

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN Sciences, LLC,
Petitioner,

v.

Tecan Genomics, Inc.,
Patent Owner.

Case IPR2025-00026

U.S. Patent No. 11,098,357

**PETITION FOR *INTER PARTES* REVIEW
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.100 *et seq.***

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1003	Expert Declaration of Michael L. Metzker, Ph.D. in support of the '357 patent IPR petition
1004	Miner et al, <i>Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR</i> , Nucleic Acid Research 32:17 (2004) (“ <i>Miner 2004</i> ”)
1005	U.S. Patent Publication No. 2007/0020640 (“ <i>McCloskey</i> ”)
1006	U.S. Patent Publication No. 2012/0165202 (“ <i>Porreca</i> ”)
1007	WO 2013/142378 (“ <i>Schmitt</i> ”)
1008	Illumina Publication No. 770-2008-011, <i>Multiplexed Sequencing with the Illumina Genome Analyze System</i> (2008) (“ <i>Illumina 2008</i> ”), available at https://web.archive.org/web/20101226144356/https://www.illumina.com/documents/products/datasheets/datasheet_sequencing_multiplex.pdf
1009	Authenticating affidavit of Nathaniel Frank-White from the Internet Archive, including the archived copy of <i>Illumina 2008</i>
1010	Michael L. Metzker, <i>Sequencing Technologies – the Next Generation</i> , Nature Reviews Genetics, Vol. 11 (2010) (“ <i>Metzker 2010</i> ”)
1011	Li et al, <i>The Sequence Alignment/Map format and SAMtools</i> , Bioinformatics 25(16) (2009) (“ <i>Li 2009</i> ”)
1012	Prosecution History of U.S. Patent No. 11,725,241
1013	Prosecution History of U.S. Patent No. 11,098,357
1014	Authenticating declaration of Sylvia D. Hall-Ellis, Ph.D.
1015	McCloskey et al., <i>Encoding PCR Products with Batch-stamps and Barcodes</i> , BIOCHEM GENET 45:761–767 (2007)
1016	Curriculum Vitae of Michael L. Metzker, Ph.D.
1017	Metzker & Caskey, <i>Polymerase Chain Reaction</i> , In ENCYCLOPEDIA OF MEDICAL DEVICES AND INSTRUMENTATION, Second Edition, Volume 5, pp.

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1019	Saiki <i>et al.</i> , <i>Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase</i> , SCIENCE 239:487-491 (1988) (“Saiki (1988)”)
1020	Gibbs <i>et al.</i> , <i>Detection of single DNA base differences by competitive oligonucleotide priming</i> , NUCLEIC ACIDS RESEARCH 17:2437-2448 (1989) (“Gibbs (1989)”)
1021	Newton <i>et al.</i> , <i>Analysis of any point mutation in DNA: The amplification refractory mutation system (ARMS)</i> , NUCLEIC ACIDS RESEARCH 17:2503-2516 (1989) (“Newton (1989)”)
1022	Chamberlain <i>et al.</i> , <i>Deletion screening of the Duchenne muscular dystrophy locus via multiplex DNA amplification</i> , NUCLEIC ACIDS RESEARCH 16:11141-11156 (1988) (“Chamberlain (1989)”)
1023	Gibbs <i>et al.</i> <i>Multiplex DNA deletion detection and exon sequencing of the hypoxanthine phosphoribosyltransferase gene in Lesch-Nyhan families</i> , GENOMICS 7:235-244 (1990) (“Gibbs (1990)”)
1024	Grompe, <i>The rapid detection of unknown mutations in nucleic acids</i> , NATURE GENETICS 5:111-117 (1993) (“Grompe (1993)”)
1025	Syvänen, <i>Accessing genetic variation: genotyping single nucleotide polymorphisms</i> , NATURE REVIEW GENETICS 2:930-942 (2011) (“Syvänen (2001)”)
1026	Metzker, <i>Emerging technologies in DNA sequencing</i> , GENOME RESEARCH 15:1767-1776 (2005) (“Metzker (2005)”)
1027	Rothberg <i>et al.</i> , <i>An integrated semiconductor device enabling non-optical genome sequencing</i> , NATURE 475:348-352 (2011) (“Rothberg (2011)”)
1028	Jain <i>et al.</i> , <i>Improved data analysis for the MinION nanopore sequencer</i> , NATURE METHODS 12:351-356 (2015) (“Jain (2015)”)
1029	Illumina, <i>Multiplexing, Sample preparation guide</i> (2010) (“Illumina Manual (2010)”)
1030	Illumina, <i>TruSeq™ RNA and DNA sample preparation kits</i> (2010)

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1031	Craig <i>et al.</i> , <i>Identification of genetic variants using barcoded multiplexed sequencing</i> , NATURE METHODS 5:887-893 (2008) ("Craig (2008)")
1032	Li & Durbin, <i>Fast and accurate short read alignment with Burrows–Wheeler transform</i> , BIOINFORMATICS 25:1754-1760 (2009) ("Li & Durbin (2009)")
1033	Quail <i>et al.</i> , <i>Improved protocols for the Illumina Genome Analyzer sequencing system</i> , CURRENT PROTOCOLS IN HUMAN GENETICS 18.2.1-18.2.27 (2009) ("Quail (2009)")

I. INTRODUCTION

Petitioner QIAGEN Sciences, LLC respectfully requests *Inter Partes* Review of U.S. Patent No. 11,098,357 (“the ’357 patent”), assigned to Tecan Genomics Inc., and cancellation of claims 1-10. Those claims are unpatentable as anticipated and/or obvious by the prior art references described below.

As explained by Dr. Michael Metzker,¹ the ’357 patent is directed to methods for detecting duplicate nucleic acid sequences that may arise from the PCR amplification process. To detect such duplicates, the ’357 patent claims the use of an identifier site, which is a sequence of nucleotides that is included in an adaptor appended to a target nucleic acid sequence. These identifier sites uniquely tag each nucleic acid molecule and are added to the target sequences prior to PCR amplification. After the nucleic acid products are amplified and sequenced, identical target sequences that also bear the same identifier sequence are identified as PCR duplicates. The use of an identifier sequence to detect duplicates, however, was well-known in the art since well before the ’357 patent.

By the earliest possible priority date of the ’357 patent, November 13, 2013, the use of identifier sequences to detect PCR duplicates was well-known. *Porreca*, *Schmitt*, and *McCloskey* are all prior art references that disclose this and that were

¹ Dr. Metzker is an expert in nucleic acid sequencing. EX1003¶¶4-19. Dr. Metzker provides a declaration supporting Petitioner’s positions that claims 1-16 of the ’241 patent are invalid. EX1003¶¶1-150.

not considered by the examiner. As discussed in detail below, all of the challenged claims are anticipated and/or rendered obvious by the asserted art.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest for Petitioner are QIAGEN Sciences, LLC, QIAGEN Gaithersburg, LLC f/k/a QIAGEN Gaithersburg, Inc., QIAGEN GmbH, and QIAGEN N.V.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

The following judicial or administrative matters may affect or be affected by a decision in this proceeding: *Tecan Genomics, Inc. v QIAGEN Sciences, LLC et al*, 1:23-cv-01115-GBW (D. Del.) (“District Court litigation”). In that action, Patent Owner has asserted the ’357 patent. Patent Owner also asserts U.S. Patent Nos. 10,036,012 (“the ’012 patent”), 10,876,108 (“the ’108 patent”), and 11,725,241 (the “’241 patent”). The ’241 patent is a continuation of the ’357 patent and shares a similar specification. Patent Owner has also asserted the ’357 patent in *Tecan Genomics, Inc. v. Invitae Corp. et al*, No. 23-cv-1114-GBW (D. Del.).

Petitioner concurrently is filing a petition challenging the asserted claims of the ’241 patent, ’012 patent, and ’108 patent and thus lists: Petitions for *Inter Partes* Review of U.S. Patent Nos. 10,036,012, 10,876,108, and 11,725,241 (Petitions filed contemporaneously). Petitioner also notes the petitions filed by Integrated DNA Technologies, Inc. (“IDT”) in cases IPR2024-01506, IPR2024-01504, and IPR2024-

01502, which request IPR of the '241 patent, '357 patent, and related U.S. Patent No. 9,546,399.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4))

Petitioner hereby identifies its lead and backup counsel as follows:

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at the following address: qe-qiagen-tecan@quinnemanuel.com.

E. Payment of Fees (37 C.F.R. §§ 42.103 and 42.15(a))

The requisite filing fee of \$41,500 (request fee of \$19,000, post-institution fee of \$22,500) for a Petition for *Inter Partes* Review is submitted herewith. Claims 1-10 of the '357 patent are being reviewed as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 505708. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a); 37 C.F.R. §§ 42.101(a)-(c))

Petitioners certify that the '357 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review. Patent Owner served the summons and complaint in the District Court litigation on Petitioner on October 10, 2023, which is not more than one year from the filing of this Petition. *See e.g., Brinkmann Corp. v. A&J Mfg., LLC*, IPR2015-00056, Paper No. 10, 6-7 (P.T.A.B. March 23, 2015).

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of claims 1-10 of the '357 patent (“the Challenged Claims”) and that the PTAB cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioners respectfully request that the Board grant institution of IPR on the Challenged Claims based on the following grounds:²

Ground I	Claims 1-3, 5-10 are anticipated under 35 U.S.C. § 102(a) ³ by <i>Porreca</i>
Ground II	Claims 1-3, 5-10 are rendered obvious under 35 U.S.C. § 103 over <i>Schmitt</i> in view of <i>McCloskey</i>
Ground III	Claim 4 is rendered obvious under 35 U.S.C. § 103 over <i>Porreca</i> in view of <i>Illumina 2008</i>
Ground IV	Claim 4 is rendered obvious under 35 U.S.C. § 103 over <i>Schmitt</i> in view of <i>McCloskey</i> and in further view of <i>Illumina 2008</i>
Ground V	Claim 7 is rendered obvious under 35 U.S.C. § 103 over <i>Porreca</i> in view of <i>Illumina 2008</i>
Ground VI	Claim 7 is rendered obvious under 35 U.S.C. § 103 over <i>Schmitt</i> in view of <i>McCloskey</i> and in further view of <i>Illumina 2008</i>

² See EX1003.¶3.

³ The earliest potential priority date is November 13, 2013. Accordingly, the post-AIA version of 35 U.S.C. §§ 102 and 103 applies to the Challenged Claims.

V. THE '357 PATENT

A. Overview

The '357 patent issued from Application No. 16/743,604 (“’604 application”), filed on January 15, 2020. The '357 patent claims priority to U.S. Provisional Application No. 61/903,826 (“’826 Provisional”), filed on November 13, 2013.⁴

The '357 patent is related to the field of “high throughput sequencing reactions” and directed to methods of detecting duplicate nucleic acid sequences in multiplex sequencing reads. EX1002 at 1:27-30, Claim 1; EX1003.¶¶20-21,47-51. The patent refers to identical sequences resulting from PCR amplification as “PCR duplicates” or “true duplicates.” *Id.* at 1:37-42, 2:3-9. When sequencing nucleic acid, such as DNA or RNA, “accurate gene expression measurements may be hampered by PCR duplicate artifacts that occur during library amplification.” *Id.* at 1:35-37. In a sequencing read where “two or more identical sequences are found,” it can be difficult to determine whether those identical sequences represent unique nucleic acid molecules, or if they are “PCR duplicates derived from a single” nucleic

⁴ Petitioner applies November 13, 2013 as the priority date for the '357 patent in this Petition, EX1003.¶¶39-40; however, Petitioner does not concede that Tecan is entitled to this priority date.

acid molecule. *Id.* at 1:36-42. Including PCR duplicates, or true duplicates, in the sequencing read can result in biased data and inefficiencies.

The '357 patent purports to solve the problems created by PCR duplicates or true duplicates by providing “methods for identifying true duplicate reads during sequencing, such as to improve data analysis of sequencing data.” *Id.* at 2:7-10. To identify true duplicate reads, the patent discloses the use of an “identifier site” that can be included in an “adaptor” ligated to the target nucleotide to be sequenced. *Id.* at 4:19-39. The identifier site “is a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” *Id.* at 4:49-51. Because the identifier site is attached to the DNA prior to amplification, *id.* at Figure 2A, DNA fragments containing the same identifier sequence can be identified as PCR duplicates, or true duplicates. *Id.* at 14:28-31.

B. The Challenged Claims

Among the Challenged Claims, only claim 1 is independent. For ease of reference, Petitioner has labeled the limitations of claim 1 as follows:

Claim 1	
1.p	A method for detecting duplicate sequencing reads, the method comprising:
1.a	ligating an adaptor to each of a plurality of nucleic acid fragments;
1.b	wherein each adaptor comprises a unique identifier having from about 1 to about 8 nucleotides,
1.c	an indexing site unique to a subset of the adaptors,

1.d	and a primer binding site;
1.e	amplifying the adaptor-ligated fragments into amplicons;
1.f	sequencing the amplicons to produce sequence reads that include identifier and target sequences; and
1.g	identifying sequence reads with identical identifier and target sequences as duplicates

C. Prosecution History

As noted above, the '357 patent issued from the '604 application, which was filed on January 15, 2020. On December 8, 2020, the examiner issued an office action, rejecting all pending claims as obvious. EX1013.0077-86. In rejecting the claims, the examiner interpreted several claim terms, including “adaptor” and “junction.” EX1013.0077-78. The examiner noted that the patent’s definition of “adapter” means that “any oligonucleotide is considered to anticipate this term.” And with respect to “junction,” the examiner remarked that “Applicant did not define the term ‘junction’, therefore it is considered as any region of the adapter.” EX1013.0077-78. Patent Owner then amended the claims to add the “indexing site” limitation, EX1013.0066, and the examiner thereafter allowed the claims. EX1013.0035-37.

VI. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSA”) as of the earliest possible priority date of the patent (November 13, 2013) would have (i) a Ph.D. in molecular

biology, molecular genetics, bioinformatics, biochemistry, or a related field and 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 or (ii) a Master’s degree in one of the same fields with at least four years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and high-throughput sequencing technologies. EX1003.¶41.

VII. CONSTRUCTION OF THE CHALLENGED CLAIMS⁵

Rules 42.104(b)(3) and (4) require a petition to identify, for each challenged claim, “[h]ow the challenged claim is to be construed” and “[h]ow the construed claim is unpatentable” under that construction. 37 C.F.R. §§ 42.104(b)(3), (4).

The Board should construe “adaptor” as “any oligonucleotide that is attached to the target sequence.” The ’357 patent refers to an “adaptor” as “an oligonucleotide sequence, the ligation of which to a target polynucleotide or a target polynucleotide

⁵ Petitioners reserve the right to pursue different claim constructions, including that certain claim terms are indefinite, during this and related proceedings as well as in any district court litigation concerning the ’357 patent. *See Samsung Elecs. Am., Inc. v. Prisia Eng’g Corp.*, 948 F.3d 1342, 1350 (Fed. Cir. 2020) (“[T]he Board may not cancel claims for indefiniteness in an IPR proceeding.”).

strand of interest enables the generation of amplification-ready products of the target polynucleotide or the target polynucleotide strand of interest.” EX1002 at 4:20-25. This described function, however, is performed by any oligonucleotide. Indeed, during prosecution, the examiner considered the above language from the specification and explained “since any oligonucleotide can perform such function, any oligonucleotide is considered to anticipate this term.” EX1013.0077.

Petitioner also notes that adaptors are not limited to only those that are ligated. The patent states that “appending the adaptor to the nucleic acid fragments generated by methods described herein can be achieved using a ligation reaction **or a priming reaction**.” EX1002 at 9:43-46 (emphasis added). Additionally, Claim 10 of the ’241 patent, which is a continuation of the ’357 patent, allows for the adaptor to be appended via a priming reaction. EX1001.claim.10. “Because NTP's patents all derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.” *NTP, Inc. v. Rsch. In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005). As such, the Board should adopt Petitioner’s construction, which is also consistent with the examiner’s interpretation. EX1003.¶¶52-53.

VIII. THE PRIOR ART

Polymerase chain reaction (PCR) is a technique that can rapidly amplify (*i.e.*, create multiple copies of) DNA from only a small sample, and is a critical step in

DNA sequencing analysis. EX1003.¶¶22-37. One of the consequences in using PCR amplification, however, is that there may be uncertainty as to the source of the template DNA that gave rise to a particular PCR product. Because PCR amplification results in multiple copies (*i.e.*, duplicates) of the exact same sequence of nucleotides, it may be unclear whether those duplicates are PCR amplification products or whether the same sequence independently exists in another portion of the genome. It is desirable to identify which duplicates are merely PCR amplification products, as those copies do not provide useful information and will overrepresent the data. For instance, if a particular sequence contains a mutation, and that sequence is amplified ten-fold, then there will be ten copies of that mutation in the sequencing read even though there was only a single occurrence of the mutation.

Since at least the mid-2000s, and certainly before November 13, 2013, the priority date of the '357 patent, the use of molecular identifiers to identify PCR duplicates was well understood in the art. EX1003.¶¶22-38,54-69. For example, Miner, published in 2004, discloses the use of “molecular barcoding to label each genomic DNA template with an individual sequence tag prior to PCR amplification.” EX1004.0001. Miner recognized that there was “frequent observation of multiple amplified sequences derived from a single original molecule,” and taught the marking of each genomic fragment to allow for the identification of “redundant

sequences.” EX1004.0001. Miner’s method allowed for the “confirmation of the independent genomic origin of all sequences in final data sets derived from PCR amplification,” EX1004.0001, and thus taught the identification of PCR duplicates as all sequences that derive from the same genomic origin. EX1003.¶38.

The references below further demonstrate that the ’357 patent’s claimed method of identifying PCR duplicates was well-known in the art. Each of the references below qualifies as prior art under 35 U.S.C. § 102(a) to the Challenged Claims, which are entitled to a priority date of no earlier than November 13, 2013, the date on which the ’826 provisional was filed.

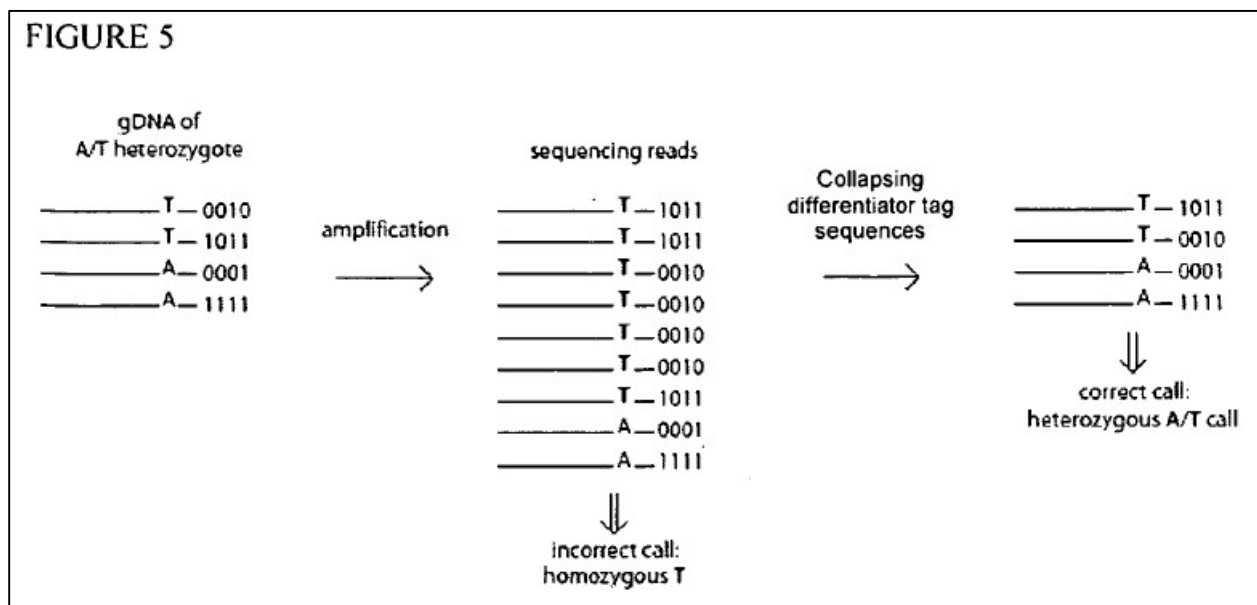
A. *Porreca*

Porreca (EX1006) is a U.S. Patent Application titled “Methods and Compositions for Evaluating Genetic Markers.” It was filed as a PCT on April 30, 2010 and published on June 28, 2012. It is prior art under 35 U.S.C. § 102(a), but was not cited during prosecution. *Porreca* is directed to next generation sequencing (NGS) techniques, specifically, the sequencing and analysis of nucleic acids and the disclosure of various methods of preparing nucleic acid libraries and sequencing regions of interest. EX1003.¶¶55-59.

Porreca teaches methods of identifying PCR duplicates and samples from which the sequences originated. *Porreca* teaches the use of “differentiator tag sequences” that “uniquely tag individual nucleic acid molecules.” EX1006.¶23.

Porreca teaches 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).” EX1006.¶24.

To address the over-representation by PCR duplicates, *Porreca* teaches that “any target:differentiator tag combination observed more than once” should be “‘collapsed’ into a single read.” EX1006.¶298. Figure 5 depicts this process:



EX1006.Fig.5. Figure 5 shows several PCR duplicates resulting from the amplification step. The sequencing reads show that there are three copies of the sequence containing the “1011” differentiator tag and four copies containing the “0010” tag. These duplicates are eliminated from the final read after the step “[c]ollapsing differentiator tag sequences,” which results in a single read for each

differentiator tag sequence. EX1003.¶¶55-59. *Porreca* further teaches the use of “barcodes” that can “uniquely identify individual samples (e.g., patient samples) that may be mixed together.” EX1006.¶149; EX1003.¶¶55-59.

B. *Schmitt*

Schmitt (EX1007) is a PCT application titled “Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing.” It was filed on March 15, 2013 and was published on September 26, 2013. It is prior art under 35 U.S.C. § 102(a), but was not cited during prosecution. *Schmitt* is also directed to NGS techniques and teaches methods of addressing errors and bias associated with NGS, including through the use of small molecule identifiers. EX1003.¶¶60-62.

Schmitt teaches a method of identifying PCR duplicates, here through the use of a “single molecule identifier (SMI) adaptor molecule” that can be attached to the DNA fragments being sequenced and that uniquely identifies each fragment. EX1007.¶9. *Schmitt* further teaches 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.” EX1007.¶85; EX1003.¶¶60-62. Because it is desirable to “restrict sequencing analysis to uniquely sequenced DNA fragments, many sequencing studies include a step to filter out PCR

duplicates.” EX1007.¶85. *Schmitt* eliminates PCR duplicates by grouping reads with common target and SMI sequences and collapsing them to “generate a consensus read.” EX1007.¶96;EX1003.¶¶60-62.

C. *McCloskey*

McCloskey (EX1005) is a U.S. Patent Application titled “Molecular encoding of nucleic acid templates for PCR and other forms of sequence analysis.” It was filed on July 21, 2005, published on January 25, 2007, and is prior art under 35 U.S.C. § 102(a), but was not cited during prosecution. *McCloskey* names Brooks Miner as a co-inventor, who is the first author of the Miner 2004 paper described above. *McCloskey* is directed to methods of authenticating a nucleic acid molecule and its sequence with a molecular barcode and batch-stamp, which allow for the identification of individual DNA molecules and the sample from which the DNA originated, respectively. *McCloskey* explains that PCR can generate multiple copies of DNA sequences from a limited amount of DNA, but that such reactions 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.” EX1005.¶3. To address this problem, *McCloskey* discloses the tagging of individual DNA molecules with a “barcode” to distinguish redundant sequences (i.e., duplicates). EX1005.¶5. Specifically, *McCloskey* teaches an adaptor containing both a “random barcode” and a “batch-stamp” that is attached to a target DNA sequence prior to PCR

amplification. EX1005.¶46. The barcode allows for the identification of redundant sequences, EX1005.¶5;EX1003.¶¶63-66, and the batch-stamp identifies which sample each sequence originated from, EX1005.¶16;EX1003.¶¶63-66. McCloskey further teaches the removal of duplicate reads. EX1005.¶63;EX1003.¶¶63-66.

D. *Illumina 2008*

Illumina 2008 (EX1008) is datasheet published by Illumina titled “Multiplexed Sequencing with the Illumina Genome Analyzer System.” This datasheet is dated December 2, 2008, EX1008.0004, and was available on Illumina’s website as early as December 26, 2010. EX1009.0002,05. *Illumina 2008* is directed to Illumina’s NGS platform and explains Illumina’s sample preparation methods. As Illumina was the largest provider of NGS instruments as of November 13, 2013, the earliest possible priority date for the ’357 patent, a POSA would have been well-aware of Illumina’s NGS platform and sample preparation methods. EX1003.¶¶67,143-150.

E. *Metzker 2010*

Metzker 2010 (EX1010) is an article published in the journal *Nature Reviews* and is titled “Sequencing technologies – the next generation.” *Metzker 2010* was published online on December 8, 2009. It is prior art under 35 U.S.C. § 102(a). EX1014.0026-31. *Metzker 2010* is a review article on next generation sequencing technology that discusses “template preparation, sequencing and imaging, genome

alignment and assembly approaches, and recent advances in current and near-term commercially available NGS instruments.” EX1010.0004;EX1003.¶¶68-69. It focuses on technologies from “Roche/454, Illumina/Solexa, Life/APG and Helicos BioSciences, the Polonator instrument and the near-term technology of Pacific Biosciences.” EX1010.0004.

IX. DETAILED EXPLANATION OF GROUNDS FOR INVALIDITY

A. Ground I: Claims 1-3, 5-10 Are Anticipated by *Porreca*⁶

For the reasons set forth below, the Challenged Claims are invalid as anticipated under 35 U.S.C. § 102 by *Porreca*.

1. Independent Claim 1

(a) Limitation 1.p

To the extent the preamble is considered limiting, *Porreca* discloses a “method for detecting duplicate sequencing reads, the method comprising.” EX1003.¶¶71-72. *Porreca* teaches “the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules.” EX1006.¶23. “[E]ach nucleic acid molecule may be tagged with a unique differentiator tag,” EX1006.¶142, 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

⁶ EX1003.¶¶42-43,70-99.

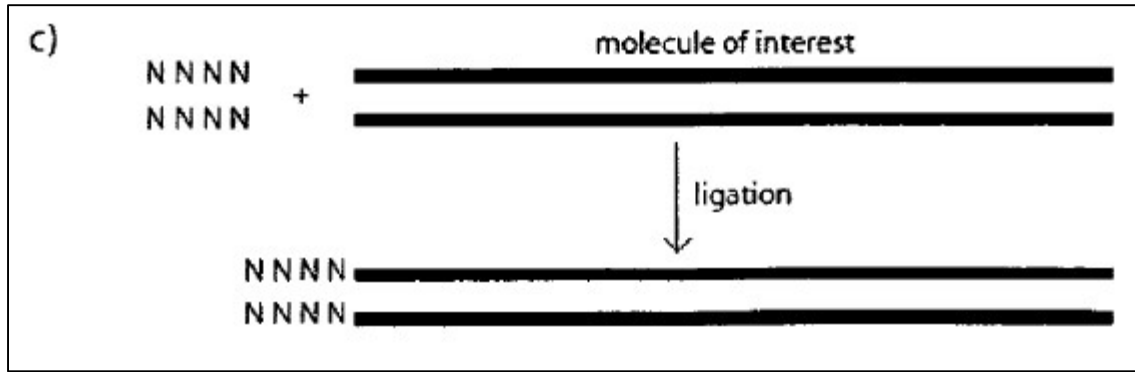
step, for example, **amplification**.” EX1006.¶24 (emphases added). And because the differentiator tags are attached to the nucleic acid fragments prior to amplification, *see* EX1006.¶¶ 253-298; *see also* EX1006.Fig.5, each identical sequence bearing the same differentiator tag will be PCR duplicates of one another. EX1003.¶¶71-72.

(b) Limitation 1.a

Porreca discloses “ligating an adaptor to each of a plurality of nucleic acid fragments.” EX1003.¶¶73-74. *Porreca* discloses an adaptor comprising a differentiator tag sequence that can be appended via ligation to the sequence of interest:

The 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. This is a flexible method, because molecules having differentiator tag sequence can be ligated to any blunt-ended nucleic acids.

EX1006.¶150. Figure 4C illustrates an example of this, where an adaptor comprising a differentiator tag sequence (NNNN) is ligated to the nucleic acid molecule of interest:



EX1006.Fig.4C. *Porreca* further discloses that the differentiator tag may also be included as part of a sequencing adaptor: “[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.” EX1006.¶150. This adaptor also includes a barcode and a primer binding site, as explained below in Limitations 1.c and 1.d.

(c) Limitation 1.b

Porreca discloses “wherein each adaptor comprises a unique identifier having from about 1 to about 8 nucleotides.” EX1003.¶¶75-76. *Porreca*’s differentiator tag sequence discloses the claimed “unique identifier.” These differentiator tags “may be created by using degenerate, random-sequence polynucleotides of defined length,” EX1006.¶143, and may be “up to 5...up to 8...up to 25, or more nucleotides in length.” EX1006.¶141. These differentiator tags are compatible with any of the amplification based methods disclosed in *Porreca*: “It 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.”

EX1006.¶31.

Porreca further teaches that each nucleic acid molecule is uniquely tagged with its own differentiator tag sequence. *See, e.g.*, EX1006.¶23 (“the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules”); EX1006.¶142 (“During a library preparation process, each nucleic acid molecule may be tagged with a unique differentiator tag sequence”); EX1006.¶143 (“A large library of unique differentiator tag sequences may be created....”); EX1006.¶139 (“In some embodiments, a threshold number of independently isolated molecules (e.g., unique combinations of differentiator tag and target sequences) is analyzed to determine the genotype of a subject”).

(d) Limitation 1.c

Porreca discloses “an indexing site unique to a subset of the adaptors.” EX1003.¶¶77-79. *Porreca* teaches adaptors that include “barcodes” to uniquely identify particular samples. “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.” EX1006.¶149 (emphases added). *Porreca* additionally teaches 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.” EX1006.¶102.

A POSA would have known that *Porreca*’s “barcode” is appended to the target nucleic acid sequence as part of the adaptor described in Limitations 1.a and that all nucleic acids from the same sample would have an identical barcode. EX1003.¶¶77-79. This allows for multiple samples to be run together, which is known as “multiplexing.” After amplification and sequencing, the sample can be “demultiplexed” by grouping together the sequencing reads that bear the same barcode. *Porreca*’s barcode disclosure thus satisfies the ’357 patent’s “indexing site” limitation. EX1003.¶¶77-79; *see also* EX1002 at 4:40-44.

(e) Limitation 1.d

Porreca discloses “a primer binding site.” EX1003.¶¶80-81. *Porreca* teaches that, in addition to including differentiator tags, adaptors include primer binding sites. “Adapters often contain PCR primer sites (for amplification or emulsion PCR) and/or sequencing primer sites.” EX1006.¶149. “Primers 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.” EX1006.¶29. *Porreca* additionally teaches that sequencing primers may be included as part of the adaptor: “The sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence. Alternatively, 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.” EX1006.¶150.

Porreca also teaches the use of a “common adaptor,” which a POSA would know is also known as a universal adaptor and includes a primer binding site to enable amplification and/or sequencing of all amplicons with a common primer sequence. EX1003.¶¶80-81.

Another method is to incorporate the differentiator tag sequence into a PCR primer, such that the primer structure is arranged with the **common adaptor sequence** followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5' to 3' order). A differentiator tag sequence and adaptor sequence (which may contain the sequencing primer site) are incorporated as tags.

EX1006.¶150 (emphasis added).

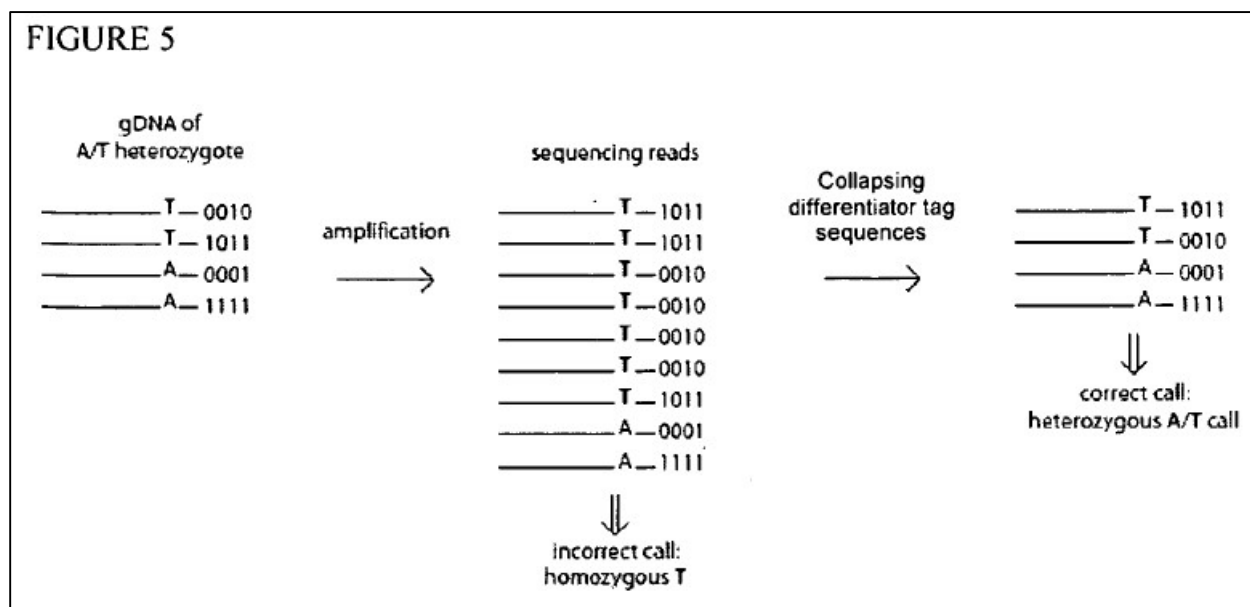
(f) Limitation 1.e

Porreca discloses “amplifying the adaptor-ligated fragments into amplicons.” EX1003.¶¶82-83. Once the adaptor described above in Limitations 1.a-d is ligated to the nucleic acid molecule of interest, the resulting product is amplified by PCR to produce amplicons. EX1003.¶¶82-83. For example, *Porreca* states that:

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**).

EX1006.¶24 (emphasis added). PCR amplifies the target sequence as well: “[i]n amplification-based (e.g., PCR-based or LCRbased, etc.) preparative methods, genomic loci (target nucleic acids) are isolated directly by means of a polymerase chain reaction or ligase chain reaction (or other amplification method) that selectively amplifies each locus using a pair of oligonucleotide primers.” EX1006.¶66.

Figure 5 shows an example of this:



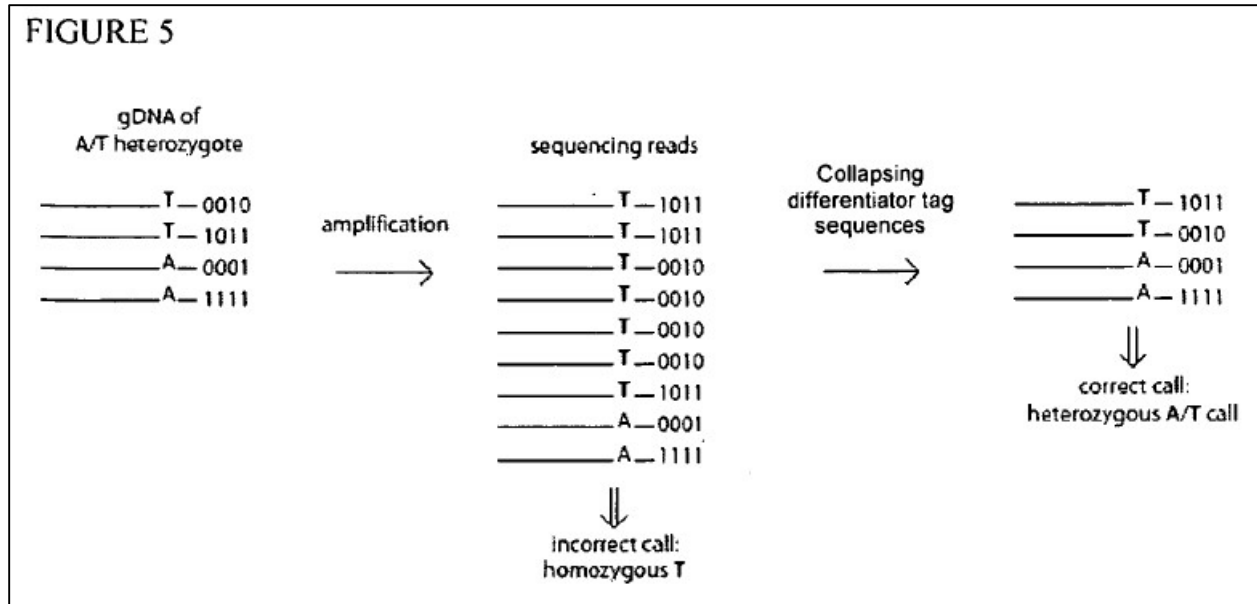
EX1006.Fig.5. Figure 5 shows four nucleic acid molecules of interest, each with an appended adaptor comprising a differentiator tag sequence (e.g., “0010” or “1011”).

These molecules are then amplified to produce several amplicons, which are shown under “sequencing reads.” *Porreca*’s disclosure of PCR products containing the target sequence as well as an appended adaptor (the differentiator tag) meets this claim limitation. EX1003.¶¶82-83.

(g) Limitation 1.f

Porreca discloses “sequencing the amplicons to produce sequence reads that include identifier and target sequences.” EX1003.¶¶84-85. *Porreca* teaches that amplicons comprising a differentiator tag appended to a target nucleic acid molecule (described above in Limitation 1.a) are sequenced, and that the resulting sequencing reads contain both differentiator and target sequences. “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).” EX1006.¶142. “[T]he 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.” EX1006.¶138. “The sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence.” EX1006.¶150.

Figure 5 discloses this limitation as well:



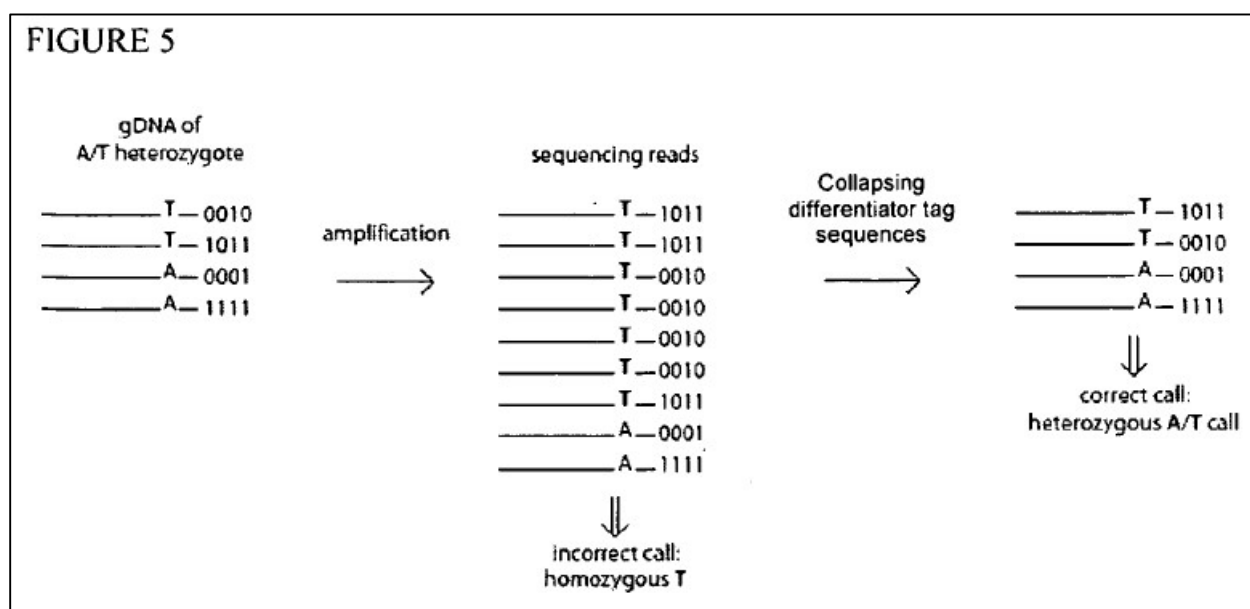
EX1006.Fig.5. “FIG. 5 depicts a non-limiting method for genotyping based on target and differentiator tag sequences. Sequencing reads of target and differentiator tags sequences are collapsed to make diploid genotype calls.” EX1006.¶148.

(h) Limitation 1.g

Porreca discloses “and identifying sequence reads with identical identifier and target sequences as duplicates.” EX1003.¶¶86-88. *Porreca* teaches that differentiator tags can be used to determine whether particular nucleic acid molecules are copies from PCR amplification (i.e., duplicates). Because each nucleic acid molecule is appended to a unique differentiator tag prior to amplification, molecules having identical nucleic acid sequences and bearing the same differentiator tag are duplicates of one another. EX1003.¶¶86-88. *Porreca* explains that:

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**).

EX1006.¶24 (emphases added). A POSA would understand that in order to have “multiple copies of the same target nucleic acid molecule,” the target nucleic acid sequence must be identical. Figure 5 demonstrates that sequences having the same target nucleic acid sequence and differentiator tag are identified and collapsed:



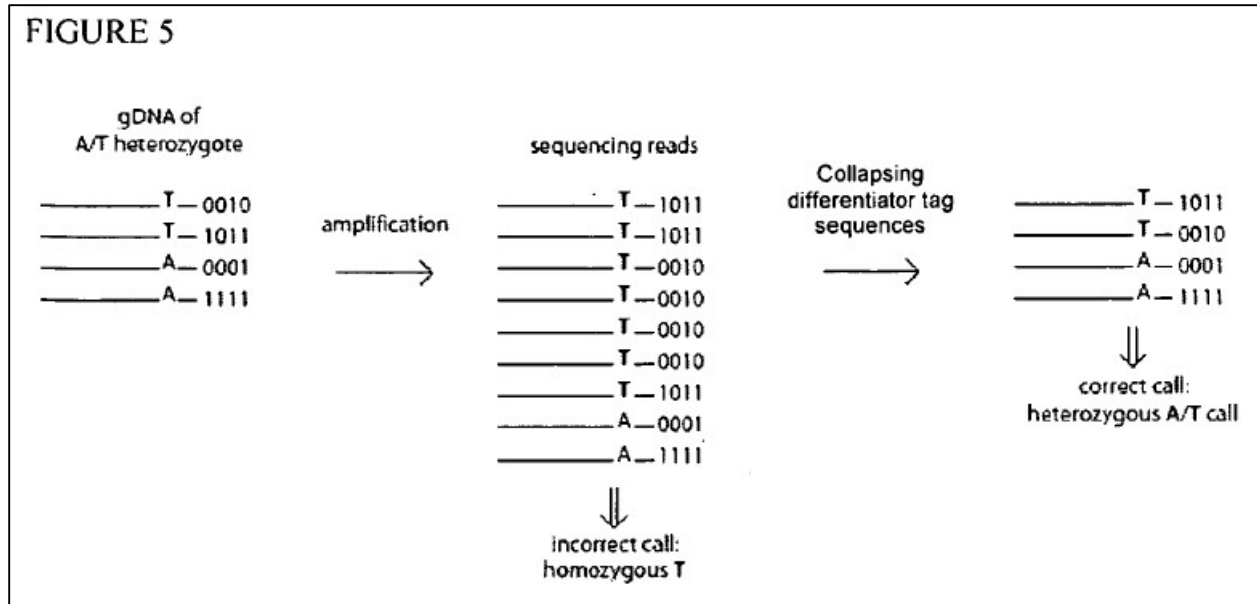
EX1006.Fig.5. *Porreca* explains that Figure 5’s identification and collapsing of duplicate sequencing reads occurs after both the target and differentiator tag sequences are sequenced. “FIG. 5 depicts a non-limiting method for genotyping based on target and differentiator tag sequences. Sequencing reads of target and differentiator tags sequences are collapsed to make diploid genotype calls.”

EX1006.¶148. Figure 5 shows that duplicate sequences, such as two of the “T-1011” and three of the “T-0010” sequences, were identified as duplicates and collapsed in the final read.

A POSA would have understood that the “T” represents a single nucleotide of the target sequence shown in Figure 5. EX1003.¶¶86-88. A POSA would have further understood 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. EX1003.¶¶86-88; *see also* EX1006.¶298 (“For any target:differentiator tag combination observed more than once, all such reads are 'collapsed' into a single read before consensus basecalls are determined”).

2. Claim 2

Porreca discloses “[t]he method of claim 1, further comprising removing a duplicate read from the sequence reads.” EX1003.¶¶89-90. As explained above for Limitation 1.g, *Porreca* discloses the identification and “collapsing” of duplicate reads. A POSA would have understood that “collapsing” the sequences means that the sequences having identical target and differentiator tag sequences are removed from the analysis. EX1003.¶¶89-90. This is shown in Figure 5:



EX1006.Fig.5. There are four copies of the “T-0010” nucleic acid product, all of which have the same target sequence (one nucleotide of which is “T”) and the same “0010” differentiator tag sequence. EX1003.¶¶89-90. There are also three copies of the “T-1011” nucleic acid product, all of which have the same target sequence (one nucleotide of which is “T”) and the same “1011” differentiator tag sequence. EX1003.¶¶89-90. After the collapsing step, only a single copy of the “T-0010” product and “T-1011” product remain. This demonstrates removal of the duplicate copies of both of those products. EX1003.¶¶89-90. Indeed, the ’357 patent mentions that collapsing reads is one method of removing duplicates: “duplicate reads can be considered noninformative and may be collapsed down to a single read, thus reducing the number of sequencing reads used in final analysis.” EX1002 at 1:43-46; EX1003.¶¶89-90.

3. Claim 3

Porreca discloses “[t]he method of claim 1, wherein the identifier site is sequenced with the target sequence.” EX1003.¶91. *Porreca* explains that the differentiator tag and the target sequence can be sequenced together. “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...” EX1006.¶142. “In 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.” EX1006.¶138; *see also* EX1006.¶150, Fig. 5.

4. Claim 5

Porreca discloses “[t]he method of claim 1, wherein the nucleic acid fragments comprise RNA.” EX1003.¶92. *Porreca* teaches the application of its methods to the analysis of RNA. “It should be appreciated that probes, primers, and other nucleic acids designed or used herein may be synthetic, natural, or a combination thereof...The nucleic acid may be DNA or RNA, such as genomic DNA, mitochondrial DNA, mRNA, cDNA, rRNA, miRNA, or a combination thereof.” EX1006.¶200. “A nucleic acid may be a peptide nucleic acid (PNA), locked nucleic acid (LNA), DNA, RNA, or co-nucleic acids of the same such as

DNA-LNA co-nucleic acids.” EX1006.¶204. *Porreca*’s discussion of RNA sequencing, “RNA-seq for gene expression,” EX1006.¶136, discloses the claimed use of RNA as well.

5. Claim 6

Porreca discloses “[t]he method of claim 1, wherein the nucleic acid fragments are genomic DNA fragments or cDNA fragments.” EX1003.¶¶93-94. *Porreca* explains that its disclosed methods can be applied to the analysis of various types of nucleic acids, including genomic DNA. “It should be appreciated that probes, primers, and other nucleic acids designed or used herein may be synthetic, natural, or a combination thereof...Nucleic acids can be obtained from **natural sources**...The nucleic acid may be DNA or RNA, such as **genomic DNA**....” EX1006.¶200 (emphases added).

Porreca also discloses embodiments analyzing genomic DNA:

This ensures that products of the preparative methods include only unique target:differentiator tag sequence; e.g., in a MIP reaction the capture step would undersample the total population of unique differentiator tag sequences in the MIP. For example, an experiment utilizing 1 µg of **genomic DNA** will contain about ~150,000 copies of a diploid genome.

EX1006.¶147 (emphasis added). *Porreca* also discloses the application of its methods to the analysis of cDNA. “It should be appreciated that probes, primers, and other nucleic acids designed or used herein may be synthetic, natural, or a

combination thereof...The nucleic acid may be DNA or RNA, such as genomic DNA, mitochondrial DNA, mRNA, cDNA, rRNA, miRNA, or a combination thereof.” EX1006.¶200. *Porreca* additionally discloses a method of incorporating the differentiator tag at the cDNA level: “[a]nother method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer. This allows the differentiator tag sequence to be incorporated directly at the cDNA level.” EX1006.¶150.

6. Claim 7

Porreca discloses “[t]he method of claim 1, wherein the primer binding site is a universal target sequencing primer binding site.” EX1003.¶¶95-96. For example, *Porreca* discloses “sequencing primer sites,” which a POSA would understand to satisfy this limitation. EX1003.¶¶95-96. “Adapters often contain PCR primer sites (for amplification or emulsion PCR) and/or sequencing primer sites.” EX1006.¶149 (emphasis added). “Alternatively, the sequencing adaptors can be synthesized with the random differentiator tag sequences at their 3’ end.” EX1006.¶150. *Porreca* also discloses a “common adaptor,” which a POSA would have known is also referred to as a universal adaptor, and would have understood includes a “universal target sequencing primer binding site” to enable sequencing of all amplicons with a common primer sequence. EX1003.¶¶95-96.

Another method is to incorporate the differentiator tag sequence into a PCR primer, such that the primer structure is arranged with the

common adaptor sequence followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5' to 3' order). A differentiator tag sequence and adaptor sequence (which may contain the sequencing primer site) are incorporated as tags.

EX1006.¶150 (emphasis added).

7. Claim 8

Porreca discloses “[t]he method of claim 1, wherein each unique identifier is 6 nucleotides in length.” EX1003.¶97. *Porreca* teaches differentiator tag sequences having a variety of nucleotide lengths, including those with 6 nucleotides: “Differentiator tag sequences may be, up to 5... up to 6... or more nucleotides in length.” EX1006.¶141.

8. Claim 9

Porreca discloses “[t]he method of claim 1, wherein each unique identifier is 8 nucleotides in length.” EX1003.¶98. *Porreca* teaches differentiator tag sequences having a variety of nucleotide lengths, including those with 8 nucleotides: “Differentiator tag sequences may be, up to 5... up to 8... or more nucleotides in length.” EX1006.¶141.

9. Claim 10

Porreca discloses “[t]he method of claim 1, wherein each unique identifier is at a junction between the adapter and the nucleic fragment.” EX1003.¶99. *Porreca* teaches several embodiments with this configuration. *Porreca* discloses that “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.” EX1006.¶150; *see also* EX1006.Fig.4c. A POSA would have understood that adaptors having a unique identifier at their 3' end upon ligation to the nucleic acid fragments would result in a configuration whereby the unique identifier is at a junction between the adapter and the nucleic acid fragment. EX1003.¶99.

B. Ground II: Claims 1-3, 5-10 Would Have Been Obvious Over *Schmitt* In View Of *McCloskey*⁷

1. Independent Claim 1

(a) Limitation 1.p

To the extent the preamble is considered limiting, *Schmitt* discloses a “method for detecting duplicate sequencing reads, the method comprising.” EX1003.¶101. *Schmitt* discloses the use of a “single molecule identifier (SMI),” and explains that “the SMI adaptor molecules may be used in methods for unambiguous identification of PCR duplicates.” EX1007.¶85. *Schmitt*’s Example 1 also discloses the detection of PCR duplicates: “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...[t]he improved sequence coverage arose from use of the SMI to identify PCR duplicates.” EX1007.¶104.

⁷ EX1003.¶¶44-46,100-142.

(b) Limitation 1.a

Schmitt discloses “ligating an adaptor to each of a plurality of nucleic acid fragments.” EX1003.¶¶102-03. *Schmitt* discloses the ligation of an SMI adaptor molecule to a target nucleic acid. “Such a method may include steps of ligating a double-stranded target nucleic acid molecule to at least one SMI adaptor molecule to form a doublestranded 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.” EX1007.¶10. *Schmitt* further discloses 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.” EX1007.¶74. A POSA would understand these disclosures to satisfy this limitation. EX1003.¶¶102-03. *Schmitt*’s Example 1 additionally discloses the claimed adaptor-nucleic acid products. EX1007.¶98; *see also* EX1007.¶¶89-95. *Schmitt*’s adaptor also includes a primer binding site, as discussed below in Limitation 1.d.

(c) Limitation 1.b

Schmitt discloses “wherein each adaptor comprises a unique identifier having from about 1 to about 8 nucleotides.” EX1003.¶¶104-07. *Schmitt*’s SMI adaptor molecule satisfies the claimed “unique identifier.” *Schmitt* teaches that the SMI

sequence is made up of nucleotides and “may be any suitable length to produce a sufficiently large number of unique tags to label a set of sheared DNA fragments from a segment of DNA.” EX1007.¶26. *Schmitt* also teaches that the SMI sequence “may be between approximately 3 to 20 nucleotides in length.” Other disclosures in *Schmitt* further emphasize that every DNA fragment bears its own unique SMI. Regarding Figure 1’s embodiment, *Schmitt* states that “[b]ecause **every adaptor contains a unique, double-stranded, complementary n-mer random tag** on each end (n-mer = 12 bp according to one embodiment), every DNA fragment becomes labeled with two distinct SMI sequences.” EX1007.¶12 (emphasis added) *Schmitt* explains 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.” EX1007.¶85.

(d) Limitation 1.c

It would have been obvious to include *McCloskey*’s batch-stamp (the claimed indexing site) in *Schmitt*’s adaptor. EX1003.¶¶108-16.

(i) A POSA would have been motivated to add the claimed indexing site to *Schmitt*’s adaptor

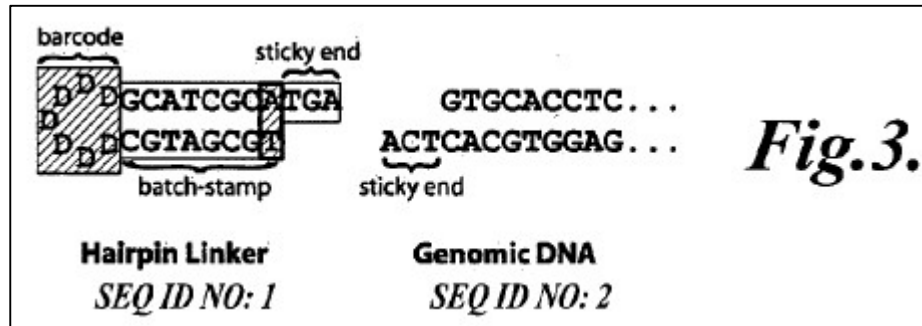
A POSA would have been motivated to include the claimed indexing site in *Schmitt*’s adaptor, which is described above in Limitation 1.a. EX1003.¶¶109-16. *Schmitt*’s Example 1 discloses that, after the DNA capture step, the resulting

products were amplified with PCR primers that included a “fixed multiplexing barcode sequence.” EX1007.¶¶95. A POSA would have known that a multiplexing barcode sequence allows for the identification of the sample from which a particular sequence read originated. EX1003.¶¶109. This barcode sequence, however, is appended to the target DNA sequences only after several steps of the disclosed method had been performed. For example, library preparation, pre-capture amplification, and DNA capture steps all occur prior to the addition of the barcode. EX1007.¶¶92-95. A POSA 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 pooling different samples together prior to labeling. EX1003.¶¶110. A POSA thus would have been motivated to include the multiplexing barcode to the adaptor described in Limitation 1.a, which occurs before the first amplification and DNA capture steps. EX1003.¶¶109-16.

(ii) *McCloskey* discloses the claimed indexing site

McCloskey discloses “an indexing site unique to a subset of the adaptors.” *McCloskey*’s “batch-stamp” satisfies the claimed “indexing site.” EX1003.¶¶111-13. *McCloskey* explains that a “‘batch-stamp’ refers to information that uniquely identifies a specific experiment. For example, a batch-stamp may identify a sample, a patient, and/or an analysis date.” EX1005.¶27. *McCloskey*’s Example 6 shows a hairpin linker adaptor that includes a batch-stamp. “Ligation of the hairpin linker

(5' AGC-GATGCDDDDDDDDGCATCGCTTGA 3', SEQ ID NO:1) with variations in the non-random nucleotides for batch-stamps....” EX1005.¶95; *see also* EX1005.¶¶92-96. The batch-stamp is also shown in Figure 3:



EX1005.Fig.3. Sequence (“2”) in *McCloskey*’s Figure 1 shows the batch-stamp as well. EX1005.¶13, Fig.1.

(iii) A POSA would have been motivated to combine *Schmitt*’s adaptor with *McCloskey*’s indexing site

A POSA would have been motivated to combine *Schmitt* with *McCloskey*’s batch-stamp. EX1003.¶¶109-10,114-16. Both references are in the same field of endeavor and contain disclosures that solve the same problem, *i.e.*, using identifier and indexing sites to identify PCR duplicates and to match sequencing reads to the originating sample. For example, *McCloskey* discloses the use of “barcodes” to distinguish “valid sequences” from “redundant sequences” (*i.e.*, duplicate sequences), EX1005.¶5, as well as the use of a “batch-stamp” to identify which sample each sequencing read originated from. *See* §IX.B.1(d)(ii). *Schmitt* contains similar disclosures. *See* §§IX.B.1(c), IX.B.1(d)(i).

Schmitt also contains a citation to “McCloskey 2007,”⁸ which is an article written by Megan L. McCloskey, the primary named inventor of *McCloskey*. EX1005.¶6 (citing reference 35). *McCloskey 2007* and *McCloskey* contain some overlapping disclosures, such as an oligonucleotide adaptor that includes an identifier and indexing site. Compare EX1015.Fig.1, with EX1005.Fig.1. However, as explained below in §X.A, *McCloskey* contains a more robust disclosure. Nonetheless, a POSA would have been aware of *McCloskey*, particularly in light of *Schmitt*’s explicit citation to *McCloskey 2007*, and would have been motivated to select *McCloskey* given *McCloskey*’s disclosure of a batch-stamp, which allows *Schmitt*’s adaptor to be used in multiplex sequencing reactions. EX1003.¶115.

A POSA also would have reasonably expected success from the combination. EX1003.¶116. A POSA would have known how to include *McCloskey*’s batch-stamp in *Schmitt*’s adaptor. *Schmitt* teaches that adaptors may contain different types of sequences. For example, *Schmitt*’s adaptor can include an “SMI adaptor molecule,” “PCR primer binding sites,” “sequencing primer binding sites,” or a “multiplexing barcode sequence.” EX1007.¶¶10,22,95. *Schmitt* further teaches that there may be multiple sequences on a single adaptor. “Optionally, the SMI adaptor

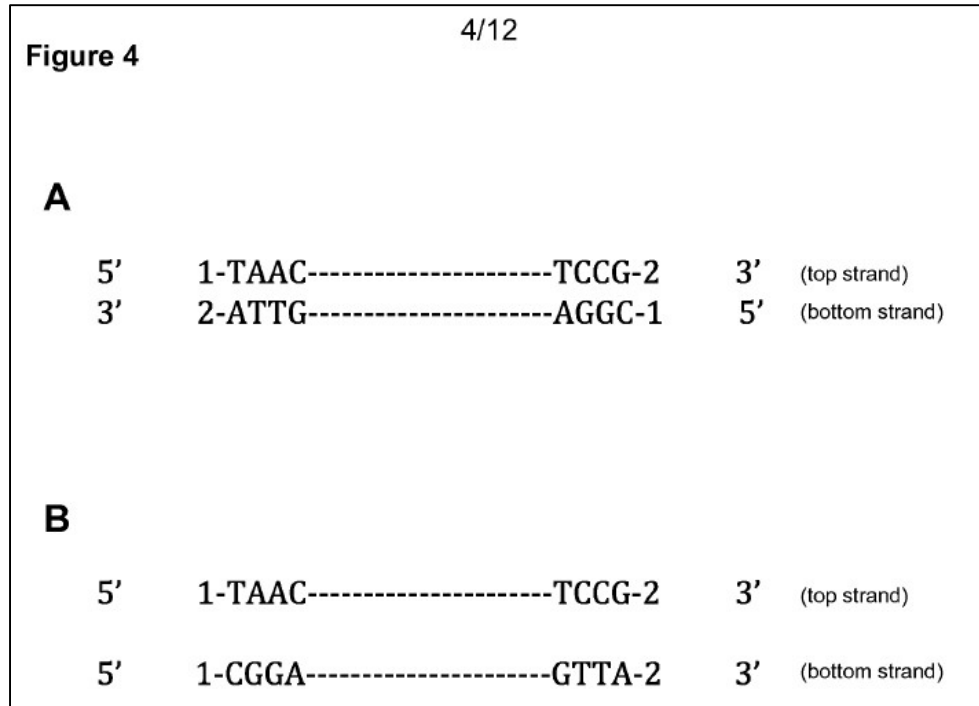
⁸ Mccloskey ML, Stager R, Hansen RS, Laird CD. Encoding PCR products with batch-stamps and barcodes. *Biochem Genet.* 2007;45:761-7.

molecule further includes at least two PCR primer binding sites, at least two sequencing primer binding sites, or both.” EX1007.¶22. A POSA thus would have known how to include different types of sequences into an adaptor, such as an SMI sequence and *McCloskey*’s batch-stamp. EX1003.¶¶109-16.

(e) Limitation 1.d

Schmitt discloses “a primer binding site.” EX1003.¶¶117-18. *Schmitt* teaches that “[o]ptionally, the SMI adaptor molecule further includes at least two PCR primer binding sites, at least two sequencing primer binding sites, or both.” EX1007.¶22. *Schmitt* also discloses that “[i]n some embodiments, the SMI adaptor molecule is a “Y-shaped” adaptor, which allows both strands to be independently amplified by a PCR method prior to sequencing because both the top and bottom strands have binding sites for PCR primers FC1 and FC2 as shown in the examples below.” EX1007.¶23. Moreover, “the SMI adaptor molecule may include at least two PCR primer or ‘flow cell’ binding sites: a forward PCR primer binding site (or a ‘flow cell 1’ (FC1) binding site); and a reverse PCR primer binding site (or a ‘flow cell 2’ (FC2) binding site).” EX1007.¶31.

Schmitt’s Figures 4A and 4B show PCR primer binding sites as well:



EX1007.Fig.4 (excerpt). Figure 4A “shows the 4-mers with the PCR primer binding sites (or flow cell sequences) 1 and 2 indicated at each end,” and Figure 4B “shows the same molecules as in (A) but with the strands separated and the lower strand now written in the 5'-3' direction.” EX1007.¶15. *Schmitt*’s claim 5 also discloses this limitation: “The single molecule identifier adaptor molecule of claim 1, further comprising at least two PCR primer binding sites, or at least two sequencing primer binding sites, or both.” EX1007.claim.5.

(f) Limitation 1.e

Schmitt discloses “amplifying the adaptor-ligated fragments into amplicons.” EX1003.¶¶119-22. *Schmitt* discloses the attachment of an SMI adaptor molecule to a target nucleic acid and the subsequent amplification of the resulting product to produce amplicons, or PCR amplification products. “Such a method may include

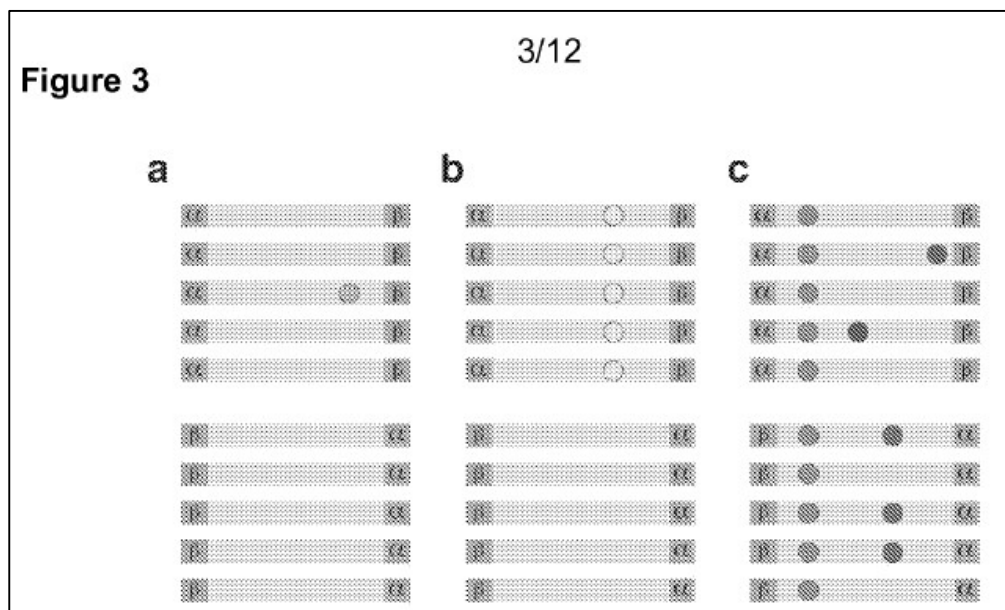
steps of ligating a double-stranded target nucleic acid molecule to at least one SMI adaptor molecule to form a doublestranded SMI-target nucleic acid complex; amplifying the double-stranded SMI-target nucleic acid complex, resulting in a set of amplified SMI-target nucleic acid products.” EX1007.¶10. *Schmitt* further discloses 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.” EX1007.¶74. A POSA would understand these disclosures to satisfy the claimed amplicons. EX1003.¶¶119-22. *Schmitt*’s Example 1 additionally discloses the claimed amplicons. EX1007.¶98; *see also* EX1007.¶¶89-95.

(g) Limitation 1.f

Schmitt discloses “sequencing the amplicons to generate sequence reads that include identifier and target sequences.” EX1003.¶123-26. *Schmitt* teaches “a method of obtaining the sequence of a doublestranded target nucleic acid” that is “also known as Duplex Consensus Sequencing or DCS.” EX1007.¶10. This method includes generating “a set of amplified SMI-target nucleic acid products” and “sequencing the amplified SMI-target nucleic acid products.” EX1007.¶10. *Schmitt* further explains that the “amplified SMI-target nucleic acid products” are

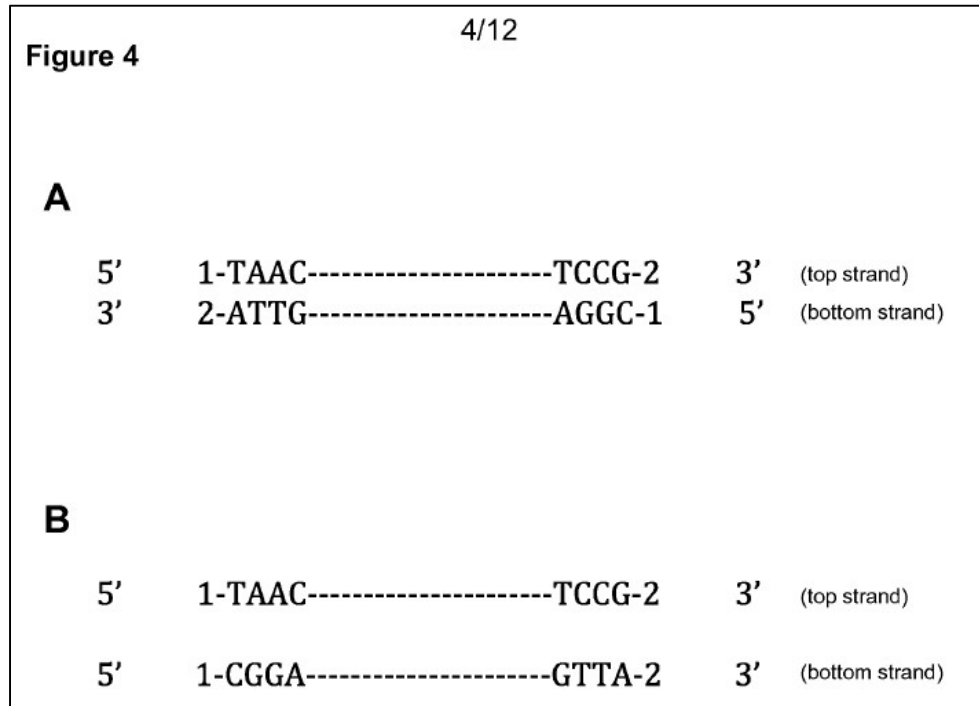
“sequenced using any suitable method known in the art including, but not limited to, the Illumina sequencing platform, ABI SOLiD sequencing platform, Pacific Biosciences sequencing platform, 454 Life Sciences sequencing platform, Ion Torrent sequencing platform, Helicos sequencing platform, and nanopore sequencing technology.” EX1007.¶74.

Schmitt also discloses the sequencing of several SMI-nucleic acid embodiments. For example, Figures 3a-c show sequence reads that include both the identifier (*i.e.*, α and β) and target sequence (*i.e.*, region between α and β):



EX1007.¶Fig.3 (excerpt). *Schmitt* explains that “(a-c) shows sequence reads (brown) sharing a unique set of SMI tags are grouped into paired families with members having strand identifiers in either the $\alpha\beta$ or $\beta\alpha$ orientation.” EX1007.¶14.

Figure 4 also shows an example of sequencing reads of both the identifier and target sequences:



EX1007.¶¶Fig.4. When the molecules shown in 4A and 4B “are amplified with PCR and sequenced, they will yield the following sequence reads: The top strand will give a read 1 file of TAAC—and a read 2 file of GCCA---.” EX1007.¶15. Combining the reads “will give TAACCGGA as the SMI for the top strand” and “CGGATAAC as the SMI for the bottom strand.” EX1007.¶15.

And regarding Example 1, *Schmitt* explains that SMI-ligated DNA was PCR amplified and sequenced. EX1007.¶¶98-99. “[M]embers 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.” EX1007.¶99; *see also* EX1007.¶96. This further demonstrates that both the SMI and target sequences are included in the sequencing reads. *See also*. EX1007.¶¶103-105.

(h) Limitation 1.g

Schmitt discloses “identifying sequence reads with identical identifier and target sequences as duplicates.” EX1003.¶¶127-28. *Schmitt* teaches that SMI sequences are used in the identification of PCR duplicates. “SMI adaptor molecules may be used in methods for unambiguous identification of PCR duplicates.” EX1007.¶85. *Schmitt* further teaches that strands with identical sequences that result from a single strand of DNA (“duplicates”) will also have the same SMI, and that the amplification products of such strands are known as “PCR duplicates”:

Every duplicate that arises from a single strand of DNA will have the same SMI, and thus each strand in a DNA duplex pair generates a distinct, yet related population of PCR duplicates after amplification owing to the complementary nature of the SMIs on the two strands of the duplex.

EX1007.¶98. *Schmitt* further explains 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.” EX1007.¶85. A POSA would have understood that “true PCR duplicates” have target nucleic acid

sequences that are identical in addition to having the same SMI sequence. EX1003.¶¶127-28.

Schmitt further discloses that the sequences of the duplicates were identified and compared, then collapsed to generate a consensus read. “[M]embers 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.” EX1007.¶99. A POSA would have known that, in order to generate a consensus read, the target sequences must be identical. EX1003.¶¶127-28.

2. Claim 2

Schmitt discloses “[t]he method of claim 1, further comprising removing a duplicate read from the sequence reads.” EX1003.¶129. *Schmitt*’s Example 1 involves the removal of duplicate reads. After the amplified SMI-nucleic acid products were sequenced in Example 1’s method, “[r]eads having common (i.e., identical) SMI sequences were grouped together, and were collapsed to generate a consensus read.” EX1007.¶96. Example 1’s data processing workflow also includes the following steps: “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.” EX1007.¶96. A POSA would have understood that collapsing duplicate reads into a consensus read

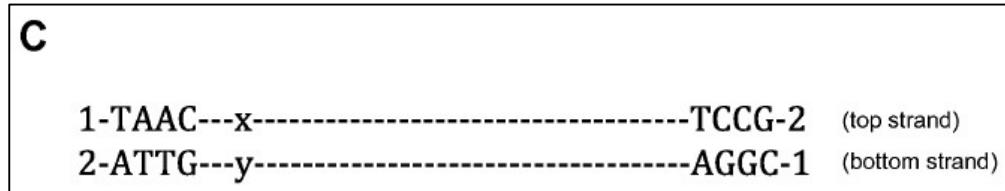
would be one way of removing duplicate reads from the sequence reads. EX1003.¶129. Indeed, the '357 patent mentions that collapsing reads is one method of removing duplicates: “duplicate reads can be considered noninformative and may be collapsed down to a single read, thus reducing the number of sequencing reads used in final analysis.” EX1002 at 1:43-46; EX1003.¶129.

3. Claim 3

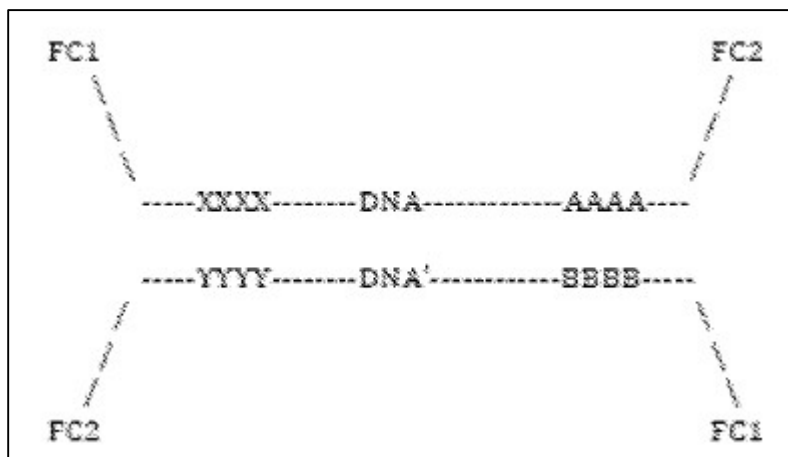
Schmitt discloses “[t]he method of claim 1, wherein the identifier site is sequenced with the target sequence.” EX1003.¶¶130-32. *Schmitt*’s duplex consensus sequencing method involves “ligating a double-stranded target nucleic acid molecule to at least one SMI adaptor molecule to form a doublestranded 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.” EX1007.¶10. This method sequences the identifier site with the target sequence. EX1003.¶¶130-32.

The embodiments shown in Figures 3 and 4 satisfy this limitation as well. EX1003.¶¶130-32. Figure 3a-c “shows sequence reads (brown) sharing a unique set of SMI tags are grouped into paired families with members having strand identifiers in either the $\alpha\beta$ or $\beta\alpha$ orientation.” EX1007.¶14. *Schmitt* also explains that when the molecules shown in 4A and 4B “are amplified with PCR and sequenced, they will yield the following sequence reads: The top strand will give a read 1 file of

TAAC—and a read 2 file of GCCA---.” EX1007.¶15. Combining the reads “will give TAACCGGA as the SMI for the top strand” and “CGGATAAC as the SMI for the bottom strand.” EX1007.¶15. The reads shown in Figure 4C additionally include both identifier and target sequences:



EX1007.¶Fig.4C. *Schmitt*’s illustration of Product II shows another example of the identifier site sequenced with the target sequence.



EX1007.¶42. This sequence read includes identifier (*i.e.*, XXXX and AAAA for the top strand and BBBB and YYYY for the bottom strand) and target sequences (*i.e.*, DNA for the top strand and DNA’ for the bottom strand). EX1007.¶45.

The sequence read in Example 1 additionally meets this limitation. *Schmitt* discloses that “[r]eads with intact SMI adaptors include a 12 nucleotide random

sequence, followed by a 5 nucleotide fixed sequence” and that the “SMI sequence from both the forward and reverse sequencing reads (i.e., the first and second degenerate n-mer sequences) was computationally added to the read header, and the fixed sequence removed.” EX1007.¶96. *Schmitt* further explains that “[r]eads having common (i.e., identical) SMI sequences were grouped together, and were collapsed to generate a consensus read.” A POSA would have known from these data processing steps that Example 1 includes a sequencing read with both identifier and target sequences. EX1003.¶¶130-32.

4. Claim 5

Schmitt discloses “[t]he method of claim 1, wherein the nucleic acid fragments comprise RNA.” EX1003.¶133. *Schmitt* teaches the application of its methods to the analysis of RNA. For example, *Schmitt* teaches that

the SMI adaptor molecules and methods of use described herein are applicable to genotyping and other applications related to sequencing of DNA molecules, but are also applicable to **RNA sequencing applications** such as for sequencing of double-stranded RNA viruses. Methods for sequencing **RNA** may include any of the embodiments described herein with respect to DNA sequencing, and vice-versa. For example, any double stranded target nucleic acid molecule may be ligated to an SMI adaptor molecule which includes a double-stranded **RNA** or DNA n-mer tag and an **RNA** or DNA ligation adapter as described above. Methods exist for directly sequencing **RNA** [51].

EX1007.¶72 (emphases added).

5. Claim 6

Schmitt discloses “[t]he method of claim 1, wherein the nucleic acid fragments are genomic DNA fragments or cDNA fragments.” EX1003.¶¶134-35. *Schmitt*’s Example 1 involves the analysis of genomic DNA. *See, e.g.* EX1007.¶89 (“DNA isolation. Genomic DNA was isolated from normal human colonic mucosa by sodium iodide extraction”); EX1007.¶92 (“Sequencing library preparation. 3 micrograms of DNA was diluted into 130 microliters of TE buffer...”).

Schmitt also discloses the method of claim 1 wherein the nucleic acid fragments are cDNA fragments. *Schmitt* teaches that “the SMI adaptor molecules and methods of use described herein are applicable to genotyping and other applications related to sequencing of DNA molecules, but are also applicable to RNA sequencing applications such as for sequencing of double-stranded RNA viruses.” EX1007.¶72. *Schmitt* further discloses that a ligated RNA molecule “may be reverse transcribed into DNA, and then sequenced as a double-stranded target DNA molecule.” EX1007.¶72. A POSA would have known that reverse transcribing RNA results in cDNA, and thus amplifying this product would have produced “amplified fragments of cDNA.” EX1003.¶¶134-35.

6. Claim 7

Schmitt discloses “[t]he method of claim 1, wherein the primer binding site is a universal target sequencing primer binding site.” EX1003.¶136-38. *Schmitt*

teaches a sequencing primer binding site that satisfies the claimed “universal target sequencing primer binding site.” EX1003.¶136-38. “The SMI adaptor molecule may also include at least two sequencing primer binding sites, each corresponding to a sequencing read. Alternatively, the sequencing primer binding sites may be added in a separate step by inclusion of the necessary sequences as tails to the PCR primers, or by ligation of the needed sequences.” EX1007.¶31. *Schmitt*’s discussion of Figure 4c additionally discloses this claim. “The ‘x’ will appear in read 1, and the complementary mutation on the opposite strand, ‘y,’ will appear in read 2. Specifically, this would appear as “x” in both read 1 and read 2 data, because ‘y’ in read 2 is read out as “x” by the sequencer owing to the nature of the sequencing primers, which generate the complementary sequence during read 2.” EX1007.¶15.

Schmitt’s claims disclose the claimed sequencing primer binding site as well. “5. The single molecule identifier adaptor molecule of claim 1, further comprising at least two PCR primer binding sites, or at least two sequencing primer binding sites, or both” EX1007.claim.5; *see also* EX1007.claim.28.

7. Claim 8

Schmitt discloses “[t]he method of claim 1, wherein each unique identifier is 6 nucleotides in length.” EX1003.¶139. *Schmitt* teaches that a SMI may be a nucleotide n-mer sequence, and that “[e]ach n-mer sequence may be between approximately 3 to 20 nucleotides in length. Therefore, each n-mer sequence may

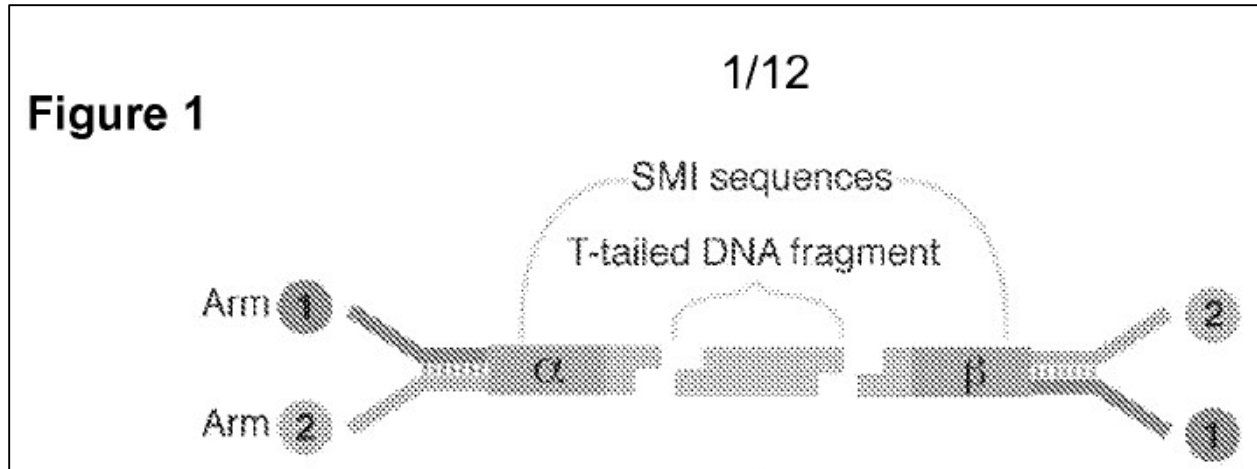
be approximately 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 nucleotides in length.” EX1007.¶26.

8. Claim 9

Schmitt discloses “[t]he method of claim 1, wherein each unique identifier is 8 nucleotides in length.” EX1003.¶140. *Schmitt* teaches that a SMI may be a nucleotide n-mer sequence, and that “[e]ach n-mer sequence may be between approximately 3 to 20 nucleotides in length. Therefore, each n-mer sequence may be approximately 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 nucleotides in length.” EX1007.¶26.

9. Claim 10

Schmitt discloses “[t]he method of claim 1, wherein each unique identifier is at a junction between the adapter and the nucleic fragment.” EX1003.¶141-42. During prosecution, the examiner remarked in December 8, 2020 non-final rejection that because “Applicant did not define the term ‘junction’, therefore it is considered as any region of the adapter.” EX1013.0078. Figure 1, which illustrates Example 1’s duplex consensus sequencing method, shows that the SMI is located at the junction between the adapter and the nucleic acid fragment:



EX1007.Fig.1 (excerpt). The SMI sequence (α and β) is located between the t-tailed DNA fragment and the adapter (sequences 1 and 2). *Schmitt* explains:

Figure 1 illustrates an overview of Duplex Consensus Sequencing. 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...every DNA fragment becomes labeled with two distinct SMI sequences (arbitrarily designated α and β in the single capture event shown)...Those derived from one strand will have the α SMI sequence adjacent to flow-cell sequence 1 and the β SMI sequence adjacent to flow cell sequence 2.

EX1007.¶12.

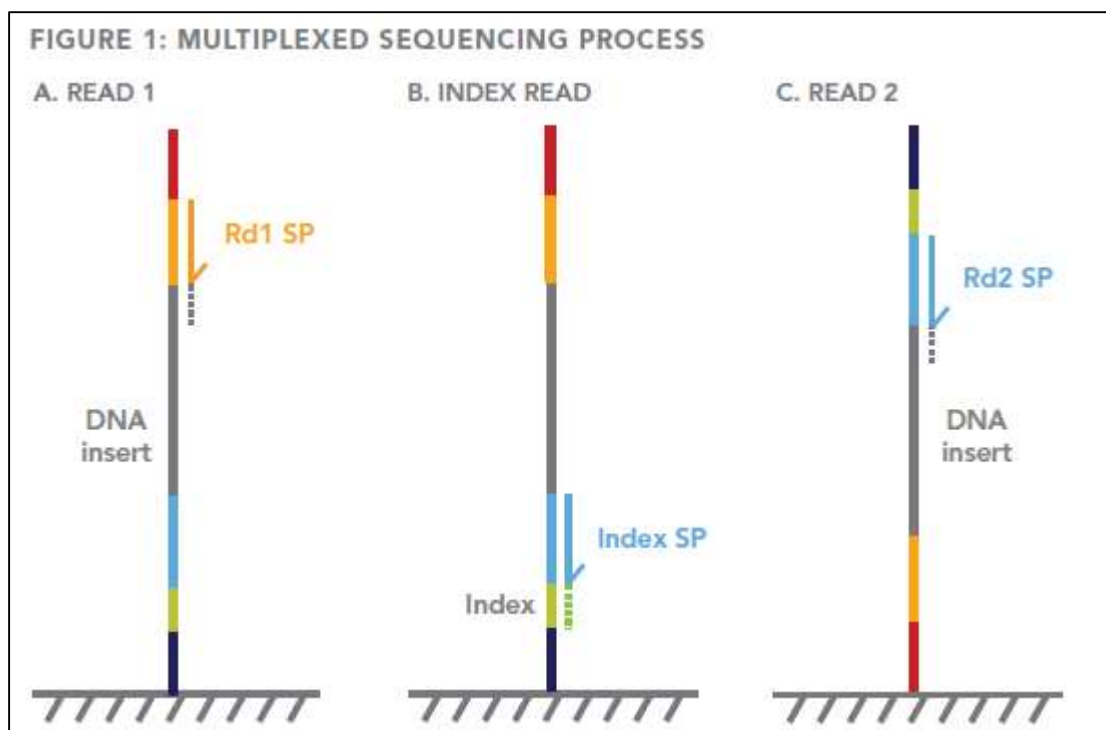
C. Grounds III and IV: Claim 4 Would Have Been Obvious Over *Porreca* In View Of *Illumina 2008* And Over *Schmitt* In View Of *McCloskey* And In Further View Of *Illumina 2008*⁹

Claim 4 recites “[t]he method of claim 1, wherein the identifier site is sequenced separately from the target sequence.” A POSA would have been

⁹ EX1003.¶¶44-46,143-45.

motivated to sequence the identifier site separately from the target sequence in both *Porreca*'s and *Schmitt*'s systems. EX1003.¶¶143-45. A POSA would have known that, due to the limited amount of bases that can be sequenced in each read, sequencing the identifier site separately from the target sequence results in a larger target sequence read, as the bases comprising the identifier site would not be included in that read. EX1003.¶¶143-45. A POSA would have understood that including more target sequence bases in a read would increase efficiency, and would have therefore been motivated to sequence the identifier site separately from the target sequence. EX1003.¶¶143-45.

A POSA also would have been motivated to apply the teachings of the Illumina system in order to do so. EX1003.¶¶143-45. A POSA would have known of the Illumina sequencing platform since well before November 13, 2013, the priority date of the '357 patent. EX1003.¶¶144. A POSA would have further known that the Illumina platform sequences adaptor sequences separately from the target sequence. For instance, *Illumina 2008* shows that the target sequence is sequenced separately from the index sequence:



EX1008.0001. *Illumina 2008* explains that “[s]ample multiplexing involves a total of three sequencing reads, including a separate index read.” EX1008.0001. This demonstrates that a POSA would have known how to successfully sequence an adaptor sequence separately from the target sequence. EX1003.¶¶143-45. And while *Illumina 2008* demonstrates this with an index sequence, it would have been obvious for a POSA to include an identifier sequence in lieu of the index sequence, and to include the identifier at the same location in the adaptor such that the identifier would similarly be sequenced separately. EX1003.¶¶143-45.

In addition to the reasons discussed above, a POSA would have been further motivated to apply *Illumina 2008*’s teachings to *Porreca* and *Schmitt* because both references explicitly refer to the Illumina platform. For example, *Porreca* teaches

the following sequencing step: “Perform Sequencing of Library According to Manufacturer’s Directions (e.g. Illumina, ABI, etc).” EX1006.¶295. *Schmitt* also includes similar disclosures: “These products are then sequenced using any suitable method known in the art including, but not limited to, the Illumina sequencing platform....” EX1007.¶74. “[U]se of DCS does not require any significant deviations from the normal workflow of sample preparation for Illumina DNA sequencing.” EX1007.¶86. *Schmitt* additionally mentions the benefits of having longer target sequencing reads, which would further motivate a POSA to sequence the identifier separately: “Combining information regarding the shear points of DNA with the SMI tag sequence would allow a shorter SMI to be used, thus minimizing loss of sequencing capacity due to sequencing of the SMI itself.” EX1007.¶83.

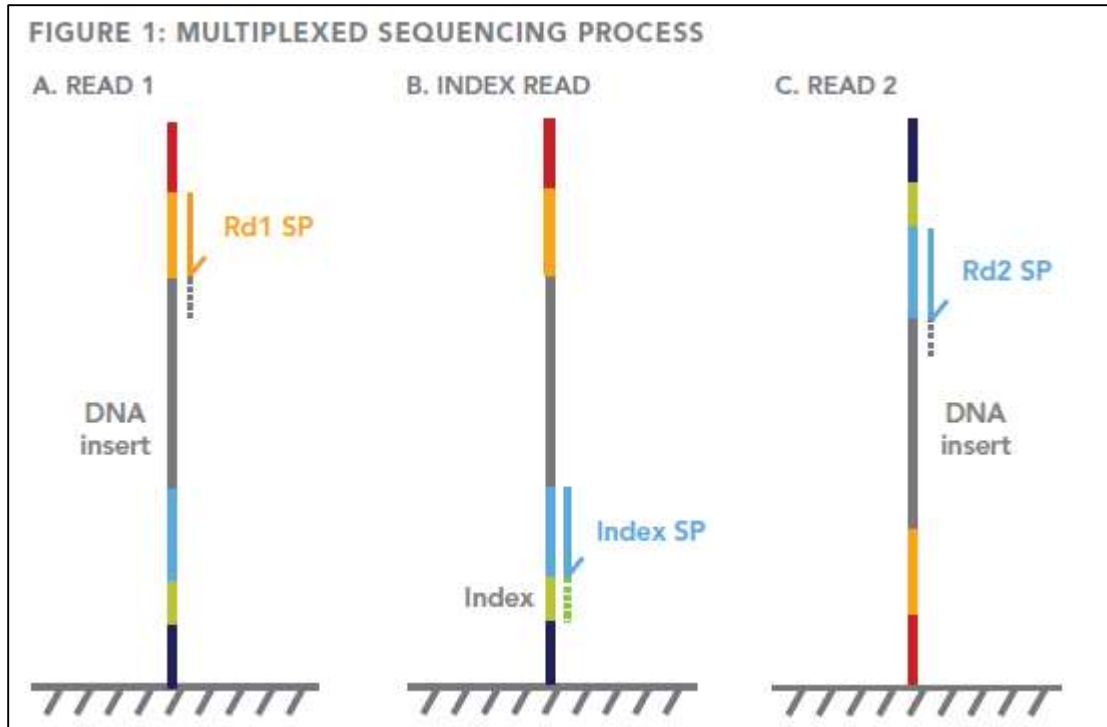
D. Grounds V And VI: Claim 7 Would Have Been Obvious Over *Porreca* In View Of *Illumina 2008* And Over *Schmitt* In View Of *McCloskey* And In Further View Of *Illumina 2008*¹⁰

As discussed above in Grounds I and III, both *Porreca* and *Schmitt* disclose this claim. See §§IX.A.6.IX.B.6. To the extent Patent Owner contends that *Porreca*’s “sequencing primer site,” *Porreca*’s “common adaptor sequence,” or *Schmitt*’s “sequencing primer binding site” fail to disclose the claimed universal target sequencing primer binding site, it would have been obvious to include such a binding site in both the *Porreca* and *Schmitt* adaptors. EX1003.¶¶146-50. A POSA

¹⁰ EX1003.¶¶44-46,146-50.

would have known that including a universal target sequencing primer binding site in the adaptor is necessary to carry out an NGS sequencing reaction. EX1003.¶¶146-50. A POSA thus would have been motivated to include the claimed binding site into the *Porreca* and *Schmitt* adaptors as both references are directed to NGS techniques. EX1003.¶¶146-50.

A POSA also would have been motivated to apply the teachings of the Illumina system in order to do so. A POSA would have known of the Illumina sequencing platform since well before November 13, 2013, the priority date of the '357 patent. EX1003.¶¶144. A POSA would have further known that the sites where the “Rd1 SP” and “Rd2 SP” primers bind to in Illumina’s system are part of the adaptors and are universal target sequencing primer binding sites. *Illumina 2008* shows both of these primer binding sites:



EX1008.0001. It instructs that “A: Application read 1 (dotted line) is generated using the Read 1 Sequencing Primer (Rd1 SP)...the original strand is removed and the complementary strand acts as a template for application read 2 (dotted line), primed by the Read 2 Sequencing Primer (Rd2 SP).” EX1008.0001. A POSA thus would have known how to successfully include the claimed binding site into the *Porreca* and *Schmitt* adaptors. EX1003.¶¶146-48.

A POSA’s understanding that Illumina’s sequencing primer binding sites are universal target sequencing primer binding sites is further confirmed by *Metzker 2010*, an article from the journal *Nature Reviews*, which discusses the use of this technology:

adaptors containing universal priming sites are ligated to the target ends, allowing complex genomes to be amplified with common PCR primers...Solid-phase amplification can produce 100–200 million spatially separated template clusters (Illumina/Solexa), providing free ends to which a **universal sequencing primer** can be hybridized to initiate the NGS reaction.

EX1010.0005 (emphasis added). The Illumina system thus provides a universal target sequencing primer binding site.

In addition to the reasons discussed above, a POSA would have been further motivated to apply *Illumina 2008*'s teachings to *Porreca* and *Schmitt* because both references explicitly refer to the Illumina platform. For example, *Porreca* teaches the following sequencing step: "Perform Sequencing of Library According to Manufacturer's Directions (e.g. Illumina, ABI, etc)." EX1006.¶295. *Schmitt* also includes similar disclosures: "These products are then sequenced using any suitable method known in the art including, but not limited to, the Illumina sequencing platform...." EX1007.¶74. "[U]se of DCS does not require any significant deviations from the normal workflow of sample preparation for Illumina DNA sequencing." EX1007.¶86.

E. No Secondary Considerations of Nonobviousness

Grounds 2-6 render the challenged claims obvious. Petitioner is not aware of any relevant secondary considerations of nonobviousness. Petitioner reserves its

right to respond to any assertion of secondary considerations advanced by Patent Owner.

X. 35 U.S.C. § 325(d) DOES NOT FAVOR DENIAL

The Board uses a two-part framework to analyze whether denial under § 325(d) is proper. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020). The Board considers several nonexclusive factors (“*Becton Dickinson* factors”) within this framework to provide useful insight into how to apply each prong, each of which is discussed below. *Id.* at 4; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”).

Becton Dickinson factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics* at 10. Factors (c), (e), and (f) are only considered if the same or substantially the same art or arguments were previously presented to the Office. *Id.*

A. *Becton Dickinson* Factors (a), (b), and (d)

Petitioner’s arguments and prior art here are neither the same nor substantially the same art or arguments previously before the Office during prosecution of the ’357 patent. These factors thus weigh against discretionary denial. *Porreca*,

Schmitt, and *McCloskey* were never before the Patent Office. And while *Illumina 2008* was addressed by the examiner in a December 8, 2020 office action, EX1013.0079-81, it was analyzed in the context of a combination with the Samuels reference, which is not at issue here. *Illumina 2008* is also asserted only against two dependent claims in conjunction with *Porreca* and *Schmitt*, which were never before the Patent Office. The examiner thus could not have considered the arguments involving *Illumina 2008* that Petitioner presents here.

Petitioner additionally notes that *McCloskey* is different from and contains substantially more material than the “McCloskey 2007”¹¹ paper that was discussed during prosecution, even though both references were first authored / invented by the same Megan L. McCloskey. *McCloskey* also includes Brooks Miner as an inventor, who was not an author on the McCloskey 2007 paper.

McCloskey includes several disclosures that were not included in the *McCloskey 2007*. For example, *McCloskey* discloses the hairpin linker adaptor, EX1005.¶¶10,36,95.Figs.3-4, sequencing data from the disclosed examples, EX1005.¶¶51-53,63-64,76,103-14, Fig.4, and data analysis techniques, EX1005.¶63,

¹¹ McCloskey, 2007, Encoding PCR products with batch-stamps and barcodes, *Biochem Genet* 45:761-767, discussed in the examiner’s December 8, 2020 non-final rejection. EX1013.0078-81.

that are all missing from the McCloskey 2007 paper. These two references are thus not cumulative of each other.

B. *Becton Dickinson* Factors (c), (e), and (f)

As explained above, factors (c), (e), and (f) are only considered if the same or substantially the same art or arguments were previously presented to the Patent Office. As discussed above, the only reference previously before the office was *Illumina 2008*, and Petitioner relies on that reference for only two dependent claims in conjunction with *Porreca* and *Schmitt*, which were never before the Office. The Board thus need not consider factors (c), (e), and (f).

To the extent the Board does consider these factors, they also support not exercising discretion to deny under §325(d). For example, material error by the Patent Office “may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.” *Advanced Bionics*, Paper 6, at 3 n.9. The Examiner erred here in a way that was material to patentability because they did not appreciate *Illumina 2008*’s disclosure and also did not have the benefit of analyzing *Illumina 2008* in view of *Porreca* and *Schmitt*. In addition, the Examiner also did not have the benefit of Dr. Metzker’s detailed expert testimony and the other evidence of record. For at least these reasons, the Board should not discretionarily deny institution under §325(d).

XI. 35 U.S.C. § 314(a) DOES NOT FAVOR DENIAL

A. The *General Plastic* Factors Weigh in Favor of institution

General Plastic is applicable to a petition that challenges the same patent as a previous petition. IPR2016-01357, Paper 19, 9-10 (PTAB Sept. 6, 2017) (precedential). While IDT filed a petition against the '241 patent in IPR2024-01506, the *General Plastic* factors favor institution here.

The primary General Plastic factor examines “whether the same petitioner previously filed a petition directed to the same claims....” *Qualcomm Inc. v. Monterey Research, LLC*, IPR2020-01493, Paper 11, 15 (March 8, 2021). The purpose of this inquiry is primarily to determine whether the petition seeks to harass or burden the Patent Owner, or to gain strategic advantage through serial filings. But in this case, Petitioner had nothing to do with IDT’s petition, and asserts a new set of prior art, grounds, and arguments.

IDT and QIAGEN are separate entities, and the mere fact that both entities have been sued by Patent Owner is insufficient to demonstrate a relationship. *See id.* (“We also do not agree with Patent Owner that two parties being sued for infringement of the same patent and participating in a joint-defense group, of itself, establishes a significant relationship between the parties that counsels for denying institution”).

There is also no evidence that Petitioner seeks to harass or unduly burden Patent Owner with its petition. There was no coordination between Petitioner and IDT, or any other relationship as to the preparation of this petition. The fact that there is no evidence Petitioner is seeking to burden Patent Owner with serial petitions should “weigh[] especially heavily against a discretionary denial.” *See Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7, 7-8 (Sept. 5, 2018). Absent “extenuating circumstances,” such as a showing of coordination between petitioners, once resolution of factor 1 indicates that Petitioner had not previously filed a petition against the same patent claims, factors 2-5 bear little relevance. *See id.* These factors thus weigh in favor of institution.

B. The *Fintiv* Factors Weigh in Favor of Institution

Likewise, the *Fintiv* Factors weigh in favor of institution:

1. *Fintiv* Factor 1: Whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted

The Court has not granted a stay. Accordingly, this factor is neutral.

2. *Fintiv* Factor 2: Proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision

The Court in the District Court litigation has set a trial date of July 27, 2026. This petition is being filed on October 10, 2024. Thus, the approximate date of the PTAB final written decision is April 2026. The PTAB final written decision will thus pre-date the district court trial. Accordingly, this factor weighs in favor of

institution. “We determine that Fintiv Factor 2 also favors institution, especially given that the trials in the district court cases will not likely take place until after we issue our Final Written Decisions in these proceedings.” *Medtronic, Inc. v. Teleflex Innovations S.à.r.l.*, No. IPR2020-00135, 2020 WL 3053201, at *15 (P.T.A.B. June 8, 2020). “[I]t is likely that any potential trial would occur after the completion of this proceeding. Accordingly, we determine that this factor weighs against the exercise of discretionary denial.” *Apple Inc. v. Geoscope Techs. Pte. Ltd.*, No. IPR2024-00032, 2024 WL 2107693, at *7 (P.T.A.B. May 10, 2024).

3. *Fintiv* Factor 3: Investments in the parallel proceeding by the court and the parties

The district court litigation is in its early stages. Limited initial written discovery has taken place, but no depositions or other discovery have taken place, and there have been no significant investments by the Court or the parties in this case related to invalidity. A claim construction hearing has been scheduled for June 18, 2025. Close of fact discovery is not until July 18, 2025, and close of expert discovery is not until November 14, 2025. As all of these events post-date the Board’s expected time to issue its Institution Decision (April 2025), this factor weighs in favor of institution. *Med-El Elektromedizinische Geräte Ges.m.b.H. v. Advanced Bionics AG*, No. IPR2020-00190, 2020 WL 3033320, at *5 (P.T.A.B. June 3, 2020) (weighing factor 3 in favor of institution where “a claim construction order will not have issued” at the time of the institution decision); *Facebook, Inc. v.*

Usc Ip P'ship, L.P., No. IPR2021-00033, 2021 WL 1718801, at *5 (P.T.A.B. Apr. 30, 2021) (weighing in factor 3 in favor of institution where “[t]he district court proceeding is still at a relatively early stage”).

4. *Fintiv* Factor 4: Overlap between issues raised in the petition and the parallel proceeding

Petitioner agrees that, if this petition is instituted, it will not assert invalidity grounds in the litigation that are included in this petition. Petitioner’s agreement not to use the same grounds if institution is granted reduces the risk of duplicative efforts across proceedings. Thus, this factor weighs in favor of institution. *See, e.g., Sand Revolution II, LLC v. Continental Intermodal Grp.-Trucking LLC*, IPR2019-01393, Paper 24 at 11-12 (PTAB June 16, 2020) (informative) (finding Petitioner’s stipulation not to pursue the same grounds in the district court weighed in favor of institution); *Google LLC et al v. Parus Holdings, Inc.*, IPR2020-00846, Paper 9 at 22 (PTAB October 21, 2020) (“Petitioner has stipulated that it will not pursue the same grounds in the Texas court as it pursues here, which will further lessen the possibility of duplication and inconsistent results between the two forums.”).

5. *Fintiv* Factor 5: Whether the petitioner and the defendant in the parallel proceeding are the same party

The Petitioner here is the same party as the defendant in the district court case. Although this factor may weigh slightly in favor of discretionary denial, it does not outweigh the other factors discussed above.

6. *Fintiv* Factor 6: Other circumstances that impact the Board’s exercise of its discretion, including the merits

The merits of the petition also support institution. As discussed in detail above, there is no novel aspect of the ’357 patent. Every aspect of the claimed invention was already known in the art, and none *McCloskey*, *Porreca*, or *Schmitt*, was considered during prosecution as they should have been. Accordingly, the merits of the petition weigh strongly in favor of institution.

XII. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that the Challenged Claims are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the ’357 patent be granted.

DATED: October 10, 2024

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the **PETITION FOR INTER PARTES REVIEW** complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(i) and (b)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 11,942 words as counted by the word processing program used to prepare the paper.

Date: October 10, 2024

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that true and correct copies of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,098,357 and supporting exhibits were served on October 10, 2024 via USPS Priority Mail Overnight to the following correspondence address of the attorneys of record for U.S. Patent No. 11,098,357 as evidenced on the Patent Office’s public Patent Center system:

21710 - BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111
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Courtesy copies of the same documents were also sent to Timothy J. Beavers (tbeavers@goodwinlaw.com), Linnea P. Cipriano (lcipriano@goodwinlaw.com), John P. Padro (jpadro@goodwinlaw.com), and Scott T. Weingaertner (sweingaertner@goodwinlaw.com), counsel for Plaintiffs in Tecan Genomics, Inc. v. QIAGEN Sciences, LLC et al., C.A. No. 23-cv-1115-GBW (D. Del.).

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