Dr. Metzker testifies that these portions of Schmitt disclose amplifying adaptor-ligated fragments into amplicons. (*See* Ex. 1003 ¶¶ 149–152.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this limitation of claim 1 and Schmitt.

c. Element [1b]: “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment;”

Petitioner argues that the SMI of Schmitt, which is described as being approximately 3 to 20 nucleotides in length, teaches the unique identifier recited in claim 1. (*See* Pet. 46–47 (citing Ex. 1007 ¶¶ 12, 26).) Petitioner also cites the teaching in Schmitt that

[b]ecause the use of SMI tags (or ‘double-stranded SMI sequences’) allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence. This approach would thereby minimize the loss of data by overcoming the intrinsic limitations of using shear points to identify PCR duplicates.

(Ex. 1007 ¶ 85; *see* Pet. 47–48.) Petitioner argues further that Schmitt Example 1 also discloses identifier sites comprising a plurality of nucleotides unique to the amplified fragment. (*See* Pet. 48 (citing Ex. 1007 ¶¶ 88–95, 98–99, 101, 104).)

Dr. Metzker testifies that this portion of Schmitt teaches an adaptor comprising a unique identifier as recited in claim 1. (*See* Ex. 1003 ¶¶ 153–156.)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding this element of claim 1 and Schmitt.

d. Element [1c]: “sequencing the amplicons to generate sequence reads that include identifier and target sequences”

Petitioner argues that Schmitt teaches “a method of obtaining the sequence of a double-stranded target nucleic acid is provided (also known as Duplex Consensus Sequencing or DCS)” (Ex. 1007 ¶ 10; *see* Pet. 48.) Petitioner cites the further teachings of Schmitt that sequencing the “amplified SMI-Target nucleic acid products” can be done with a number of suitable methods and platforms. (Ex. 1007 ¶ 74; *see* Pet. 41–48.)

Petitioner argues further that Schmitt discloses sequencing both the identifier and the target sequence, for example in Figures 3a–c and 4, which are described as showing sequence reads of fragments with a unique set of SMI tags. (*See* Pet. 49 (citing Ex. 1007 ¶¶ 14, 15).) Petitioner cites further to the disclosure in Schmitt that

[f]ollowing tagging with a double-stranded SMI and PCR amplification, a family of molecules is obtained that arose from a single DNA molecule; members of the same PCR “family” are then grouped together by virtue of having a common (i.e., the same) SMI tag sequence. The sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.

(Ex. 1007 ¶ 99; *see* Pet. 50.)

Dr. Metzker testifies:

One of ordinary skill in the art would have understood that the “sequences of uniquely tagged PCR duplicates” refers to nucleic acid products having identical target nucleic acid

sequences, as the nucleic acid products would not be referred to as “PCR duplicates” if they were not identical. Furthermore, Example 1’s protocol in the ’389 PCT Appl. (Schmitt) “was used to sequence DNA isolated from normal colonic mucosa” and included sequence reads from tagged, amplicons with both SMI and target nucleic acid sequences.

(Ex. 1003 ¶ 160 (quoting Ex. 1007 ¶¶ 103–105) (emphasis omitted).)

At this point in the proceeding, Patent Owner does not contest Petitioner’s arguments and evidence regarding the requirement for sequencing amplicons in claim 1 and Schmitt.

e. Element [1d]: “identifying sequence reads with identical identifier and target sequences as duplicates.”

Petitioner argues that Schmitt teaches identifying sequence reads with identical identifiers and target sequences as duplicates because it teaches that “SMI adaptor molecules may be used in methods for unambiguous identification of PCR duplicates.” (Ex. 1007 ¶ 85; *see* Pet. 50–51.)

Petitioner cites further to the teaching in Schmitt that “[b]ecause the use of SMI tags (or ‘double-stranded SMI sequences’) allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence.” (Ex. 1007 ¶ 85; *see* Pet. 51.) Petitioner cites Dr. Metzker’s testimony that one of ordinary skill in the art would have understood “true PCR duplicates” to have target nucleic acid sequences that are identical in addition to having the same SMI sequence. (*See* Pet. 50–52 (citing Ex. 1003 ¶¶ 161–162).)

In addition, Petitioner cites the teaching of Schmitt that “members of the same PCR ‘family’ are then grouped together by virtue of having a

common (i.e., the same) SMI tag sequence. The sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.” (Ex. 1007 ¶ 99; *see* Pet. 51–52.) Again, Petitioner cites Dr. Metzker’s testimony that one of ordinary skill in the art would have known that the target sequences in the duplicates are identical because that is required to generate a consensus read and that, thus, “[t]hese disclosures . . . show that both the target sequence and SMI sequence are used to identify PCR duplicates in [Schmitt].” (Ex. 1003 ¶ 162; *see* Pet. 50–52.)

Patent Owner argues that Schmitt fails to teach identifying and removing duplicate sequences based on both the identifier and target sequence, as Patent Owner asserts is required in claim 1. (*See* Prelim. Resp. 16–18.) According to Patent Owner, Schmitt uses the SMI tag alone to identify duplicates because claim 30 of Schmitt recites “grouping the sequenced SMI-target nucleic acid products into families of paired target nucleic acid strands based on a common set of SMI sequences.” (Ex. 1007 p. 56 (claim 30); *see* Prelim. Resp. 16–17.) Patent Owner argues that other disclosures of Schmitt, cited by Petitioner, teach grouping sequence reads together based on identical SMIs. (*See* Prelim. Resp. 17 (citing Ex. 1007 ¶ 96 (“6. Group together reads which have identical 24 nt SMIs.”)).)

According to Patent Owner, Schmitt would also discourage one of ordinary skill in the art from using anything related to the target sequence when identifying duplicates because it discloses challenges involved with using a surrogate of a portion of the target sequence, specially sheared DNA ends. (*See id.* at 17–18 (citing Ex. 1007 ¶ 104).)

None of Patent Owner's arguments contradicts the evidence Petitioner cites to show that Schmitt teaches using both the identifier and a portion of the target sequence read to identify duplicate reads. Patent Owner does not dispute that the evidence cited by Petitioner, such as Figures 3a–c and 4 of Schmitt and Dr. Metzker's supporting testimony, teach sequencing of the target sequence along with the identifier to analyze sequence reads and identify duplicates. (*See* Pet. 41–44 (citing Ex. 1007 ¶¶ 10, 14, Figs. 3, 4; Ex. 1003 ¶¶ 127–128).) Thus, Patent Owner does not dispute the evidence that, as discussed above, we found persuasive of a reasonable likelihood that Petitioner would prevail.

Furthermore, merely because Schmitt discusses the advantages of using SMIs to identify PCR duplicates over other methods, at this point in the proceeding we are not persuaded that Schmitt discourages the determination of duplicates on the at least a portion of the target sequence in addition to an identifier, as Patent Owner argues. (*See* Prelim. Resp. 20–21.) In contrast, as Petitioner notes, Schmitt teaches reading target sequences, wherein “[t]he sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.” (Ex. 1007 ¶ 99.) We are not persuaded at this time that comparing two different methods of identifying duplicates indicates the use of SMIs excludes also using at least a portion of the target sequence.

On the record at this stage of the proceeding, Petitioner has demonstrated a reasonable likelihood that at least claim 1 of the '241 patent is anticipated by Schmitt.

3. Dependent Claims

Petitioner presents arguments and evidence regarding anticipation of claims 2, 3, 5–12, 14, and 15 by Schmitt. (*See* Pet. 52–61.) At this point in the proceeding, Patent Owner argues only that Petitioner’s challenges to the dependent claims fail because the challenge to claim 1 fails. (*See* Prelim. Resp. 18.)

As discussed above, we determine that Petitioner has shown that there is a reasonable likelihood that at least claim 1 is unpatentable under 35 U.S.C. § 102(a) over Schmitt and, accordingly, we institute review on all challenged claims. The parties will have additional opportunities to address the dependent claims after institution.

G. Grounds IV and V – Obviousness over Porreca and Illumina 2008 or Schmitt and Illumina 2008

Petitioner challenges claim 4 as being obvious over Porreca and Illumina 2008 and as being obvious over Schmitt and Illumina 2008 under 35 U.S.C. § 103. (*See* Pet. 61–63.)

1. Illumina 2008

Illumina 2008 is directed to next-generation sequencing sample preparation methods. (*See* Ex. 1008.) Illumina 2008 provides sample strategies for multiplexing to increase scalability, while maintaining low error rates. (*See id.* at abstr.)

2. Analysis of Claim 4

Claim 4 recites the method of claim 1, “wherein the identifier site is sequenced separately from the target sequence.” (Ex. 1001, 25:48–49.)

Relying on Dr. Metzker’s testimony, Petitioner argues that one of ordinary skill in the art would have known that, due to the limited amount of

bases that can be sequenced in a read, sequencing the identifier separately from the target sequence would allow sequencing more of the target sequence, which would be more efficient and would have provided motivation to do so. (*See* Pet. 61–62 (citing Ex. 1003 ¶¶ 184–185).) Petitioner cites to Illumina 2008 for its teaching that “[s]ample multiplexing involves a total of three sequence reads, including a separate index read,” which accompanies Figure 1 showing the sequencing of a DNA insert in a separate read from an attached index sequence. (Ex. 1008, 1; *see* Pet. 62.) Petitioner argues that this disclosure demonstrates that it was known that an adaptor could be sequenced separately from a target sequence. (*See* Pet. 62–63 (citing Ex. 1003 ¶¶ 184–185).)

Petitioner argues further that because Porreca and Schmitt explicitly refer to the Illumina platform, those of ordinary skill in the art would have had a reason to combine their teachings with Illumina 2008. (*See* Pet. 63 (citing Ex. 1006 ¶ 295, Ex. 1007 ¶¶ 74, 86).) Petitioner also cites to the teaching in Schmitt that “[c]ombining information regarding the shear points of DNA with the SMI tag sequence would allow a shorter SMI to be used, thus minimizing loss of sequencing capacity due to sequencing of the SMI itself.” (Ex. 1007 ¶ 83; *see* Pet. 63.)

Patent Owner argues that Petitioner fails to show that Illumina 2008 discloses a method of using both an identifier and a target sequence to identify duplicate sequencing reads, as required by claim, to cure the deficiencies of Porreca and Schmitt that Patent Owner asserts. (*See* Prelim. Resp. 18–19.)

Because, as discussed above, Petitioner presents sufficient evidence showing that Porreca and Schmitt disclose using both an identifier and a target sequence to identify duplicate sequencing reads, we are not persuaded at this stage by Patent Owner's argument regarding Illumina 2008 failing to cure a deficiency. Instead, we are persuaded that Petitioner provides sufficient evidence that there is a reasonable likelihood that claim 4 would have been obvious over Porreca and Illumina 2008 or over Schmitt and Illumina 2008.

H. Grounds VI and VII - Obviousness over Porreca and Illumina 2008 or Schmitt and Illumina 2008

Petitioner challenges claim 8 as being obvious over Porreca and Illumina 2008 or over Schmitt and Illumina 2008 under 35 U.S.C. § 103. (See Pet. 64–66.)

Claim 8 depends from independent claim 1 and dependent claim 7. More specifically, claim 8 recites the “method of claim 7, wherein the primer binding site is a universal target sequencing primer binding site,” and claim 7 recites the “method of claim 1, wherein each adaptor includes a primer binding site.” (Ex. 1001, 25:54–57.)

Petitioner argues that Illumina 2008 discloses the “Rd1 SP” and “Rd2 SP” primers, which are used in the Illumina system as part of the adaptors and were known to be universal sequencing primer binding sites, citing to Dr. Metzker's testimony in support. (See Pet. 64–65 (citing Ex. 1008, 1 (Figure 1 legend); Ex. 1003 ¶¶ 186–190).) Petitioner cites Metzker 2010,⁴

⁴ Metzker, “Sequencing technologies – the next generation,” 11 NATURE REVIEWS GENETICS 31 (2010) (Ex. 1010).

which discusses using universal sequencing primers with the Illumina platform. (*See id.* at 65–66 (citing Ex. 1010, 32).)

Patent Owner argues that Petitioner fails to show that Illumina 2008 discloses a method of using both an identifier and a target sequence to identify duplicate sequencing reads, as required by claim, to cure the deficiencies of Porreca and Schmitt that Patent Owner asserts. (*See Prelim. Resp.* 19–20.)

Because, as discussed above, Petitioner present sufficient evidence to show that Porreca and Schmitt disclose using both an identifier and a target sequence to identify duplicate sequencing reads, we are not persuaded at this point in the proceeding by Patent Owner’s argument regarding Illumina 2008 failing to cure a deficiency. Instead, we are persuaded that Petitioner provides sufficient evidence that there a reasonable likelihood that claim 8 would have been obvious over Porreca and Illumina 2008 or over Schmitt and Illumina 2008.

I. Ground VIII – Obviousness over Porreca and Li 2009

Petitioner challenges claim 12 as being rendered obvious by Porreca and Li 2009 under 35 U.S.C. § 103. (*See Pet.* 66–68.)

1. Li 2009

Li 2009 is directed to next-generation sequencing sample preparation methods. (*See Ex.* 1011.) Li 2009 discloses an alignment format called “Sequence Alignment/Map (SAM)” and discusses “SAMtools” software that provide universal tools for processing read alignments. (*See id.* at 1 (abst.).)

2. *Analysis of Claim 12*

Claim 12 depends from claim 1 and adds “further comprising determining the genomic start position for each sequencing read.” (Ex. 1001, 26:38–39.) Petitioner argues that one of ordinary skill in the art would have considered it obvious to use the SAMtools of Li 2009 with the methods disclosed in Schmitt because Schmitt teaches that “PCR duplicates were filtered out with *samtools rmdup*, a standard tool which uses the shear points of DNA molecules to identify PCR duplicates, as molecules arising from duplicated DNA will have shared shear points.” (Ex. 1007 ¶ 103 (emphasis added); *see* Pet. 67.) Petitioner cites other details of the SAM format taught in Li 2009 that demonstrate determining the genomic start position for a sequence read. (*See* Pet. 67 (citing Ex. 1011, 2 (“The coordinate shown in SAM is the position of the first aligned base. The CIGAR string for this alignment contains a P (padding) operation which correctly aligns the inserted sequences.”).)

Petitioner argues that one of ordinary skill in the art would have been motivated to use SAMtools as taught in Li 2009 in the methods of Porreca because both of these references are directed to the same field (next generation sequencing) and are complementary to one another, with SAMtools commonly being used in such analysis. (*See* Pet. 67–68 (citing Ex. 1007 ¶ 103; Ex. 1003 ¶¶ 191–196.)

Dr. Metzker testifies that “SAMtools was a well-known tool that provides a common alignment format for NGS sequence reads mapped to a reference genome sequence” and that one of ordinary skill in the art would have reasonably expected success in combining the teachings of Porreca and

Li 2009 to determine the genomic start position for each sequencing read.
(*See* Ex. 1003 ¶ 196 (citing Ex. 1011, 2).)

Patent Owner argues that Petitioner fails to show that Li 2009 discloses a method of using both an identifier and a target sequence to identify duplicate sequencing reads, as required by claim 1, instead showing only that Li 2009 relates to the “SAMtools” software package that provides for universal tools for processing read alignments. (*See* Prelim. Resp. 20.) Patent Owner argues that “Petitioner makes no attempt to cure the deficiencies of Porreca regarding this limitation” and makes no attempt to show how combining the cited references arrives at the claimed limitation of using both an identifier and a target sequence to identify duplicate sequencing reads. (*See id.* at 21.)

Because, as discussed above, Petitioner present sufficient evidence to show that Porreca discloses using both an identifier and a target sequence to identify duplicate sequencing reads, we are not persuaded at this point in the proceeding by Patent Owner’s argument regarding Li 2009 failing to cure a deficiency. Instead, we are persuaded that Petitioner provides sufficient evidence that there is a reasonable likelihood that claim 12 would have been obvious over Porreca and Li 2009.

J. Discretionary Denial under 35 U.S.C. 325(d)

Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. 35 U.S.C. § 325(d) states, in pertinent part,

In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because,

the same or substantially the same prior art or arguments previously were presented to the Office.

The Board uses a two-part framework for evaluating arguments under § 325(d):

- (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.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). “[T]he *Becton, Dickinson* factors provide useful insight into how to apply the framework under 35 U.S.C. § 325(d).” *Id.* at 9 (footnote omitted). The non-exclusive *Becton, Dickinson* factors are:

- (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 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph). *Becton, Dickinson* factors (a), (b), and (d) relate to the first part of the *Advanced Bionics* framework (whether the same or substantially the same art or arguments previously were presented to the Office), and *Becton, Dickinson* factors (c), (e), and (f) relate to the second part of that framework (previous Office error). *Advanced Bionics*, Paper 6 at 9–11. Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.*

Under § 325(d), the art and arguments must have been previously presented to the Office during proceedings, such as examination of the underlying patent application, pertaining to the challenged patent. *Id.* at 7. Previously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement (“IDS”), in the prosecution history of the challenged patent. *Id.* at 7–8.

In the underlying prosecution here, the Examiner rejected the challenged claims over Samuels,⁵ McCloskey 2007,⁶ and Illumina 2008.

⁵ US 2012/0220494 A1, published August 30, 2012 (Ex. 2018).

⁶ McCloskey et al., “Encoding PCR Products with Batch-stamps and Barcodes,” 45 BIOCHEM. GENET. 761–67 (2007) (Ex. 1015).

(Ex. 1013, 79–81.) Petitioner argues that Porreca, Schmitt, and McCloskey were never before the Examiner and that although Illumina 2008 was cited, it was cited only in combination with the Samuels reference. (*See* Pet. 70 (citing Ex. 1013, 79–81).) Petitioner argues further that it cites Illumina 2008 only in the grounds for two dependent claims and that, because Porreca and Schmitt were not previously presented to the Office, the Examiner could not have considered the arguments Petitioner presents here. (*See id.* at 70–71, n. 13.) Accordingly, Petitioner argues that the first part of the *Advanced Bionics* framework is not met and, thus, discretionary denial under 35 U.S.C. § 325(d) is not justified. (*See id.* at 70–71.)

Patent Owner argues that Porreca, Schmitt, and McCloskey disclose substantially the same information as Samuels and McCloskey 2007 and Petitioner has not identified any material error by the Examiner. (*See* Prelim. Resp. 22–29.) Specifically, Patent Owner argues that McCloskey and McCloskey 2007 contain some overlapping disclosures, specifically adaptors including “batch-stamps” and random “barcodes.” (*See id.* at 24–25 (citing Ex. 1015, 3, Fig. 1).) Patent Owner argues that during prosecution the Examiner rejected the pending claims over these disclosures in McCloskey 2007. (*See id.* at 25 (citing Ex. 1013, 80).) Patent Owner argues further that the differentiator tags in Porreca are similar in function and structure to those in McCloskey 2007 and that they are described in McCloskey 2007 as being used to identify duplicate sequence reads. (*See id.* at 25–26 (citing Ex. 1015, 4).) According to Patent Owner, although McCloskey and Porreca each teach using identifier sites and indexing sites for identification and sequencing, the references do not teach detecting

duplicates based on both the identifier sites and a portion of the target nucleic acid fragment. (*See id.* at 26.)

As discussed above, Petitioner has presented sufficient evidence showing that McCloskey and Porreca, as well as Schmitt, disclose using the sequence of the nucleic acid fragment to identify redundant or duplicate sequences. (*See, e.g.*, Pet. 26–27.) Specifically, Petitioner points to Figure 5 of Porreca, which Dr. Metzker testifies one of ordinary skill in the art would have known to provide the symbol “T” to represent a single nucleotide of the target sequence and to have further known that the rest of the target sequence in the collapsed reads would also be identical. (Ex. 1003 ¶ 124.) Petitioner supports this argument with testimony by Dr. Metzker that “collapsing a read” means removing sequences having the same target and differentiator tag sequences and the disclosure in Porreca that “[f]or any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’ into a single read before consensus basecalls are determined.” (*Id.* ¶ 88 (quoting Ex. 1006 ¶ 298) (emphasis omitted).)

In addition, as discussed above, Petitioner cites the teaching in McCloskey of identifying sequence reads with identical identifier and target sequences based on the evidence that Example 6 of McCloskey discloses observing “[r]edundant hypermethylated sequences with identical barcodes and methylation pattern” in Figures 4B and 4C and “redundant hypomethylated sequences with identical barcodes” in Figures 4E and 4F. (Ex. 1005 ¶ 103; *see* Pet. 23 (also citing Ex. 1005 ¶ 53 (“There were 22 sequences with a barcode that was identical to a sequence already obtained (i.e., redundant sequences).”).) In addition, Petitioner argues that the

disclosure in Example 2 of McCloskey that “[a] redundant sequence was also recovered, meaning that a MLM1-positive sequence with an already seen bar-code was recovered.” (Ex. 1005 ¶ 63; *see* Pet. 23.) According to Petitioner, these disclosures show that the target sequence and the barcode were both used to determine which sequences were duplicates. (*See* Pet. 23.) Petitioner supports this argument with Dr. Metzker’s testimony that the reference to “redundant hypomethylated sequences” along with identical barcodes indicate that both the identical target sequence and the identical barcodes are used to determine which sequences were duplicates. (*See* Ex. 1003 ¶¶ 87–90.)

As also discussed above, Petitioner cites the teaching in Schmitt that “SMI adaptor molecules may be used in methods for unambiguous identification of PCR duplicates” and the teaching that “[b]ecause the use of SMI tags (or ‘double-stranded SMI sequences’) allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence.” (Ex. 1007 ¶ 85; *see* Pet. 50–51.) Petitioner cites Dr. Metzker’s testimony that one of ordinary skill in the art would have understood “true PCR duplicates” to have target nucleic acid sequences that are identical in addition to having the same SMI sequence. (*See* Pet. 50–52 (citing Ex. 1003 ¶¶ 161–162).) Petitioner also cites the teaching of Schmitt that “members of the same PCR ‘family’ are then grouped together by virtue of having a common (i.e., the same) SMI tag sequence. The sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.” (Ex. 1007 ¶ 99; *see* Pet. 51–52.) Again,

Petitioner cites Dr. Metzker’s testimony that one of ordinary skill in the art “would have known that the target sequences in the duplicates are identical because that is required to generate a consensus read” and that, thus, these disclosures “show that both the target sequence and SMI sequence are used to identify PCR duplicates in Schmitt.” (Ex. 1003 ¶ 162.)

In summary, Petitioner presents evidence, which we find preliminarily persuasive, showing that McCloskey, Porreca, and Schmitt disclose aspects of the claims that were alleged in the prosecution to be missing in McCloskey 2007.

For at least the reasons noted above, we determine that each of Porreca, McCloskey 2007, and Schmitt are not substantially the same as either McCloskey 2007 or Samuels. Accordingly, the first part of the framework of *Advanced Bionics* is not met and we are not persuaded there is a reason to exercise our discretion to deny institution of review at least on the basis of anticipation under 35 U.S.C. § 102(a) over Porreca, McCloskey, or Schmitt.

Because we do not exercise discretion to deny institution of review on the basis of at least one ground of challenge raised by Petitioner, we institute trial on all claims and all grounds asserted in the Petition. *See* 35 U.S.C. § 314(a); *SAS Inst.*, 584 U.S. at 362.

III. CONCLUSION

We conclude, on the present record, that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that at least one of claims 1–16 of the ’241 patent is unpatentable.

Any argument not raised in a Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed forfeited and/or waived even if asserted in the Preliminary Response. *In re Google Tech. Holdings LLC*, 980 F.3d 858, 862–64 (Fed. Cir. 2020) (holding an argument forfeited when not timely raised before the Board); *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response or as otherwise permitted during trial).

IV. 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 1–16 of the '241 patent is instituted on all challenges included in the Petition;

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

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FOR PETITIONER:

David Bilsker
Matthew Traupman
Tara Srinivasan
Landon Smith
QUINN EMANUEL URQUHART & SULLIVAN, LLP
davidbilsker@quinnemanuel.com
matthewtraupman@quinnemanuel.com
tarasrinivasan@quinnemanuel.com
landonsmith@quinnemanuel.com

FOR PATENT OWNER:

Linnea Cipriano
Scott Weingaertner
GOODWIN PROCTER LLP
lcipriano@goodwinlaw.com
sweingaertner@goodwinlaw.com