

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN SCIENCES, LLC,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00026
Patent 11,098,357 B2

Before GEORGIANNA W. BRADEN, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

BRADEN, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Denying Motion to Strike
37 C.F.R. § 42.20(b)

I. INTRODUCTION

In this *inter partes* review, Qiagen Sciences, LLC (“Petitioner”) challenges the patentability of claims 1–10 of U.S. Patent No. 11,098,357 B2 (Ex. 1002, “the ’357 patent”), which is assigned to Tecan Genomics, Inc. (“Patent Owner”).

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the trial in this *inter partes* review. For the reasons discussed below, we determine Petitioner has proven by a preponderance of the evidence that claims 1–10 of the ’357 patent are unpatentable in view of the challenges based on Porreca alone as well as the combined teachings of (i) Schmitt and McCloskey, (ii) Schmitt, McCloskey, and Illumina 2008, and (iii) Porreca and Illumina 2008. *See* 35 U.S.C. § 316(e) (2018) (“In an *inter partes* review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.”).

A. *Procedural History*

Integrated DNA Technologies, Inc. filed a Petition (Paper 2, “Pet.”) challenging claims 1–10 of the ’357 patent on the following basis:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–3, 5–10	102(a)	Porreca ¹
1–3, 5–10	103	Schmitt, ² McCloskey ³
4	103	Porreca, Illumina 2008 ⁴
4	103	Schmitt, McCloskey, Illumina 2008
7	103	Porreca, Illumina 2008
7	103	Schmitt, McCloskey, Illumina 2008

Pet. 5. In support of its patentability challenge, Petitioner relies on, *inter alia*, two declarations from Michael L. Metzker, Ph.D. (“Dr. Metzker”). Ex. 1003; Ex. 1035. Patent Owner filed a Preliminary Response. Paper 7 (“Prelim. Resp.”). Trial was instituted on the asserted challenges to patentability. Paper 8 (“Inst. Dec.”), 46.

During the trial, Patent Owner filed a Response (Paper 19, “PO Resp.”) to the Petition. In support of its Response, Patent Owner relies on, *inter alia*, the Declaration of Carlos D. Bustamante, Ph.D. (“Dr. Bustamante”). Ex. 2107. Petitioner filed a Reply to Patent Owner’s Response (Paper 23, “Pet. Reply”), and Patent Owner filed a Sur-Reply to Petitioner’s Reply (Paper 28, “PO Sur-Reply”).

¹ U.S. Patent Application Publication No. US2012/0165202 A1, published June 28, 2012 (Ex. 1006) (“Porreca”).

² International Patent Application Publication No. WO 2013/142389 A1, published September 26, 2013 (Ex. 1007) (“Schmitt”).

³ U.S. Patent Application Publication No. US 2007/0020640 A1, published January 25, 2007 (Ex. 1005) (“McCloskey”).

⁴ Illumina Sequencing, “*Multiplexed Sequencing with the Illumina Genome Analyzer System*,” dated December 26, 2008 (Ex. 1008) (“Illumina 2008”). 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.)

Additionally, Petitioner filed a Motion to Strike (Paper 32, “Mot.”), which was opposed by Patent Owner (Paper 34, “Opp.”).

An oral hearing was held on February 11, 2026, a transcript of which appears in the record. Paper 41 (“Tr.”).

B. Real Parties-in-Interest

Petitioner identifies “QIAGEN Sciences, LLC, QIAGEN Gaithersburg, LLC f/k/a QIAGEN Gaithersburg, Inc., QIAGEN GmbH, and QIAGEN N.V.,” as real parties-in-interest. Pet. 2.

Patent Owner identifies “Tecan Group AG (also known as Tecan Group Ltd.)” as a real-party-in-interest. Paper 3 (Patent Owner’s Mandatory Notices), 1; Paper 27 (Patent Owner’s Updated Mandatory Notices), 1.

C. Related Matters

The parties indicate that the ’357 patent has been asserted in the following district court 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 ’357 and other patents, are related matters. See Pet. 2; Paper 3, 1; Paper 27, 1–2. Furthermore, Petitioner and Patent Owner identify IPR2024-01504, which involves a challenge to ’357 patent, as a related matter.⁵ See Pet. 2–3; Paper 3, 1.

In addition, IPR2024-01506 and IPR2025-00027, challenging Patent No. 11,725,241 (“the ’241 patent”), IPR2025-00015 and IPR2025-00028, challenging Patent No. 10,036,012, and IPR2025-00016 and IPR2025-

⁵ A Final Written Decision was entered in IPR2024-01504 as Paper 41 on April 8, 2026.

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.

D. The '357 Patent

The '357 patent is titled “Compositions and Methods for Identification of a Duplicate Sequencing Read” and issued on August 24, 2021. Ex. 1002, codes (45), (54). It issued from an application filed January 15, 2020 and claims priority to a provisional application filed on November 13, 2013. *Id.* at codes (21), (22), (60).

1. Written Description

The '357 patent “relates generally to the field of high throughput sequencing reactions and the ability to discern artifacts arising through sequence duplications from nucleotide molecules that are unique molecules.” *Id.* at 1:27–30. The '357 patent explains that PCR duplicate artifacts may occur in RNA sequencing applications during library amplification, which hampers accurate gene expression measurements. *Id.* at 1:35–37. The '357 patent also states that paired end sequencing adds cost in expression analysis studies. See *id.* at 1:56–62. In view of this, the '357 patent expresses a need for improved methods of “low-cost, high through-put sequencing of regions of interest, genotyping or simple detection of RNA transcripts without inherent instrument inefficiencies that drive up sequencing costs due to the generation of unusable or non-desired data reads.” *Id.* at 1:65–2:3.

The '357 patent states that it is based on methods for discerning “duplicate sequencing reads from a population of sequencing reads.” *Id.* at 2:15–17. The method includes “ligating an adaptor to a 5' end of each nucleic acid fragment of a plurality of nucleic acid fragments from one or more samples, wherein the adaptor comprises an indexing primer binding

site, an indexing site, an identifier site, and a target sequence primer binding site.” *Id.* at 2:24–29. The ’357 patent describes an embodiment in which “the identifier site is between 1 and 8 nucleotides in length.” *Id.* at 2:62–64. The ’357 patent explains that “[t]he ligated adaptor-nucleic acid fragment products can be amplified, thus generating a population of sequencing reads from the amplified adaptor-nucleic acid ligation products.” *Id.* at 2:29–32. In addition, “[t]he sequencing reads with a duplicate identifier site and target sequence can then be detected from the population of sequencing reads.” *Id.* at 2:32–34.

2. *Illustrative Claim*

Claim 1, reproduced below, is the sole independent challenged claim and is illustrative of the subject matter:

1. A method for detecting duplicate sequencing reads, the method comprising:
 - ligating an adaptor to each of a plurality of nucleic acid fragments, wherein each adaptor comprises a unique identifier having from about 1 to about 8 nucleotides; an indexing site unique to a subset of the adaptors, and a primer binding site;
 - amplifying the adaptor-ligated fragments into amplicons;
 - sequencing the amplicons to produce sequence reads that include identifier and target sequences; and
 - identifying sequence reads with identical identifier and target sequences as duplicates.

Ex. 1001, 25:36–47.

II. PRELIMINARY MATTERS

A. *Legal Standards*

A “prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of

the document, but must also disclose those elements ‘arranged as in the claim.’” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). “A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference.” *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014).

“[A]nticipation by inherent disclosure is appropriate only when the [single prior art] reference discloses prior art that must *necessarily* include the unstated limitation.” *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (citation omitted). “Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *Cont’l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (internal quotation marks and citations omitted). Rather, “[t]he inherent result must inevitably result from the disclosed steps.” *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012). Of course, anticipation “is not an ‘ipsissimis verbis’ test.” *In re Bond*, 910 F.2d 831, 832–33 (Fed. Cir. 1990) (citing *Akzo N.V. v. United States Int’l Trade Comm’n*, 808 F.2d 1471, 1479 & n.11 (Fed. Cir. 1986)). “An anticipatory reference . . . need not duplicate word for word what is in the claims.” *Standard Havens Prods. Inc. v. Gencor Indus. Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991).

A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter 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. 35 U.S.C. § 103; *KSR Int’l Co. v. Teleflex Inc.*, 550

U.S. 398, 406 (2007). “[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.” *KSR*, 550 U.S. at 416 (citing *United States v. Adams*, 383 U.S. 39, 50–51 (1966)). The question of obviousness is resolved based on 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 non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In an *inter partes* review, a petition must identify “with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim.” 35 U.S.C. § 312(a)(3) (2018); *see also* 37 C.F.R. § 42.104(b) (2024) (requiring a petition for *inter partes* review to identify how the challenged claim is to be construed and where each element of the claim is found in the prior art patents or printed publications relied upon).

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)); *see Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review). Therefore, to prevail in an *inter partes* review, Petitioner must explain how the proposed combination of prior art would have rendered the challenged claims unpatentable. At this final stage, we determine whether the information

presented in the Petition demonstrates by a preponderance of the evidence that the challenged claims would have been obvious over the asserted prior art.

We analyze the challenges presented in the Petition in accordance with the above-stated principles.

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).

Here, 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. Pet. 8–9 (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. *Id.* Petitioner argues that an ordinarily skilled artisan with a Master’s degree would have at least four years of similar experience. *Id.*

Patent Owner initially disputed the experience level Petitioner asserts for one of ordinary skill in the art. Prelim. Resp. 8–9. Specifically, Patent

Owner argued 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. *Id.* at 8.

According to Patent Owner, the appropriate level of ordinary skill in the art would be 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. *Id.*

On the initial trial record, we agreed with Patent Owner that one of ordinary skill in the art would have had experience with next generation sequencing, but were not persuaded that this would only be possible in the field of molecular biology. Instead, we found that a person of ordinary skill would have had either (1) a Ph.D. in the field of chemistry, molecular biology, or biochemistry or (2) a B.S. or M.S. degree with three to five years of experience working in any of those fields. Inst. Dec. 8. We specifically found that "[t]he person of ordinary skill would have had experience with next generation sequencing methods and a working knowledge of how those methods functioned." *Id.* at 8–9.

Patent Owner now submits that it does not dispute the definition of a person of ordinary skill in the art as laid out in the Institution Decision. PO Resp. 13.

Reviewing the entire trial record, we maintain the same definition of a person of ordinary skill in the art and note that it is consistent with the skill level reflected in the disclosures of the '357 patent and prior art. We further note that the skill level does not affect our analysis or our final decision.

C. Claim Construction

Claims are construed “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).

The following terms were either identified by the parties (Pet. 22–23; PO Resp. 9–19) or the Board for construction (Inst. Dec. 10–13).

1. “adaptor”

Petitioner argues that we should construe the claim term “adaptor” as “any oligonucleotide that is attached to the target sequence.” Pet. 9. Petitioner cites the ’357 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. 1002, 4:20–25; *see* Pet. 9–10. According to Petitioner, this described function can be performed by any oligonucleotide. Pet. 10. 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.” *Id.* at 10 (citing Ex. 1013, 77). Petitioner further cites the specification of the ’357

patent and claims of the '241 patent, which is a continuation of the '357 patent, in support of this construction. *Id.* at 9–10 (citing Ex. 1002, 9:43–46 (“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, claim 10).

In the Institution Decision, the Board adopted Petitioner’s construction of the term “adaptor.” Inst. Dec. 9. Patent Owner does not dispute this construction. PO Resp. 13–14.

During oral argument, Petitioner argued that claim 1 requires “an adapter to be ligated onto a target DNA, and that adapter needs to have two different sequences of DNA that are used for identification” including a “so-called identifier that’s one to eight nucleotides in an indexing site.”

Tr. 6:19–7:2. Patent Owner, again, did not dispute this characterization of “adaptor.” *See generally* Tr.

Based on the entirety of the trial record, we continue to apply Petitioner’s construction of the term “adaptor,” although we note that it does not affect our analysis.

2. *“identifying sequence reads with identical identifier and target sequences as duplicates”*

The parties did not submit constructions of this limitation initially.

Patent Owner contends the limitation should be construed as “identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence.” PO Resp. 14; PO Sur-Reply 2. Patent Owner argues that Example 5 of the '357 patent supports its interpretation because it describes a process of identifying duplicate sequencing reads using both the identifier and a portion of the target sequence. PO Resp. 16 (citing Ex. 1002, 20:19–21; Ex. 2107 ¶ 94).

Patent Owner further argues that the “target sequence read” includes “**both** the claimed identifier sequence and a portion of the target sequence.” *Id.* at 17 (citing Ex. 2107 ¶ 96). Patent Owner contends that, in Example 5, “both pieces of information are used ‘in conjunction’ for the step of identifying duplicates,” which is consistent with both the Specification and the prosecution history of the ’357 patent. PO Sur-Reply 6 (citing Ex. 1002, 20:58–62; Ex. 2107 ¶¶ 95–97).

Patent Owner then relies on the prosecution history of related Patent Application No. 14/540,917 to indicate that the “identify” step of the limitation is an **active** step. PO Resp. 19 (citing Ex. 2021, 797–801). According to Patent Owner, an ordinarily skilled artisan would have understood that “Applicants were directing the claims at a method that includes a step in which duplicates are identified using a combination of the identifier site and at least a portion of the target sequence.” *Id.* at 20. Patent Owner, therefore, concludes the claims require using information from both the identifier and the portion of the target sequence together for “identifying duplicates” in the same step. PO Sur-Reply 2–7 (Ex. 2107 ¶¶ 95–97, 102).

Petitioner contends that the plain language of the claim and the Specification require the “duplicates” to be “sequence reads with identical identifier and at least a portion of the target sequences.” Pet. Reply. 2. Petitioner asserts that Patent Owner’s interpretation inappropriately rewrites the claim to require a temporal limitation (i.e., a single step). *Id.* at 2–5; Tr. 56:12–24. Petitioner specifically argues that the claim language does not impose an additional requirement that the required comparison be done in a single step. Pet. Reply 3. Rather, according to Petitioner, the claim simply requires that duplicates be identified based on the identifier and target sequences.

In rebuttal, Patent Owner asserts that the prosecution history indicates that the identifying duplicates step requires the use of these two pieces of information together. PO Sur-Reply 4. Patent Owner appears to argue that as long as the limitations are performed as some kind of “step,” then the method claims are satisfied. *Id.* at 6–7.

We observe that the ’357 patent states: “[a] duplicate sequencing read can be a sequencing read with the same identifier site and target sequence as another sequencing read in the population of sequencing reads.” Ex. 1002, 4:11–15. The claim does not use the exact wording as the Specification.

The ’357 patent states that, when analyzing RNA sequence data, and when two or more identical sequences are found, “it can be difficult to know if these represent unique cDNA molecules derived independently from different RNA molecules, or if they are PCR duplicates derived from a single RNA molecule.” Ex. 1002, 1:39–42.

The ’357 patent distinguishes between “apparent duplicates” and “true duplicates” as follows:

In some embodiments, duplicate sequencing reads are differentiated from one another as being true duplicates versus apparent or perceived duplicates. Apparent or perceived duplicates may be identified from sequencing libraries and using conventional measures of duplicate reads (i.e., reads were mapped using bowtie), where all reads with the same start and end nucleic acid coordinates were counted as duplicates. True duplicates may be identified from sequencing libraries having had an identifier site introduced through ligation to differentiate between fragments of DNA that randomly have the same start and end mapping coordinates.

Ex. 1002, 14:21–31; *see id.* at Fig. 5; *see also* Example 1, 18:6–15 (“When evaluating two million random reads, the apparent duplicates were found to

comprise 39% of all reads. However, the true duplicates, identified through the use of an identifier site, were found to comprise only 26% of all reads. The methods employing the use of an identifier site were found to considerably increase the resolution of the true number of duplicates within the pool of reads.”). The ’357 patent also discloses in Example 5: “Any read that has identical sequence to any other read is identified as a duplicate and removed from the population, thus, only a single copy is retained within the file.” *Id.* at 20:60–62.

Analyzing the patent disclosure in light of the parties’ arguments, we determine that “duplicates” in claim 1 of the ’357 patent means the sequences possess an identical sequence for both the identifier and the length of the sequence read that is obtained. Additionally, we agree with the parties that there is no temporal requirement for “identifying sequence reads” using the identifier and the target sequence, and the two do not have to be used simultaneously. Rather, based on both Examples 1 and 5 of the ’357 patent, the claims only require that the two data points be used for “identifying sequence reads.”

III. ANALYSIS

A. Alleged Anticipation of Claims 1–3 and 5–10 by Porreca

Petitioner challenges claims 1–3 and 5–10 as being anticipated by Porreca under 35 U.S.C. § 102(a). Pet. 17–33. Patent Owner disagrees. See PO Resp. 1–2, 21–29.

1. Summary of the Prior Art – Porreca

Porreca is directed to methods of genotyping subjects and identifying and addressing different sources of ambiguity and error in genetic analyses. 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).

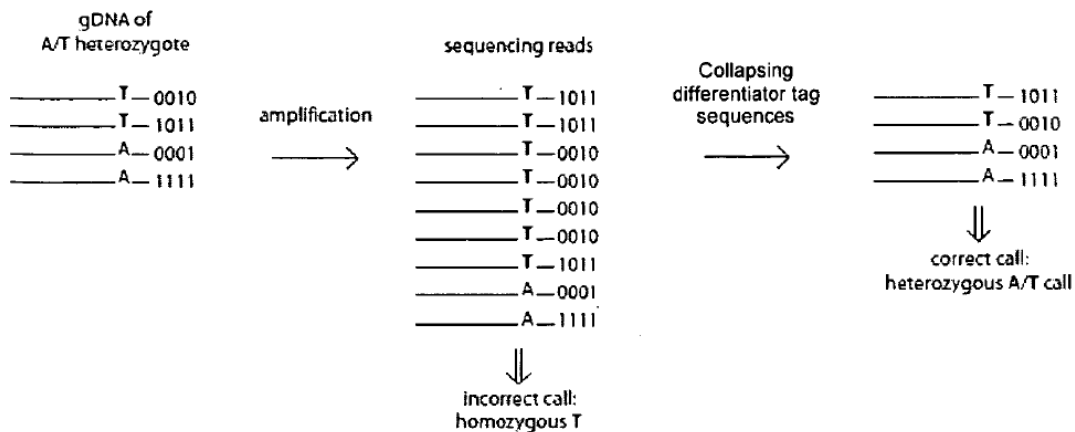
Id. ¶ 24.

Porreca refers to combining or “collaps[ing]” 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 an illustration depicting a non-limiting method for genotyping based on target and differentiator tag sequences (*id.* ¶ 86) and reproduced below.

FIGURE 5



As shown above, 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. *Id.* 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. *Id.* 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. *Id.* 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 [(molecular inversion probe)] 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.)

Ex. 1006 ¶ 149.

2. *Analysis of Independent Claim 1*

a) “A method for detecting duplicate sequencing reads, the method comprising” (preamble)

Petitioner contends that Porreca teaches “the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules.” Pet. 17 (citing Ex. 1006 ¶ 23). Petitioner argues 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).” *Id.* at 17–18 (citing Ex. 1006 ¶¶ 24, 142). 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 PCR duplicates of each other. *Id.* at 18 (citing Ex. 1006 ¶¶ 253–298, Fig. 5).

In support of this argument, Petitioner cites to the testimony of Dr. Metzker. *See* Pet. 17. Dr. Metzker opines that Porreca teaches that a differentiator tag, which corresponds to the “identifier” recited in the claims of the ’357 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 ¶¶ 70–72.

Patent Owner has not provided separate arguments regarding claim 1’s preamble. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that Porreca discloses that differentiator tags are attached to nucleic acid fragments before amplification, allowing identical sequences bearing the same differentiator tag to be PCR duplicates of each other. *See* Ex. 1006 ¶¶ 253–298, Fig. 5. We credit the testimony of Dr. Metzker in our analysis. *See* Ex. 1003 ¶¶ 70–72.

b) “ligating an adaptor to each of a plurality of nucleic acid fragments”

Petitioner contends that Porreca teaches “ligating an adaptor to each of a plurality of nucleic acid fragments,” as required in claim 1, because it teaches ligating an adaptor comprising a differentiator tag sequence to a sequence of interest. Pet. 18–19 (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. *Id.* (citing Ex. 1006 ¶¶ 85, 150, Fig. 4C). Figure 4C is reproduced below:

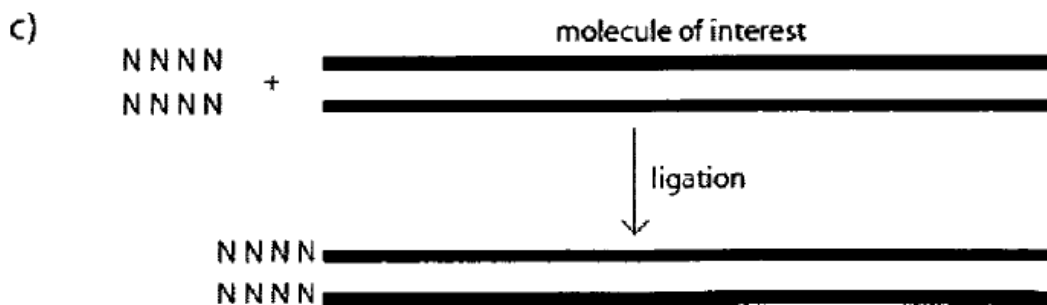


Figure 4C is an illustration depicting a sequence “NNNN” and a “molecule of interest,” which is shown to be joined by “ligation.” Ex. 1006 ¶¶ 86, 104–142. According to Porreca, Figure 4C depicts “various non-limiting methods for combining differentiator tag sequence and target sequences (NNNN depicts a differentiator tag sequence).” *Id.* ¶¶ 85, 140. Dr. Metzker testifies that these portions of Porreca disclose ligating an adaptor to each of a plurality of nucleic acid fragments. See Ex. 1003 ¶¶ 73–74.

Patent Owner has not provided separate arguments regarding this limitation. See *generally* PO Resp. Nonetheless, the burden remains on

Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner's position and find that Porreca discloses that "nucleic acids comprising differentiator tag sequences may be incorporated by ligation." *See* Ex. 1006 ¶ 150. Porreca also discloses that "[t]his is a flexible method, because molecules having differentiator tag sequence can be ligated to any blunt-ended nucleic acids." *Id.*

c) *[wherein the adaptor comprises] "a unique identifier having from about 1 to about 8 nucleotides"*

Petitioner contends 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." Pet. 19 (citing Ex. 1006 ¶¶ 141–143). Petitioner argues that these differentiator tags are used to uniquely tag each nucleic acid. *Id.* at 20 (citing Ex. 1006 ¶¶ 23, 139, 142, 143). 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. *Id.* (citing Ex. 1006 ¶¶ 142–143). Dr. Metzker testifies that these disclosures of Porreca teach a method, "wherein each adaptor comprises a unique identifier having from about 1 to about 8 nucleotides," as required in claim 1. Ex. 1003 ¶¶ 75–76.

Patent Owner has not provided separate arguments regarding this limitation. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner's position and find that Porreca discloses a method of making unique "differentiator tag[s]" 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." *See* Ex. 1006 ¶¶ 141, 143.

d) [wherein each adaptor comprises] "an indexing site unique to a subset of the adaptors" and "a primer binding site"

Petitioner contends that Porreca discloses "an indexing site unique to a subset of the adaptors," as required in claim 1, because it teaches that adaptors can include barcodes to uniquely identify particular samples. Pet. 20–21 (citing Ex. 1006 ¶¶ 102, 149). Petitioner argues that in addition to teaching inclusion of differentiator tags in an adaptor, Porreca teaches that primer binding sites can also be included. *Id.* at 21–22 (citing Ex. 1006 ¶ 149).

Petitioner cites to the teaching in Porreca that "[a]dapters often contain PCR primer sites (for amplification or emulsion PCR) and/or sequencing primer sites. *Id.* at 20 (citing Ex. 1006 ¶ 149); Tr. 61:25–62:12. Porreca also discloses that "barcodes may be included, for example, to uniquely identify individual samples (e.g., patient samples) that may be mixed together." *See* Ex. 1006 ¶ 149. Porreca further teaches that "[p]rimers may also include additional nucleic acids that are not complementary to target sequences but that facilitate downstream

applications, including for example restriction sites and differentiator tag sequences.” *Id.* ¶ 29. According to Petitioner, Porreca describes “sequencing primers” that “sequence both the differentiator tag sequence and the target sequence [or a]lternatively, the sequencing adaptors can be synthesized with the random differentiator tag sequences at their 3' end (as degenerate bases), so that only one ligation must be performed.” Pet. 22 (citing Ex. 1006 ¶ 150).

Petitioner argues that Porreca’s Paragraph 149 demonstrates that its teachings are applicable to all types of adaptors, not just those used with MIPs. Pet. Reply 9. Petitioner further argues that Porreca’s Paragraph 150 also supports the position that Porreca is applicable to more than just MIPs. *Id.* According to Petitioner, “Paragraph 150 discloses an adaptor ‘arranged with the common adaptor sequence followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5’ to 3’ order).” *Id.* (citing Ex. 1006 ¶ 150). Petitioner asserts that “this adaptor is not described as being used with MIPs.” *Id.*

Petitioner asserts that Patent Owner inappropriately interprets Porreca’s teachings about adaptors as limited only to the MIP preparative process, but Petitioner contends that is not what Porreca teaches, nor is it what a POSA would understand from reading Porreca. Pet. Reply 9. Petitioner cites further to the explanation in Porreca that “[i]n some embodiments, a plurality of captured nucleic acids from each one of a plurality of patient samples may be combined in a single multiplex analysis reaction,” and that “samples from different subjects are tagged with subject-specific (e.g., patient-specific) tags (e.g., unique sequence tags) so that the information from each product can be assigned to an identified subject.” Pet. 21 (citing Ex. 1006 ¶ 102).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker opines that one of ordinary skill in the art would have known that the barcode disclosed in Porreca, which corresponds to the claimed “indexing site,” would be “appended to the target nucleic acid sequence and that all nucleic acids from the same sample would have an identical barcode.” Ex. 1003 ¶¶ 70, 77. Dr. Metzker testifies further that the barcode taught in Porreca meets the claimed indexing site, which is known as “multiplexing.” *Id.* ¶ 78 (citing Ex. 1006 Abstr. (“In some configurations, predetermined preparative steps and/or nucleic acid sequence analysis techniques are used in multiplex analyses for a plurality of genetic loci in a plurality of samples.”) (emphasis omitted), ¶¶ 102, 149). Dr. Metzker testifies further that “[a]fter amplification and sequencing, the sample can be ‘demultiplexed’ by grouping together the sequencing reads that bear the same barcode.” *Id.* ¶ 79.

Patent Owner contends that Porreca fails to disclose any embodiment in which an adapter that includes an indexing site is ligated to the nucleic acid fragments before the amplification step, as is required by claim 1. PO Resp. 1. According to Patent Owner, Petitioner relies on Porreca’s embodiment of blunt-end ligation for disclosure of ligating an adapter to a fragment, but Porreca does not disclose using the embodiment with that adapter for adding an indexing site to the nucleic acid fragments. *Id.* at 1–2.

Patent Owner argues that Petitioner relies on two separate but distinct teachings to cobble together elements found in the claim. Tr. 33:2–8. Specifically, Patent Owner asserts that Porreca’s embodiments of (1) an adaptor with an indexing site used in a molecular inversion probe (“MIP”) and (2) blunt-end ligation are not compatible and that an ordinarily skilled artisan would not have understood the embodiments to be interchangeable.

PO Resp. 2; PO Sur-Reply 7–10. Patent Owner also argues that Porreca’s reference to McCloskey is not relevant to adaptors, because McCloskey is cited “the general concept of patient-specific barcodes used for multiplexing.” PO Sur-Reply 12. According to Patent Owner, “[t]here is no implication that the specific library preparation methods of McCloskey are being incorporated into paragraph 149 to expand the disclosure beyond MIPs.” *Id.*

After review of the entire trial record, we agree with Petitioner and find that Porreca discloses an adaptor with both a PCR primer and a sequencing primer. *See* Ex. 1006 ¶ 149. Porreca specifically states that “[a]dapters often contain PCR primer sites (for amplification or emulsion PCR) *and/or* sequencing primer sites.” *Id.* (emphasis added). The plain language of Porreca discloses that its adapters can include (1) a PCR primer site *and* a sequencing primer site, or (2) a PCR primer site *or* a sequencing primer site. Moreover, Porreca is explicit in its instruction that

[i]t should be appreciated that any of the circularization, amplification, and/or hybridization based methods described herein may be used in connection with one or more of the tiling/staggering, tagging, size-detection, and/or sensitivity enhancing algorithms described herein.

Id. at 31. Thus, Porreca is not limited to just the MIP embodiments.

This finding is supported by the fact that, after teaching that these adapters can include “barcodes” “to uniquely identify individual samples (e.g. patient samples) that may be mixed together,” Porreca cites to McCloskey. Ex. 1006 ¶ 149. McCloskey teaches adaptor design, yet none of the adaptors described in McCloskey are for use with MIPs. *See* Ex. 1006 ¶ 149; Ex. 1005 ¶ 5 (sequence tags, barcoding), ¶ 8 (methods for cbar-coding a nucleic acid molecule), ¶¶ 9, 14, 43–104 (method for authenticating

nucleic acid amplification product using bar-coded oligonucleotides). While McCloskey does disclose “the general concept of patient-specific barcodes used for multiplexing” as argued by Patent Owner, the teachings are relevant and applicable to the use of adapters with barcodes. Additionally, we credit the testimony of Dr. Metzker, who explains that McCloskey discloses two types of embodiments containing multiplexing barcodes: a hairpin linker adaptor embodiment and an oligonucleotide primer embodiment, but does not disclose the use of MIP or any padlock probe embodiments. Ex. 1035 ¶ 30. Dr. Bustamante also testifies that “I do not believe that there is a MIPs preparative process discussed in McCloskey.” Ex. 1034, 99:18–20. The lack of discussion of MIP adaptors in McCloskey undercuts Patent Owner’s arguments as does the applicability of McCloskey to more than just multiplexing.

e) *“amplifying the adaptor-ligated fragments into amplicons”; and*

Petitioner contends that Porreca teaches that once an adaptor with a unique identifier, an indexing site, and a primer binding site is ligated to a nucleic acid molecule of interest, the resulting product is amplified by PCR to produce amplicons. Pet. 22 (citing Ex. 1003 ¶¶ 82–83), 23 (citing Ex. 1006 ¶¶ 24, 66). Petitioner cites to Porreca’s disclosure of “amplification-based . . . preparative methods,” such as PCR “that selectively amplifies each locus using a pair of oligonucleotide primers” to support its position. *Id.* at 23 (citing Ex. 1006 ¶ 66.) Petitioner argues that Figure 5 of Porreca, reproduced above, provides an example of such amplification. *Id.* According to Petitioner, Porreca’s Figure 5 depicts four nucleic acid molecules of interest that are amplified, along with the

appended adaptor (called the differentiator tag in Porreca) to produce amplicons referred to as “sequence reads.” *Id.* at 23–24.

Dr. Metzker’s testimony supports a finding that Porreca discloses amplifying the adaptor-ligated fragments into amplicons; sequencing the amplicons to produce sequence reads that include identifier and target sequences. Ex. 1003 ¶¶ 82–83.

Patent Owner contends, however, that Porreca fails to disclose that the adaptor containing the unique identifier is amplified only *after* it is ligated. PO Resp. 22–23, 25. Patent Owner cites to Figure 4C, arguing that, in the MIP process, the adaptor is never ligated to the nucleic acid fragment/molecule of interest in the sample and no adaptor-ligated fragments are amplified. *Id.* at 25 (citing Ex. 2107 ¶¶ 117, 120). Rather, according to Patent Owner, “any pre-amplification ligation of the adaptor, if performed, would be to attach the adaptor to the targeting arms of the probe. *Id.* (citing Ex. 2107 ¶¶ 73, 117).

Patent Owner argues further that an ordinarily skilled artisan would have understood the ligation described in Porreca’s Paragraph 149 refers to adapters that can be ligated to the molecule of interest for purposes of sequencing *after* the MIPs are circularized and after PCR amplification. *Id.* (citing Ex. 2107 ¶¶ 117–119 (citing Ex. 1006 ¶¶ 252, 294, 380)); PO Sur-Reply 12 (discussing MIP process and using PCR primers sites for additional amplification).

Patent Owner’s argument is unavailing. Petitioner cites Figure 5 for its teaching that amplification of molecules already includes adaptors. (See Pet. 23–24.) Petitioner does not rely on Figure 4C for amplifying of the adaptor-ligated fragments. Therefore, Patent Owner’s arguments about Figure 4C do not address Petitioner’s challenge. Additionally, we agree

with Petitioner that Porreca specifically discloses amplifying adaptor-ligated nucleic acid sequences into amplicons. See Ex. 1006 ¶¶ 24, 66, Fig. 5

f) “sequencing the amplicons to produce sequence reads that include identifier and target sequences;”

Petitioner contends that Porreca teaches sequencing amplicons to produce sequence 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. Pet. 24 (citing Ex. 1006 ¶ 142). Specifically, Petitioner argues that 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).”

Id. (citing Ex. 1006 ¶ 142 (emphasis added)). Petitioner further relies on Porreca’s 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.* (citing Ex. 1006 ¶¶ 138, 150). Petitioner argues that Figure 5 of Porreca also shows this element by depicting a method for genotyping based on target and differentiator tag sequences. *Id.* at 25 (citing Ex. 1006 ¶ 148). Dr. Metzker supports Petitioner’s position with his testimony that these portions of Porreca disclose “sequencing the

amplicons to produce sequence reads that include identifier and target sequences,” as required in claim 1. Ex. 1003 ¶¶ 84–85.

Patent Owner has not provided separate arguments regarding this limitation. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that Porreca meets the claim limitation by sequencing reads of target and differentiator tag sequences. *See* Ex. 1006 ¶ 148, Fig. 5. Porreca specifically discloses using machines such as the Illumina or ABI to perform sequencing of libraries. *See id.* ¶¶ 295, 381.

g) “*identifying sequence reads with identical identifier and target sequences as duplicates*”

Petitioner contends 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.

Pet. 25–27. 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).

Id. at 25–26 (citing Ex. 1006 ¶ 24) (emphasis omitted). Petitioner cites further to Figure 5 of Porreca, arguing that it shows identification and collapse of duplicate sequencing reads after both the target and differentiator tag are sequenced. *Id.* at 26–27.

Dr. Metzker supports Petitioner’s position with his testimony that Porreca discloses 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). Ex. 1003 ¶ 86. 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.* ¶ 87 (emphasis omitted). Dr. Metzker then 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.* ¶ 88. Dr. Metzker further testifies that:

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.” *Id.* (citing Ex. 1006 ¶ 298) (emphasis omitted).

Patent Owner argues that the Petition fails to show that Porreca discloses identifying duplicate sequencing reads based on its construction of this claim limitation to mean “identifying sequence reads as duplicates

through a step that uses both the identifier and at least a portion of the target sequence.” PO Resp. 28. According to Patent Owner, Petitioner’s reliance on Figure 5 of Porreca is insufficient because neither the Petition nor Dr. Metzker could explain how the “collapsing” of Figure 5 is done or how Porreca compares sequences to determine if duplicates exist. *Id.*; PO Sur-Reply 15. Patent Owner asserts that 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. PO Resp. 29. Patent Owner specifically argues that Porreca provides “no information about whether the process depicted in Figure 5 involves the use of both identifier and target sequence in combination, as required in the challenged claims” and that there “is no method disclosed for comparing the sequences to determine if they are duplicates in the first instance.” PO Sur-Reply 15. Patent Owner further disputes Dr. Metzker’s testimony, arguing it is conclusory and improperly attempts to fill in the gaps of Porreca. PO Resp. 29; PO Sur-Reply 16.

Based on the entirety of the trial record, we do not agree with Patent Owner’s reading of either the claims or the prior art because Patent Owner takes too narrow a view of both. First, based on the plain language of Porreca, we find it uses a combination of the sequence reads of the target sequence and differentiator tag sequences to determine whether there is duplication. *See* Ex. 1006 ¶¶ 139–140, 143, 148, 153. All that the claim requires is that the method identifies sequence reads with identical identifier and target sequences as duplicates. Because claim 1 contains the transition “comprising,” the claim is still satisfied if the category of identified duplicate reads contains identical labels and also contains more.

Patent Owner admits that the identifier and target sequence do not have to be used simultaneously. Tr. 46:16–48:4. Instead, Patent Owner

challenges whether Porreca uses the required elements in combination as recited in the challenged claims. Based on the record before us, we agree with Petitioner’s position especially in view of the open-ended nature of the claims and Patent Owner’s own admission that there is no temporal requirement for the use of target sequences and differentiator tag sequences. Specifically, we find that Porreca teaches using the combination of the target sequences and the differentiator tag sequence to determine whether particular sequence reads are unique or PCR duplicates. *See* Ex. 1006 ¶¶ 139–140, 143, 148, 153. The use of both such sequences meet the claim limitations. This finding is consistent with the prosecution history of the ’357 patent and how the applicant and examiner interpreted the claims. *See* Ex. 1013, 69–70, 78–79.

Second, we find the disclosure of Porreca sufficient to demonstrate to an ordinarily skilled artisan that “collapsing” is done by comparing target sequences and differentiator tag sequences. Porreca specifically explains that:

after multiple reads have been collected for a given locus, it is possible that due to bias (e.g., caused by PCR amplification steps), a large fraction of the reads are derived from a single originating molecule. This would skew the population of target sequences observed, and would affect the outcome of the genotype call.

Ex. 1006 ¶ 153.

To address this issue, Porreca discloses using differentiator tag sequences after using the target sequence because:

if information is available on differentiator tag sequences, this situation could be averted, because the over-represented allele would be seen to also have an over-represented differentiator tag sequence (i.e., the sequences with the overrepresented differentiator tag sequence all originated from the same single

molecule). Therefore, the sequences and corresponding distribution of differentiator tag sequences can be used as an additional input to the genotype-calling algorithm to significantly improve the accuracy and confidence of the genotype calls.

Id.

Additionally, because it aligns with the disclosure of Porreca, we credit Dr. Metzker's testimony 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 ¶ 88.) Although Patent Owner argues that Dr. Metzker's testimony is merely conclusory, Patent Owner does not substantively dispute it or explain how it is inconsistent with the explicit disclosure of Porreca.

We, therefore, determine that Petitioner has demonstrated by a preponderance of the evidence that the disclosure of Porreca anticipates the claim limitation of "identifying sequence reads with identical identifier and target sequences as duplicates."

h) Summary of Claim 1

On the complete trial record before us now, we determine Petitioner has demonstrated by a preponderance of the evidence that claim 1 of the '357 patent is anticipated by Porreca.

3. Analysis of Dependent Claims 2, 3, and 5–10

Petitioner presents arguments and evidence regarding anticipation of claims 2, 3, and 5–10 by Porreca. Pet. 27–33.

Other than its arguments directed to Petitioner's challenges to independent claim 1, Patent Owner does not specifically respond to Petitioner's arguments regarding dependent claims 2, 3, and 5–10. PO Resp. 29. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have reviewed the entirety of the trial record and all evidence submitted for claims 2, 3, and 5–10. Based on the complete record, we determine that Petitioner has shown that Porreca discloses the limitations as recited in the challenged dependent claims. Accordingly, we determine that Petitioner has established by a preponderance of the evidence that claims 2, 3, and 5–10 are unpatentable under 35 U.S.C. § 102(a) in view of Porreca.

B. Alleged Obviousness of Claims 1–3 and 5–10 Over Schmitt and McCloskey

Petitioner contends that claims 1–3 and 5–10 would have been obvious to a person of ordinary skill in the art at the critical time in view of the combined teachings of Schmitt and McCloskey. Pet. 33–52; Pet. Reply 14–24. Patent Owner disagrees. PO Resp. 2, 30–35; PO Sur-Reply 17–23.

1. *Schmitt (Ex. 1007)*

Schmitt is a WIPO publication titled “Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing using Duplex Consensus Sequences” that published on September 26, 2013. Ex. 1007, codes (19), (43), (54). Schmitt is directed to addressing errors in next generation sequencing techniques. *Id.* at code (57). Schmitt teaches using a single molecule identifier (“SMI”) adaptor molecule attached to a DNA fragment to provide a unique identifier. *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. *McCloskey (Ex. 1005)*

McCloskey is a U.S. Patent Publication titled “Molecular Encoding of Nucleic Acid Templates for PCR and Other Forms of Sequence Analysis” that published on January 25, 2007. Ex. 1005, codes (19), (43), (54). McCloskey is directed to 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.” *Id.* ¶ 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.

3. *Analysis of Independent Claim 1*

a) *“A method for detecting duplicate sequencing reads, the method comprising” (preamble)*

Petitioner contends that Schmitt teaches that a single molecule identifier (SMI) “may be used in methods for unambiguous identification of PCR duplicates.” Pet. 33 (citing Ex. 1007 ¶ 85). According to Petitioner, 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. *Id.* (citing Ex. 1007 ¶ 104 (Example 1)).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that these teachings of Schmitt disclose a method of detecting duplicate sequencing reads, as recited in the preamble of claim 1. Ex. 1003 ¶ 101.

Patent Owner has not provided separate arguments regarding claim 1’s preamble. *See generally* PO Resp. Nonetheless, the burden

remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that Schmitt discloses a “method for detecting duplicate sequencing reads” in its Example 1. *See* Ex. 1007 ¶ 104. We credit the testimony of Dr. Metzker, who explains how Schmitt uses single molecule identifiers to group together and filter out PCR duplicates. *See* Ex. 1003 ¶ 101.

b) *“ligating an adaptor to each of a plurality of nucleic acid fragments”*

Petitioner contends that Schmitt teaches “ligating an adaptor to each of a plurality of nucleic acid fragments.” Pet. 34 (citing Ex. 1003 ¶¶ 102–103). Petitioner notes that Schmitt discloses the following:

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. In addition, Petitioner cites the teaching in Schmitt that each end of the double-stranded target nucleic acid molecule is ligated to an SMI adaptor molecule. The 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.

Id. ¶ 74.

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that these portions of Schmitt disclose

ligating an adaptor to each of a plurality of nucleic acid fragments. Ex. 1003 ¶¶ 102–103.

Patent Owner has not provided separate arguments regarding this limitation of claim 1. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that Schmitt discloses ligating an adaptor to each nucleic acid fragment as shown in Figure 1, which is reproduced in relevant part below.

Figure 1

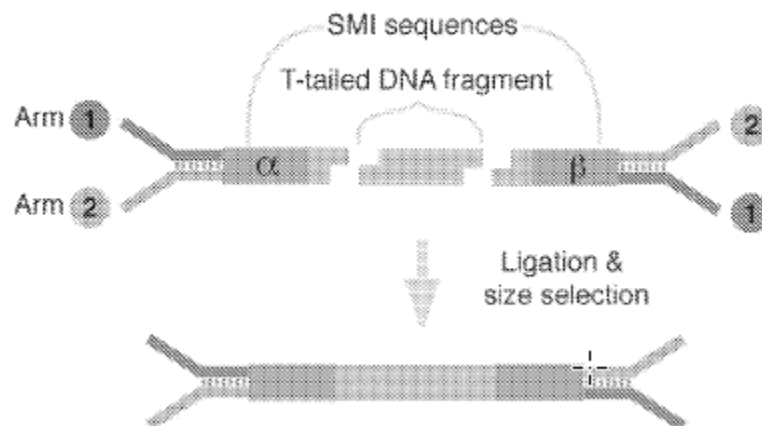


Figure 1 of Schmitt, shown above, illustrates an overview of Duplex Consensus Sequencing. Ex. 1007 ¶ 12. According to Schmitt, sheared double-stranded DNA that has been end-repaired and T-tailed is combined with A-tailed SMI adaptors and ligated according to one embodiment. *Id.*

Additionally, Schmitt explicitly discloses that the SMI includes a ligation adaptor that allows the SMI adaptor molecule to be ligated to the double-stranded target nucleic acid sequence. Ex. 1007 ¶ 9. Then, Schmitt teaches a method that “include[s] steps of 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.” *Id.* ¶ 10.

c) *[wherein each adaptor comprises] “an indexing site unique to a subset of the adaptors”*

Petitioner contends it would have been obvious to include McCloskey’s batch-stamp (as the claimed indexing site) in Schmitt’s adaptor. Pet. 35 (citing Ex. 1003 ¶¶ 108–116). According to Petitioner, an ordinarily skilled artisan would have had reason to add the indexing site to the adaptor. *Id.* Petitioner relies on the testimony of Dr. Metzker to argue that the “fixed multiplexing barcode sequence” of Schmitt would have been understood by one of ordinary skill in the art to allow identification of the sample from which a particular sequence read originated. *Id.* at 35–36 (citing Ex. 1007 ¶ 95, Ex. 1003 ¶ 109). Petitioner cites further to Dr. Metzker’s testimony that

[o]ne of ordinary skill in the art would have known that it would be beneficial to append a barcode to the target sequences earlier in the process to reduce the chance of errors that may affect the analysis, such as mixing different samples together prior to labeling. One of ordinary skill in the art thus would have been motivated to include the multiplexing barcodes to the adaptor described in Limitation 1.a, which occurs before the first amplification and DNA capture steps.

Id. at 36 (citing Ex. 1003 ¶ 110).

Petitioner argues that McCloskey teaches a “batch-stamp” as referring to information that uniquely identifies a specific experiment. Pet. 36–37 (citing Ex. 1005 ¶¶ 15, 27 (“FIG. 3 shows a schematic representation of a bar-coded and batch-stamped hairpin linker (SEQ ID NO:1), designed for ligation to DraIII-cut genomic DNA of FMR1 (SEQ ID NO:2), as described in EXAMPLE 6.”), 92–96, Figs. 1, 3.) Petitioner cites McCloskey’s

description of Figure 1 as “an exemplary bar-coded oligonucleotide of the invention containing a sequence complementary to the target nuclei acid molecules (1), a batch-stamp sequence (2), random barcode (3), a leftward primer binding site (4), and a 5' tethering sequence (5), as described in EXAMPLES 1-5.” *Id.* at 37 (citing Ex. 1005 ¶ 13).

Petitioner further argues that because Schmitt and McCloskey are in the same field and contain disclosures that solve the same problem (using identifiers and indexing sites to identify PCR duplicates and match screening reads to original samples), one of ordinary skill in the art would have considered their teachings together. Pet. 37–38. Petitioner also relies on Dr. Metzker’s testimony to argue that one of ordinary skill in the art would have had a reason to use the batch stamps of McCloskey with the adaptors of Schmitt for multiplex sequencing reactions because McCloskey discloses the use of “barcodes” to distinguish “valid sequences” from “redundant sequences” (i.e., duplicate sequences) and the use of a “batch-stamp” to identify the origin of a sequencing read and that Schmitt has similar teachings. *Id.* at 37 (citing Ex. 1003 ¶¶ 109–110, 114–116).

Petitioner additionally argues that the ordinarily skilled artisan would have had a reason to combine the teachings of McCloskey and Schmitt because Schmitt cites articles written by the same author (“McCloskey 2007”⁶), with disclosures Petitioner characterizes as overlapping McCloskey in regard to techniques for uniquely tagging DNA fragments to be sequenced. Pet. 38 (citing Ex. 1007 ¶ 6). Petitioner cites Dr. Metzker’s testimony in support. *Id.* (citing Ex. 1003 ¶ 115).)

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

Petitioner then argues that one of ordinary skill in the art would have also expected success because Schmitt teaches that adaptors can contain different types of sequences, including SMI adaptors, PCR primer binding sites, sequencing primer binding sites, and multiplexing barcode sequences. Pet. 38–39 (citing Ex. 1007 ¶¶ 10, 22, 95; Ex. 1003 ¶¶ 109–116).

Patent Owner has not provided separate arguments regarding this limitation of claim 1. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that it would have been obvious to include McCloskey’s batch-stamp (as the claimed indexing site) in Schmitt’s adaptor and that an ordinarily skilled artisan would have had reason to add the indexing site to the adaptor. *See* Ex. 1007 ¶¶ 6, 95 Ex. 1005 ¶¶ 13, 27, 92–96, Figs. 1, 3. We specifically credit the testimony of Dr. Metzker, who testified that the “fixed multiplexing barcode sequence” of Schmitt would have been understood by one of ordinary skill in the art to allow identification of the sample from which a particular sequence read originated. *See* Ex. 1003 ¶¶ 95, 108–116.

d) *[wherein the adaptor comprises] “a unique identifier having from about 1 to about 8 nucleotides”*

Petitioner contends 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. Pet. 35 (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.

Id. (citing Ex. 1007 ¶ 85).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that this portion of Schmitt teaches an adaptor comprising a unique identifier as recited in claim 1. Ex. 1003 ¶¶ 104–107.

Patent Owner has not provided separate arguments regarding this limitation of claim 1. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that Schmitt’s SMI is 3 to 20 nucleotides in length and constitutes an adaptor that falls within the range of “about 1 to about 8.” *See* Ex. 1007 ¶¶ 12, 26.

e) *[wherein the adaptor comprises] “a primer binding site”*

Petitioner contends that Schmitt discloses a primer binding site because it teaches “[o]ptionally, the SMI adaptor molecule further includes at least two PCR primer binding sites, at least two sequencing primer binding sites, or both.” Pet. 39 (citing Ex. 1007 ¶ 22, 51 (claim 5)). Petitioner cites other disclosures of Schmitt that refer to primer binding sites, including claim 5. *Id.* (citing Ex. 1007 ¶¶ 23, 31, Figs. 4A, B).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that these portions of Schmitt disclose an adaptor with a primer binding site. Ex. 1003 ¶¶ 117–118.

Patent Owner has not provided separate arguments regarding this limitation of claim 1. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner's position and find that Schmitt discloses a sequencing primer binding site/target sequence primer binding site in its SMI adaptor molecular. *See* Ex. 1007 ¶¶ 22, 23, 31, 51, Figs. 4A, B.

f) “*amplifying the adaptor-ligated fragments into amplicons*”;

Petitioner contends 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.” Pet. 40–41 (citing Ex. 1007 ¶ 10). 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.” *Id.* at 41 (citing Ex. 1007 ¶ 74).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that these portions of Schmitt disclose amplifying adaptor-ligated fragments into amplicons. Ex. 1003 ¶¶ 119–122.

Patent Owner has not provided separate arguments regarding this limitation of claim 1. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find 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.” *See* Ex. 1007 ¶ 10.

g) “*sequencing the amplicons to produce sequence reads that include identifier and target sequences;*”

Petitioner contends 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)” Pet. 41 (citing Ex. 1007 ¶ 10). 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. *Id.* at 41–42 (citing Ex. 1007 ¶ 74).

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. Pet. 42–43 (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.

Id. at 43–44 (citing Ex. 1007 ¶ 99).

Petitioner relies on the testimony of Dr. Metzker to support its position. 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 ¶ 126.

Patent Owner has not provided separate arguments regarding these limitations of claim 1. *See generally* PO Resp. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

After review of the entire trial record, we agree with Petitioner’s position and find that in Schmitt discloses an amplifying ligated fragments into amplicons using a PCR and sequencings those amplicons as shown in both Figures 3a–c and 4. *See* Ex. 1007 ¶¶ 10, 14–15, 74, 99.

h) “*identifying sequence reads with identical identifier and target sequences as duplicates*”

Petitioner contends 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.” Pet. 44 (citing Ex. 1007 ¶ 85). 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.” *Id.* (citing Ex. 1007 ¶ 85).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that one of ordinary skill in the art would have understood “true PCR duplicates” to mean nucleic acid sequences that are identical in addition to having the same SMI sequence. *Id.* at 44–45 (citing Ex. 1003 ¶¶ 127–128).

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.” Pet. 45 (citing Ex. 1007 ¶ 99). Again, Petitioner cites to Dr. Metzker’s testimony to support the argument 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 thus further show that both the target sequence and SMI sequence are used to identify PCR duplicates in the ’389 PCT Appl. (Schmitt).” *See* Ex. 1003 ¶ 128.

Patent Owner disputes Petitioner’s contentions. 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. PO Resp. 30–32; PO Sur-Reply 17–20. According to Patent Owner, Schmitt uses the SMI tag alone to identify duplicates before

the target sequence is used to create a consensus sequence without reference to the target sequence. PO Resp. 30–31; PO Sur-Reply 18. Patent Owner cites to Schmitt’s disclosure that the creation of the consensus sequence involves the comparison of “PCR duplicates”— sequences that have already been identified as duplicates without reference to the target sequences. PO Resp. 30 (citing Ex. 1007 ¶ 85); PO Sur-Reply 18.

Patent Owner argues further that Dr. Metzker’s deposition testimony does not support Petitioner, because Dr. Metzker could only point to Figure 3 of Schmitt for this limitation. PO Resp. 31 (citing Ex. 2108, 71:16–72:5). But, according to Patent Owner, nothing in Figure 3 relates to this disputed limitation. *Id.*

We disagree with Patent Owner. 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. In particular, Schmitt discloses that following SMI tagging and amplification, both the SMI and target sequences are used to collapse the reads and generate a consensus sequence and:

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 (emphasis added).

Patent Owner also does not dispute that the evidence cited by Petitioner, such as Figures 3a–c and 4 of Schmitt, teaches 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;).

We, therefore, determine that Petitioner has demonstrated by a preponderance of the evidence that the combined teaching of Schmitt and McCloskey render obvious the claim limitation of “identifying sequence reads with identical identifier and target sequences as duplicates.”

i) Reasons to Combine Schmitt and McCloskey

Petitioner contends a person of ordinary skill in the art would have had reason to combine the teachings of Schmitt with that of McCloskey because (i) both references are in the same field of endeavor, (ii) both reference are directed to solving the same problem, and (iii) Schmitt cites to McCloskey 2007—a paper by the same author as McCloskey that contains overlapping disclosures as McCloskey. Pet.37–39 (citing Ex. 1003 ¶¶ 114–16); Pet. Reply 19–23. Petitioner further contends a person of ordinary skill in the art would have reasonably expected success from the combination because they would have known how to include McCloskey’s batch stamp in Schmitt’s adaptor and because Schmitt teaches that adaptors may contain different types of sequences. Pet. 38 (citing Ex. 1003 ¶ 116).

Petitioner relies on the testimony of Dr. Metzker to support its position. Dr. Metzker testifies that an ordinarily skilled artisan would have known how to include different types of sequences into an adaptor, such as an SMI sequence and McCloskey’s batch-stamp. Ex. 1003 ¶¶ 109–116.

Patent Owner contends that Petitioner’s rationale to combine the teachings of Schmitt and McCloskey is deficient. PO Resp. 32–34. According to Patent Owner, Petitioner’s position is premised on improper hindsight and conclusory expert testimony. *Id.* at 32. Patent Owner argues that Petitioner makes no effort to explain why a POSA would have looked to the McCloskey adaptor specifically to modify the adaptors in Schmitt. *Id.* at 33. Patent Owner also argues that “Petitioner ignores the differences

between the structure of the Schmitt and McCloskey adaptors and how they might, or might not, work if combined.” *Id.* at 33–34. Patent Owner then argues that McCloskey is a “fundamentally limited” single-stranded target molecule methods that a person of ordinary skill in the art would not have combined with Schmitt. PO Sur-Reply 22–23.

We do not agree with Patent Owner for at least two reasons. First, Patent Owner fails to address the fact that Schmitt cites to McCloskey 2007. We find that the citation of McCloskey 2007 in Schmitt indicates that the ordinarily skilled artisan would have considered the teachings of McCloskey to be highly relevant to the teachings of Schmitt and would have considered them to be both useful in the field of sequencing. *See* Ex. 1005 ¶ 6.

Second, Patent Owner fails to explain or even identify the purported structural differences between Schmitt and McCloskey that would prevent the teachings of McCloskey from being relevant to Schmitt.

In addition, we credit the testimony of Dr. Metzker that one of ordinary skill in the art would have understood the benefits of adding a barcode to target sequences and would have looked to McCloskey and the batch-stamps it teaches because both Schmitt and McCloskey are in the same field and address the same problems. *See* Ex. 1003 ¶¶ 110, 114.

Accordingly, we find that Petitioner has demonstrated by a preponderance of the evidence that a person of ordinary skill in the art at the critical time would have had sufficient reason to combine the teachings of Schmitt and McCloskey to arrive at challenged claim 1.

j) Summary of Claim 1

On the complete trial record before us now, we determine Petitioner has demonstrated by a preponderance of the evidence that claim 1 of

the '357 patent would have been obvious in view of the combined teachings of Schmitt and McCloskey.

4. Analysis of Dependent Claims 2, 3, and 5–10

Petitioner presents arguments and evidence regarding obviousness of claims 2, 3, and 5–10 over Schmitt and McCloskey. Pet. 45–52; Pet. Reply 24.

Patent Owner argues only that Petitioner's challenges to the dependent claims fail because the challenge to claim 1 fails. PO Resp. 34–35; PO Sur-Reply 23. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have reviewed the entirety of the trial record and all evidence submitted for the challenged dependent claims. Based on the complete record, we determine that Petitioner has established by a preponderance of the evidence that the combined teachings of Schmitt and McCloskey render obvious the limitations as recited in claims 2, 3, and 5–10.

C. Alleged Obviousness of Claim 4 over Porreca and Illumina 2008 or Schmitt, McCloskey, and Illumina 2008

Petitioner challenges claim 4 as being obvious over the combined teaching of Porreca and Illumina 2008 under 35 U.S.C. § 103 and as being obvious over Schmitt, McCloskey, and Illumina 2008. Pet. 52–55; Pet. Reply 24. Patent Owner disputes Petitioner's position based upon its previous analysis of claim 1. PO Resp. 35; PO Sur-Reply 23–24; *see supra*, Sections III.A. and III.B.

1. Illumina 2008

Illumina 2008 is a brochure directed to next-generation sequencing sample preparation methods. Ex. 1008. Illumina 2008 provides sample strategies for multiplexing to increase scalability, while maintaining low

error rates. *Id.* at Abstr. Illumina discloses the use of adapter-modified ends of nucleic acid fragments, PCR amplification of said fragments, and indexing the fragments in a library. *Id.* at 2, Figs. 2, 3.

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. 1002, 26:36–37. 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. Pet. 52–53 (citing Ex. 1003 ¶¶ 143–154). Petitioner cites 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. *Id.* at 54 (citing Ex. 1008, 1). Petitioner contends that this disclosure demonstrates it was known that an adaptor could be sequenced separately from a target sequence. *Id.* (citing Ex. 1003 ¶¶ 143–145).

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. Pet. 54–55 (citing Ex. 1006 ¶ 295, Ex. 1007 ¶¶ 74, 86).

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 1, to cure the deficiencies of Porreca, Schmitt, and McCloskey that Patent Owner asserts. PO Resp. 35; PO Sur-Reply 23–24.

Because, as discussed above, Petitioner presents 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 that Petitioner fails to meet its burden regarding these challenges. Accordingly, we determine that Petitioner has established by a preponderance of the evidence that claim 4 is unpatentable under 35 U.S.C. § 103 over the combined teaching of Porreca and Illumina 2008 and over the combination of Schmitt, McCloskey, and Illumina 2008.

D. Alleged Obviousness of Claim 7 over Porreca and Illumina 2008 or Schmitt, McCloskey, and Illumina 2008

Petitioner challenges claim 7 as being rendered obvious by Porreca and Illumina 2008 or by Schmitt, McCloskey, and Illumina 2008 under 35 U.S.C. § 103. Pet. 55–58; Pet. Reply 24. Patent Owner disputes Petitioner’s position based upon its previous analysis of claim 1. PO Resp. 35; PO Sur-Reply 23–24; *see supra*, Sections III.A. and III.B.

Claim 7 recites the method of claim 1, “wherein the primer binding site is a universal target sequencing primer binding site.” Ex. 1002, 26:42–43.

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 are universal sequencing primer binding sites, citing to Dr. Metzker’s testimony in support. Pet. 55–58 (citing Ex. 1008, 1 (Figure 1 legend); Ex. 1003 ¶ 144). Petitioner argues further that one of ordinary skill in the art would have known how to successfully include the claimed binding sites into the Porreca or Schmitt adaptors. *Id.* at 57 (citing Ex. 1003 ¶¶ 146–148).

Petitioner cites Metzker 2010,⁷ which discusses using universal sequencing primers with the Illumina platform. *Id.* at 57–58 (citing Ex. 1010, 5).

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 1, to cure the deficiencies of Porreca, Schmitt, and McCloskey that Patent Owner asserts. PO Resp. 35; PO Sur-Reply 23–24.

Because, as discussed above, Petitioner presents 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 that Petitioner fails to meet its burden regarding these challenges. Accordingly, we determine that Petitioner has established by a preponderance of the evidence that claim 7 is unpatentable under 35 U.S.C. § 103 over the combined teaching of Porreca and Illumina 2008 and over the combination of Schmitt, McCloskey, and Illumina 2008.

IV. MOTION TO STRIKE

Petitioner moves to strike two arguments presented in Patent Owner's Sur-Reply. Mot. 1. Specifically, Petitioner contends that we should strike Patent Owner's arguments that (1) Schmitt's paragraph 99 does not disclose limitation 1.g of the '357 patent, and (2) McCloskey discloses "fundamentally limited" technology such that there would not have been a motivation to combine it with Schmitt. *Id.* According Petitioner, Patent Owner failed to raise these arguments in its Patent Owner Response, thus

⁷ Metzker, "Sequencing technologies – the next generation," 11 NATURE REVIEWS GENETICS 31 (2010) (Ex. 1010).

preventing Petitioner the opportunity to respond fully to the arguments and evidence. *Id.*

Patent Owner opposes Petitioner’s argument, asserting that motion to strike is premised on baseless procedural grounds. Opp. 1. Patent Owner contends that its Sur-Reply arguments are not new but are appropriate responses to Petitioner’s expanded arguments in its Reply. *Id.* at 7; 9–10. Patent Owner first argues that its citations to Schmitt Paragraph 99 actually “adds nothing on this issue, [and is] simply repeating that the duplicates are identified by only using the SMI tag.” *Id.* at 7 (citing Ex. 1007, 32–33). According to Patent Owner, its Sur-Reply specifically addresses Petitioner’s arguments in connection with the consensus sequence disclosures in Schmitt. *Id.* at 8.

Patent Owner next argues its Sur-Reply addresses Petitioner’s new and expanded arguments regarding the alleged motivation to combine McCloskey and Schmitt. *Id.* at 9–10. According to Patent Owner, its Sur-Reply responded to Petitioner’s expanded arguments and demonstrated why the statements did not address [Patent Owner]’s arguments on the differences of the adaptors of these references. *Id.* at 10 (citing Paper 28, 20–23). Patent Owner then concludes that its arguments are not new, the Board should not strike them, and that to do so would “unfairly allow Petitioner to get a free hand to expand upon its arguments while prohibiting [Patent Owner] from responding to those arguments.” *Id.*

We agree with Patent Owner. Specifically, we find that its citations and arguments were reasonably responsive to the arguments made by Petitioner in its Reply.

Additionally, the Board acts as both the gatekeeper of evidence and as the weigher of evidence. Rather than excluding evidence that is allegedly

untimely, confusing, misleading, and/or irrelevant, we will simply not rely on it or give it little weight, as appropriate, in our analysis. Similar to a district court in a bench trial, the Board, sitting as a non-jury tribunal with administrative expertise, is well positioned to determine and assign appropriate weight to evidence presented, including giving it no weight. *See, e.g., Donnelly Garment Co. v. N.L.R.B.*, 123 F.2d 215, 224 (8th Cir. 1941) (“One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received . . .”). Thus, in this *inter partes* review, the better course is to have a complete record of the evidence to facilitate public access as well as appellate review.

Moreover, Petitioner’s arguments are moot because the limitations of claim 1 have been shown to be met by both Porreca and by the combination of Schmitt and McCloskey notwithstanding Patent Owner’s arguments to the contrary. Thus, we deny the Petitioner’s Motion to Strike.

V. CONCLUSION⁸

For the foregoing reasons, we are persuaded that Petitioner establishes by a preponderance of the evidence that claims 1–10 of the ’357 patent have been shown to be unpatentable.

⁸ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner’s attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

In summary:

Claims	35 U.S.C. §	References/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–3, 5–10	102(a)	Porreca	1–3, 5–10	
1–3, 5–10	103	Schmitt, McCloskey	1–3, 5–10	
4	103	Porreca, Illumina 2008	4	
4	103	Schmitt, McCloskey, Illumina 2008	4	
7	103	Porreca, Illumina 2008	7	
7	103	Schmitt, McCloskey, Illumina 2008	7	
Overall Outcome			1–10	

VI. ORDER

In consideration of the foregoing, it is hereby

ORDERED that claims 1–10 of U.S. Patent No. 11,098,357 B2 have been shown to be unpatentable under 35 U.S.C. § 102 and § 103;

FURTHER ORDERED that Petitioner’s Motion to Strike is denied; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2025-00026
Patent 11,098,357 B2

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