

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN Sciences, LLC,
Petitioner,

v.

Tecan Genomics, Inc.,
Patent Owner.

Case IPR2025-00027

U.S. Patent No. 11,725,241

**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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1004	Miner et al, <i>Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR</i> , Nucleic Acid Research 32:17 (2004) (“Miner”)
1005	U.S. Patent Publication No. 2007/0020640 (“McCloskey”)
1006	U.S. Patent Publication No. 2012/0165202 (“Porreca”)
1007	WO 2013/142378 (“Schmitt”)
1008	Illumina Publication No. 770-2008-011, <i>Multiplexed Sequencing with the Illumina Genome Analyze System</i> (2008) (“Illumina 2008”), 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) (“Metzker 2010”)
1011	Li et al, <i>The Sequence Alignment/Map format and SAMtools</i> , Bioinformatics 25(16) (2009) (“Li 2009”)
1012	Prosecution History of U.S. Patent No. 11,725,241
1013	Prosecution History of U.S. Patent No. 11,098,357
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1016	Curriculum Vitae of Michael L. Metzker, Ph.D.
1017	Metzker & Caskey, <i>Polymerase Chain Reaction</i> , In ENCYCLOPEDIA OF

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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)”)
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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)”)

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I. INTRODUCTION

Petitioner QIAGEN Sciences, LLC respectfully requests *Inter Partes* Review of U.S. Patent No. 11,725,241 (“the ’241 patent”), assigned to Tecan Genomics Inc., and cancellation of claims 1-16. Those claims are unpatentable as anticipated and/or obvious by the prior art references described below.

As explained by Dr. Michael Metzker,¹ the ’241 patent is directed to methods for detecting duplicate nucleic acid sequences that may arise from the PCR amplification process. To detect such duplicates, the ’241 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 ’241 patent.

By the earliest priority date of the ’241 patent, November 13, 2013, the use of identifier sequences to detect PCR duplicates was well-known. *McCloskey*, *Porreca*, and *Schmitt* are all prior art references that disclose this and that were not

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.¶¶1-196.

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*, No. 1:23-cv-01115-GBW (D. Del.) (“District Court litigation”). In that action, Patent Owner has asserted the ’241 patent. Patent Owner also asserts U.S. Patent Nos. 10,036,012 (“the ’012 patent”), 10,876,108 (“the ’108 patent”), and 11,098,357 (the “’357 patent”). The ’241 patent is a continuation of the ’357 patent and shares a similar specification. Patent Owner has also asserted the ’241 patent in *Tecan Genomics, Inc. v. Invitae Corp. et al*, No. 23-cv-1114-GBW (D. Del.).

Petitioner concurrently is filing petitions challenging the asserted claims of the ’357 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 11,098,357 (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 1-16 of the '241 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 '241 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 1-16 of the '241 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, 5-7, 9-10, and 13-16 are anticipated under 35 U.S.C. § 102(a) ³ by <i>McCloskey</i>
Ground II	Claims 1-3, 5-11, and 13-16 are anticipated under 35 U.S.C. § 102(a) by <i>Porreca</i> .
Ground III	Claims 1-3, 5-12, and 14-15 are anticipated under 35 U.S.C. § 102(a) by <i>Schmitt</i> .
Ground IV	Claim 4 would have been obvious under 35 U.S.C. § 103 over <i>Porreca</i> in view of <i>Illumina 2008</i>
Ground V	Claim 4 would have been obvious under 35 U.S.C. § 103 over <i>Schmitt</i> in view of <i>Illumina 2008</i>
Ground VI	Claim 8 would have been obvious under 35 U.S.C. § 103 over <i>Porreca</i> in view of <i>Illumina 2008</i>
Ground VII	Claim 8 would have been obvious under 35 U.S.C. § 103 over <i>Schmitt</i> in 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.

Ground VIII	Claim 12 would have been obvious under 35 U.S.C. § 103 over <i>Porreca</i> in combination with <i>Li 2009</i>
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V. THE '241 PATENT

A. Overview

The '241 patent issued from Application No. 17/381,888 (“’888 application”), filed on July 21, 2021. The '241 patent claims priority to U.S. Provisional Application No. 61/903,826 (“’826 Provisional”), filed on November 13, 2013.⁴

The '241 patent is related to the field of “high throughput sequencing reactions” and directed to methods of detecting duplicate nucleic acid sequencing reads. EX1001 at 1:26-29, 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 1:35-41, 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 1:34-36. 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

⁴ Petitioner applies November 13, 2013 as the priority date for the '241 patent in this Petition, EX1003.¶39-40; however, Petitioner does not agree that Tecan is entitled to this priority date.

molecules, or if they are “PCR duplicates derived from a single” nucleic acid molecule. *Id.* at 1:36-41. Including PCR duplicates, or true duplicates, in the sequencing read can result in biased data and inefficiencies.

The '241 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 2:6-8. To identify true duplicate reads, the patent discloses the use of an “identifier site” that can be included in an “adaptor” appended to the target nucleotide to be sequenced. *Id.* at 4:16-34. The identifier site “is a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” *Id.* at 4:45-48. 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 14:14-17.

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	obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor;

1.b	wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment;
1.c	sequencing the amplicons to generate sequence reads that include identifier and target sequences;
1.d	identifying sequence reads with identical identifier and target sequences as duplicates.

C. Prosecution History

As noted above, the '241 patent issued from the '888 application, which was filed on July 21, 2021. On July 28, 2021, the applicant submitted a preliminary amendment withdrawing its original 21 claims and adding claims 22-37. EX1012.0203-07. The examiner did not issue any rejections and sent a Notice of Allowance on March 27, 2023. EX1012.0014-18.

In the Notice of Allowance, the examiner remarked that “the priority date of the instant claims is the filing date of the instant application, July 21, 2021.” EX1012.0016. The examiner found that the “prior-filed applications,” including Provisional App. No. 61/903,826, “fail to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph for one or more claims of this application.” EX1012.0015 Specifically, the examiner found that the prior applications failed to provide support for the limitation “an adapter comprising an identifier site comprising a plurality of nucleotides unique to the amplified fragment,” EX1012.0016, which appears in issued claim 1 of the '241 patent.

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).

⁵ Petitioners reserve the right to pursue different claim constructions during this and related proceedings as well as in any district court litigation concerning the ’241 patent. *See Samsung Elecs. Am., Inc. v. Prisia Eng’g Corp.*, 948 F.3d 1342, 1350 (Fed. Cir. 2020).

The Board should construe “adaptor” as “any oligonucleotide that is attached to the target sequence.” The ’241 patent refers to an “adaptor” as “an oligonucleotide sequence, the ligation of which to a target polynucleotide or a target polynucleotide strand of interest enables the generation of amplification-ready products of the target polynucleotide or the target polynucleotide strand of interest.” EX1001 at 4:14-21. This described function, however, is performed by any oligonucleotide. Indeed, during prosecution of the ’357 patent, which is the ’241 patent’s direct parent and which also shares the same specification, 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 notes that although the patent explains 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,” EX1001 at 9:34-37, claim 10 allows for the adaptor to be appended via a priming reaction. The recited adaptors are thus not limited to only those that are ligated. 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 '241 patent, the use of molecular identifiers to identify PCR duplicates was well understood in the art. EX1003.¶¶22-38,54-72. 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 ’241 patent’s claimed method of identifying PCR duplicates was well-known in the art.

A. *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.¶¶55-58, and the batch-stamp identifies which sample each sequence originated from, EX1005.¶16; EX1003.¶¶55-58. McCloskey further teaches the removal of duplicate reads. EX1005.¶63; EX1003.¶¶55-58.

B. *Porreca*

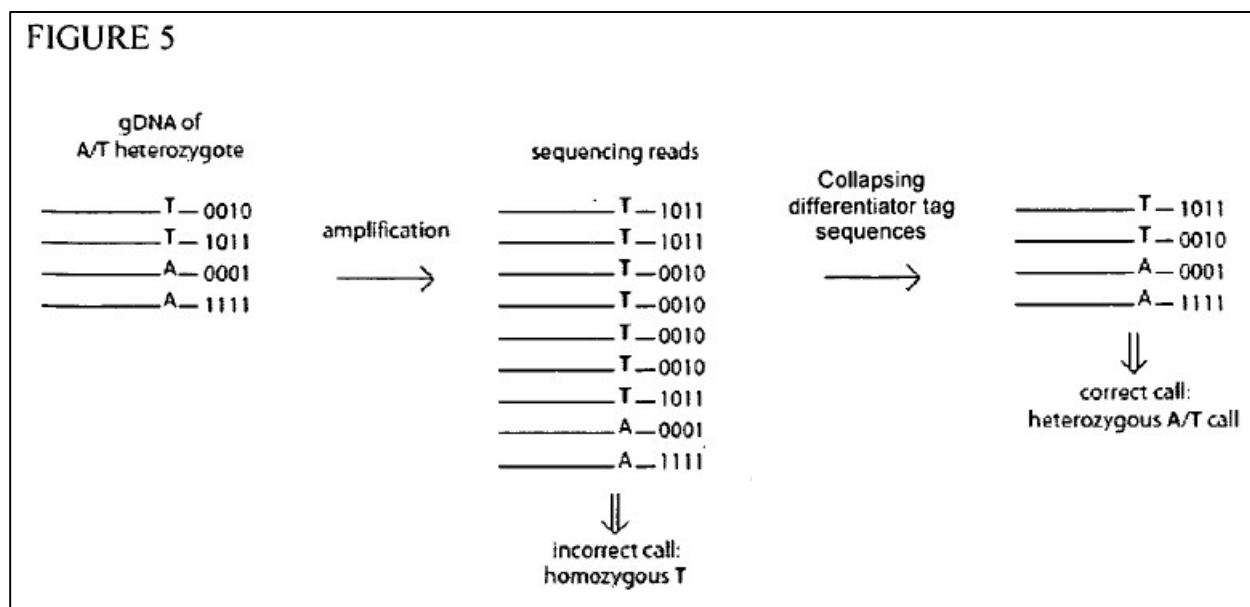
Porreca (EX1006) is a U.S. Patent Application titled “Methods and Compositions for Evaluating Genetic Markers.” It was filed as a PCT on April 30, 2010 and published on June 28, 2012. It is prior art under 35 U.S.C. § 102(a), but was not cited during prosecution. *Porreca* is directed to next generation 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.¶¶59-63.

Like *McCloskey*, *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.¶¶59-63 *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.¶¶59-63.

C. *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.¶¶64-66.

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.¶¶64-66. 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.¶¶64-66..

D. *Li 2009*

Li 2009 (EX1011) is titled “The Sequence Alignment/Map format and SAMtools” and was published on June 8, 2009. It is prior art under 35 U.S.C. § 102(a), EX1014.0022-26,31, but was not cited during prosecution.

Li 2009 describes the “Sequence Alignment/Map (SAM)” format, which is “a generic alignment format for storing read alignments against reference sequences” and supports short and long reads “produced by different sequencing platforms. EX1011.0001. *Li 2009* explains that different novel sequencing technologies have produced a “variety of new alignment tools” that generate alignments in different formats, which can complicate downstream processing. EX1011.0001. It further describes a need in the art for a “common alignment format that supports all sequence types and aligners” and “a well-defined interface between alignment and downstream analyses, including variant detection, genotyping and assembly.” EX1011.0001. *Li 2009* discloses SAM as a format that achieves these goals.

Li 2009 also introduces SAMtools, which is “a library and software package for parsing and manipulating alignments in the SAM/BAM format.” SAMtools can

perform various tasks, including “convert from other alignment formats, sort and merge alignments, remove PCR duplicates,” and “show alignments in a text-based viewer.” EX1011.0002. *Li 2009* can also identify “the position of the first aligned base” of the sequence read mapped to a reference genome. EX1011.0002;EX1003.¶¶67-69.

E. *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 explain 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 ’241 patent, a POSA would have been well-aware of Illumina’s NGS platform and sample preparation methods. EX1003.¶¶70,184.

F. *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.¶¶71-72. 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, 5-7, 9-10, and 13-16 Are Anticipated By *McCloskey*⁶

1. Independent Claim 1

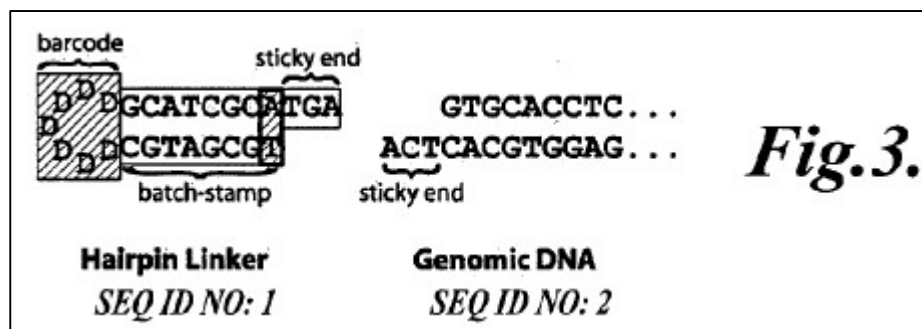
(a) Limitation 1.p

To the extent the preamble is considered limiting, *McCloskey* discloses a “method for detecting duplicate sequencing reads, the method comprising.” EX1003.¶¶74-75. *McCloskey* discloses the use of “barcodes” to distinguish “valid sequences” from “redundant sequences” (*i.e.*, duplicate sequences). EX1005.¶5. *McCloskey* teaches that sequences having “identical barcodes” are redundant, EX1005.¶16, and discloses several experiments utilizing barcodes where redundant sequences were observed. *See* EX1005.¶¶46,57,63,68,93,100,103,106.

⁶ EX1003.¶¶42-43.73-112.

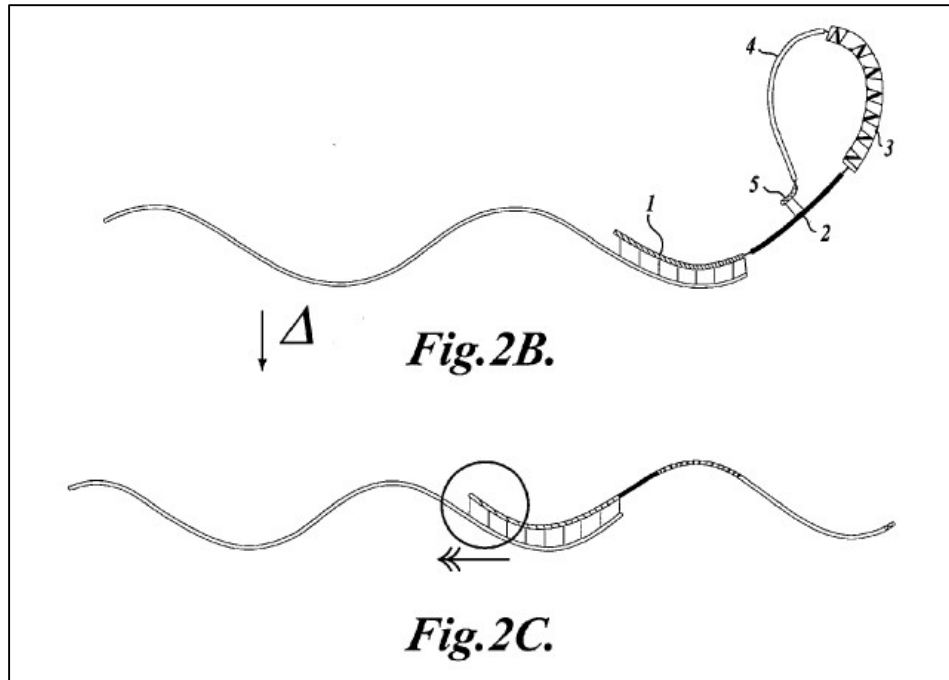
(b) Limitation 1.a

McCloskey discloses “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor.” EX1003.¶¶76-77. *McCloskey* teaches two embodiments that meet this limitation: (1) a hairpin linker embodiment and (2) an oligonucleotide embodiment. With respect to the first embodiment, *McCloskey* teaches that a hairpin linker containing a barcode and a batch-stamp may be ligated onto a target nucleic acid sequence. EX1005.¶¶10,36,95. This is shown in Figure 3:



EX1005.Fig.3. The hairpin linker satisfies the claimed adaptor. EX1003.¶¶76-77. The resulting DNA molecule is then amplified by PCR, which produces amplicons. EX1005¶¶,92-98; EX1003.¶¶76-77.

McCloskey's second embodiment discloses a method where an oligonucleotide containing a barcode and a batch-stamp first anneals to a target nucleic acid sequence. EX1005.¶35. The annealed oligonucleotide is then extended to produce a bar-coded and batch-stamped nucleic acid molecule. EX1005.¶35. This process is shown in Figures 2B and 2C:



EX1005.Figs.2B,2C. Figure 2B shows the “random barcode (3)” as well as the “batch-stamp sequence (2).” EX1005.¶13. This oligonucleotide also satisfies the claimed adaptor. EX1003.¶¶76-77. The resulting molecule is then amplified by PCR to produce amplicons. EX1005.¶14; *see also* EX1005.¶¶43-91.

(c) Limitation 1.b

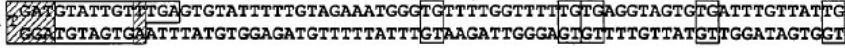
McCloskey discloses “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment.” *McCloskey*’s barcode, which is incorporated into both the hairpin linker and oligonucleotide embodiments, *see supra* Limitation 1.a, satisfies the claimed “identifier site.” EX1003.¶¶78-80. *McCloskey*’s barcode “refers to an arbitrary sequence that can uniquely identify a target nucleic acid in an experiment.” EX1005.¶21. This sequence should be of sufficient length to provide “a unique

identity to each target nucleic acid molecule in the sample prior to amplification” and can range “between 3 and 30 nucleotides.” EX1005.¶21.

McCloskey provides several examples where a barcode appended target sequence is amplified by PCR. For instance, the oligonucleotide adaptor in Example 2 includes “a 7-nucleotide random barcode,” which after an annealing and extension step, is amplified by PCR. EX1005.¶57,Figs.2A-D. The barcode in Example 6 is included in a hairpin linker adaptor, which is ligated to a target DNA sequence and subsequently amplified by PCR. EX1005.¶¶95,98,Figs.3-4. Other examples similarly disclose barcoded DNA products. EX1005.¶¶46-47,57-60,68-73,76,81-84,95-98,100-104.

(d) Limitation 1.c

McCloskey discloses “sequencing the amplicons to generate sequence reads that include identifier and target sequences.” EX1003.¶¶81-86. *McCloskey* discloses that its “[m]ethods and conditions for analyzing nucleic acid molecules by gel electrophoresis, cloning, and sequencing are standard in the art.” *McCloskey*’s Example 6 shows that the amplification products of the hairpin linker embodiment are sequenced. EX1005.¶¶ 98-107. Figure 4 below shows several sequence reads of both the barcode and the target sequence from Example 6:

Fig.4A.		<i>SEQ ID NO: 3</i>
Fig.4B.	* 	<i>SEQ ID NO: 4</i>
Fig.4C.	* 	<i>SEQ ID NO: 5</i>
Fig.4D.		<i>SEQ ID NO: 6</i>
Fig.4E.	+ 	<i>SEQ ID NO: 7</i>
Fig.4F.	+ 	<i>SEQ ID NO: 8</i>
Fig.4G.		<i>SEQ ID NO: 9</i>

EX1005.Figs.4A-G.

The barcode and target sequences of the oligonucleotide embodiments are also shown to be sequenced in Examples 1-3. EX1005.¶¶43-77. For instance, Example 2's results state that "46 sequences were obtained from this experiment. The barcodes, batch-stamps, and the annealing temperature of four exemplary bar-coded sequences are shown in TABLE 1. 36 of the 46 were desirable and valid sequences, each of which had a unique barcode." EX1005.¶63.

(e) Limitation 1.d

McCloskey discloses "identifying sequence reads with identical identifier and target sequences as duplicates." EX1003.¶¶87-90. *McCloskey* teaches that in both the hairpin linker and oligonucleotide embodiments, identical sequence reads having the same barcode are identified as redundant (*i.e.*, duplicates). Regarding the hairpin

linker embodiment in Example 6, *McCloskey* explains that “redundant hypermethylated sequences with identical barcodes and methylation patterns (FIGS. 4B and 4C)” and “redundant hypomethylated sequences with identical barcodes (FIGS. 4E and 4F)” were observed. EX1005.¶103; *see also* EX1005.¶106. And regarding the oligonucleotide embodiment, *McCloskey* explains with respect to Example 1 that “[t]here were 22 sequences with a barcode that was identical to a sequence already obtained (i.e., redundant sequences).” EX1005.¶53. And Example 2’s description explains that “[a] redundant sequence was also recovered, meaning that a MLM1-positive sequence with an already seen bar-code was recovered.” EX1005.¶63.

These disclosures show that both the target sequence (*e.g.*, “redundant hypomethylated sequences” in the hairpin linker embodiment and “MLM1-positive sequence” in the oligonucleotide embodiment) and the barcode are used to determine which sequences are duplicates. EX1003.¶¶87-90.

2. Claim 2

McCloskey discloses “removing a duplicate read from the sequence reads.” EX1003.¶91. *McCloskey*’s Example 2, which involves the oligonucleotide embodiment, resulted in the identification of two identical sequences, where both sequences were tagged with the same barcode. EX1005.¶63. *McCloskey* disclosed that one of the two redundant sequences were removed from the analysis: “A

redundant sequence was also recovered, meaning that a MLM1-positive sequence with an already seen bar-code was recovered. One of these two sequences was counted as a valid sequence.” EX1005.¶63.

3. Claim 3

McCloskey discloses “wherein the identifier site is sequenced with the target sequence.” EX1003.¶¶92-94. As discussed above, §IX.A.1(b), *McCloskey* discloses barcoded DNA amplification products that result from ligation of a hairpin adaptor as well as from extension of an oligonucleotide adaptor. In both embodiments, the barcode is sequenced with the target DNA sequence. EX1003.¶¶92-94. For example, Figures 4A-G show that the barcode in the hairpin adaptor is sequenced with the target DNA sequence. EX1005.Figs.4A-G. And *McCloskey* explains that the barcodes are sequenced with the target sequence. “Redundant hypermethylated sequences recovered from independent bacterial colonies (SEQ ID NO:4 and SEQ ID NO:5), with identical barcodes and methylation patterns.” EX1005.¶16. The barcodes and target sequences were sequenced together in Examples 1 and 2 as well, which involve the oligonucleotide embodiment. See EX1005.¶¶53,63.

4. Claim 5

McCloskey discloses “wherein the amplicons include amplified fragments of cDNA.” EX1003.¶¶95-97. *McCloskey*’s Example 5 discloses barcoding a target

RNA molecule, explaining that a barcoded oligonucleotide molecule is generated that “contains a region complementary to the target RNA strand.” EX1005.¶89. This barcoded product is then “used in a reverse transcriptase reaction as is standard in the art. After one round of reverse transcription, the reaction is stopped and the mixture is digested with an appropriate amount of uracil glycosylase to destroy any remaining RNA template (which includes uracil) in the mix.” EX1005.¶90. A POSA would have known that the reverse transcribed product of the barcoded RNA oligonucleotide is a barcoded cDNA molecule. The subsequent PCR amplification process generates cDNA amplicons that satisfy this limitation. EX1003.¶¶95-97.

5. Claim 6

McCloskey discloses “wherein the amplicons include amplified fragments of genomic DNA.” EX1003.¶98. *McCloskey* teaches that “[i]n the practice of the present invention nucleic acid molecules (e.g., genomic DNA fragments) are labeled with distinct sequence tags prior to PCR amplification.” EX1005.¶5. *McCloskey*’s examples use genomic DNA as well. EX1005.¶¶15,45,95.

6. Claim 7

McCloskey discloses “wherein each adaptor includes a primer binding site.” EX1003.¶99. As explained above, *McCloskey* discloses an embodiment in which an oligonucleotide adaptor anneals to a target nucleic acid sequence, the resulting product of which is then extended to produce a bar-coded and batch-stamped nucleic

acid molecule. *See* §IX.A.1(b). This oligonucleotide adaptor also contains a “leftward primer binding side.” EX1005.¶13,Figs.1,2B,2C.

7. Claim 9

McCloskey discloses “wherein each unique identifier is at least 6 nucleotides in length.” EX1003.¶100. *McCloskey* teaches that the barcode included in the adaptor, *see* §§IX.A.1(b),IX.A.1(c), “refers to an arbitrary sequence that can uniquely identify a target nucleic acid in an experiment.” EX1005.¶21. “In some embodiments,” the length of this barcode “is between 3 and 30 nucleotides, such as between 5 and 25 nucleotides or between 7 and 13 nucleotides.” EX1005.¶21.

8. Claim 10

McCloskey discloses “wherein the adaptors have been appended to the fragments using a ligation reaction or a priming reaction.” EX1003.¶¶101-102. The hairpin linker embodiment discloses a ligation reaction and the oligonucleotide embodiment discloses a priming reaction. *McCloskey* teaches that a hairpin linker adaptor containing a barcode sequence can be ligated to the target nucleic acid sequence. EX1005.¶¶10,15,37,40,95,100,Fig.3; *see also* §IX.A.1(b). *McCloskey* also teaches that an oligonucleotide adaptor containing a barcode can be annealed to a target nucleic acid sequence, the product of which is then extended to produce a barcoded nucleic acid product. EX1005.¶¶8-

9,13,14,17,30,32,35,48,58,71,82,Figs.2B,2C; *see also* IX.A.1(b). This barcoded nucleic acid product is the result of a priming reaction.

9. Claim 13

McCloskey discloses “wherein each adaptor further comprises an indexing site.” EX1003.¶¶103-05. *McCloskey*’s “batch-stamp” satisfies the claimed “indexing site.” *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. As explained above in Limitation 1.a, *McCloskey* discloses two adaptor embodiments, both of which contain a batch-stamp. *See* §IX.A.1(b).

10. Claim 14

McCloskey discloses “wherein each identifier site is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length.” *See supra* IX.A.7; EX1003.¶106.

11. Claim 15

McCloskey discloses “further comprising obtaining a sample comprising the nucleic acid, fragmenting the nucleic acid to yield the fragments of nucleic acid, appending the adaptors to the fragments of nucleic acid, and performing an amplification reaction to obtain the amplicons.” EX1003.¶¶107-08. *McCloskey* explains that “[i]n the practice of the present invention nucleic acid molecules (e.g., genomic DNA *fragments*) are labeled with distinct sequence tags prior to PCR amplification.” EX1005.¶5. As explained above, §IX.A.1(b), *McCloskey* discloses

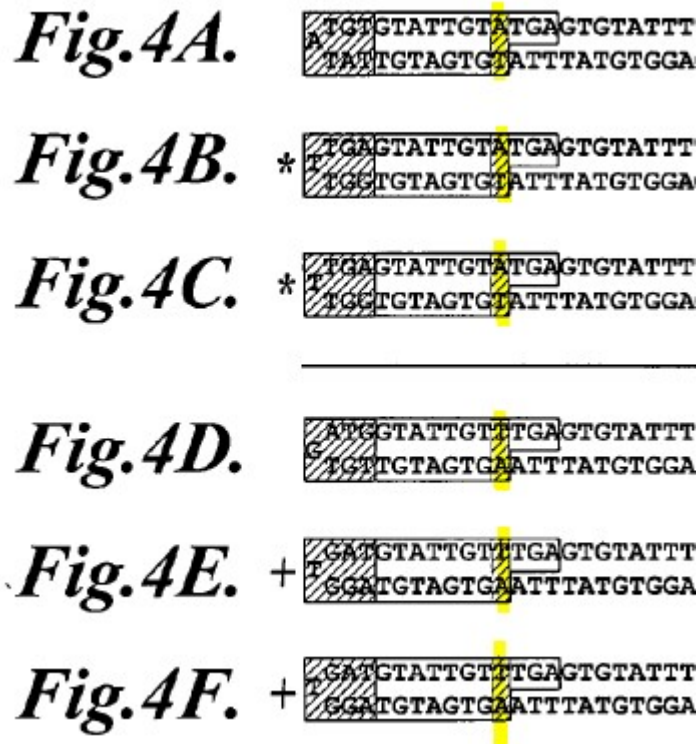
two adaptor embodiments, both of which are appended to nucleic acid fragments prior to amplification. For example, the oligonucleotide adaptor is appended to DNA fragments, the product of which is extended and then amplified. *See id*; *see also* EX1005.¶¶57-59. The hairpin linker adaptor is also appended to DNA fragments prior to amplification. “[G]enomic DNA fragments were labeled with molecular sequence barcodes and ‘batchstamps’ prior to PCR amplification by including these molecular labels in the hairpin linker sequence (FIG. 3) that is used in hairpin-bisulfite PCR.” EX1005.¶93.

12. Claim 16

McCloskey discloses “[t]he method of claim 1, wherein the amplicons include amplified fragment of a nucleic acid from a first sample with an appended adaptor that includes a first index and amplified fragment of a nucleic acid from a second sample with an appended adaptor that includes a second index, and the method includes separating sequence reads by sample based on the first or second index.” EX1003.¶¶109-12. As described above, *McCloskey*’s batch-stamp discloses the claimed index. *See* §IX.A.9.

McCloskey further discloses that batch-stamps were used to identify different samples, which satisfies claim 16. It teaches that “molecules were ‘batch-stamped’ by encoding the hairpin linker with information that would designate the sample analyzed” and that this change to the linker “represented different batches of linkers,

each of which were used for the analysis of a different sample.” EX1005.¶102. Additionally, *McCloskey*’s Figures 4A-F show that sequences with different batch-stamps originated from different samples, and that those with the same batch stamp were grouped together.



EX1005.Figs.A-F (excerpt, annotated). The highlighted nucleotides represent a portion of the batch-stamp and show that sequences A-C have a different batch-stamp than sequences D-F. *McCloskey* explains that “[s]equences A to C carry a different batch-stamp than sequences D to F, with the inversion of the A-T base pair, confirming that these sequence sets came from different DNA samples.” EX1005.¶16. *McCloskey*’s tagging of sequences with two different batch stamps

and subsequent identification and separation of different samples meets this claim.

EX1003.¶¶109-12.

B. Ground II: Claims 1-3, 5-11, and 13-16 Are Anticipated by *Porreca*⁷

1. Independent Claim 1

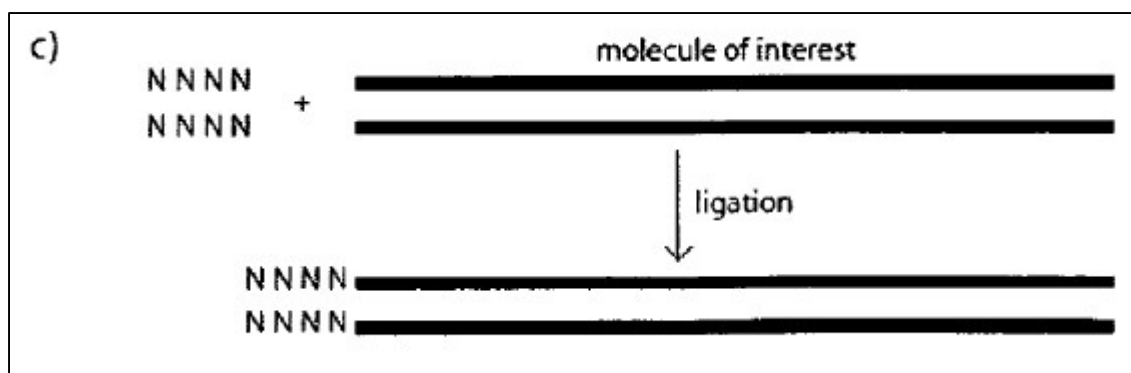
(a) Limitation 1.p

To the extent the preamble is considered limiting, *Porreca* discloses a “method for detecting duplicate sequencing reads, the method comprising.” EX1003.¶¶114-15. *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 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.Fig.5, each identical sequence bearing the same differentiator tag will be PCR duplicates of one another. EX1003.¶¶114-15.

⁷ EX1003.¶¶42-43,113-46.

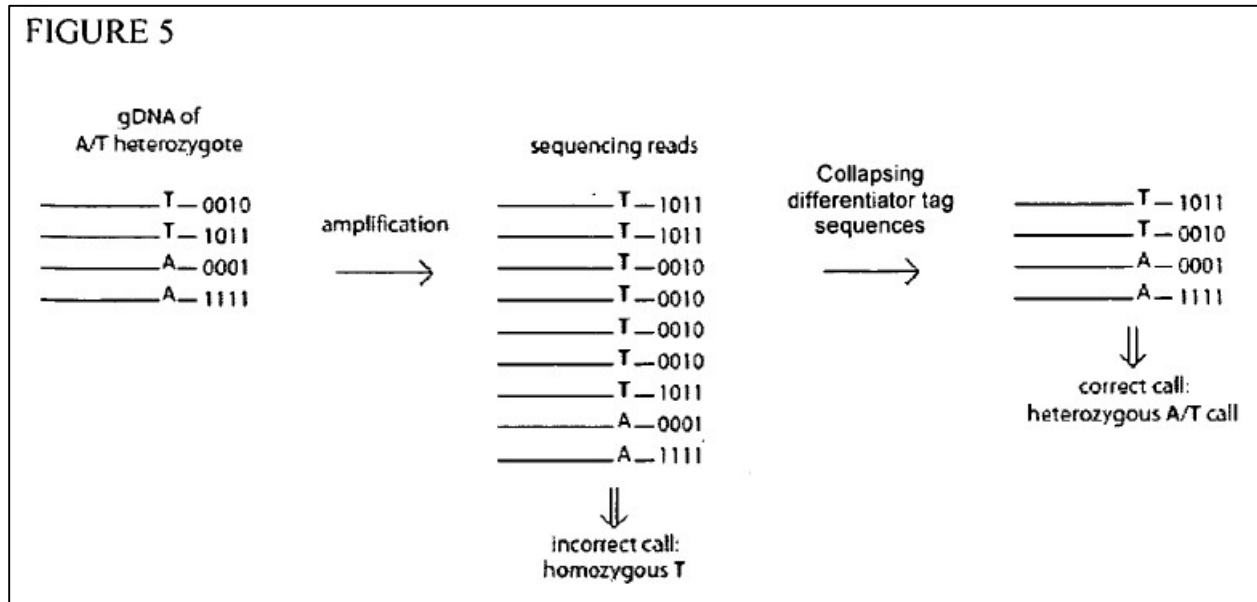
(b) Limitation 1.a

Porreca discloses “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor.” EX1003.¶¶116-17. *Porreca* discloses an adaptor comprising a differentiator tag sequence that can be appended via ligation to the sequence of interest: “[t]he actual incorporation of the random differentiator tag sequences can be performed through various methods known in the art. For example, nucleic acids comprising differentiator tag sequences may be incorporated by ligation.” EX1006.¶150. Figure 4C illustrates an example of this:



EX1006.Fig.4C. *Porreca* further discloses that the differentiator tag may also be included as part of a sequencing 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.

Once the adaptor comprising a differentiator tag is appended to the molecule of interest, the resulting product is amplified by PCR to produce amplicons, as shown in Figure 5:



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.”

(c) Limitation 1.b

Porreca discloses “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment.” EX1003.¶118-19. The ’241 patent explains that an “identifier site” is “a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” EX1001 at 4:45-47. *Porreca*’s differentiator tag sequence discloses the

claimed “identifier site.” These differentiator tags “may be created by using degenerate, random-sequence polynucleotides of defined length,” EX1006.¶143, and may be “up to 25, or more nucleotides in length.” EX1006.¶141. A differentiator tag sequence having 25 nucleotides provides 4^{25} , or 1.125×10^{15} , unique identifiers. EX1003.¶118-19. In other words, *Porreca* discloses a sufficient number of identifier sequences to uniquely tag up to 1.125×10^{15} nucleic acid fragments. EX1003.¶118-19.

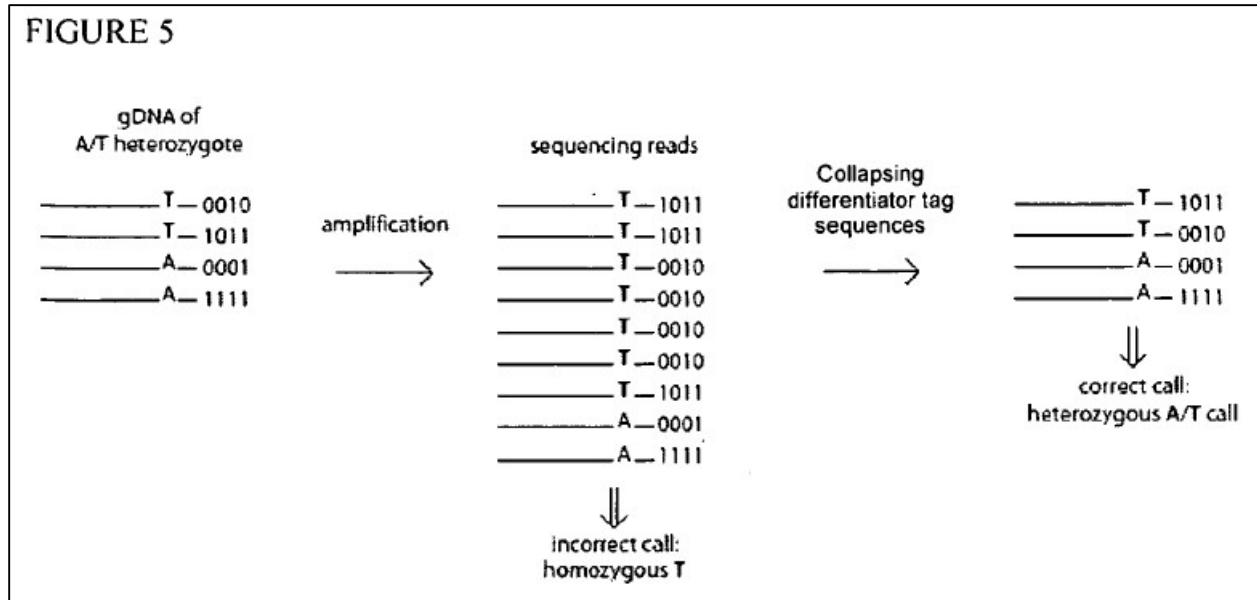
Porreca further teaches that each nucleic acid molecule is uniquely tagged with its own differentiator tag sequence. *See, e.g.*, EX1006.¶142 (“During a library preparation process, each nucleic acid molecule may be tagged with a unique differentiator tag sequence”); EX1006.¶143 (“A large library of 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”); *see also* EX1006.¶23.

(d) Limitation 1.c

Porreca discloses “sequencing the amplicons to generate sequence reads that include identifier and target sequences.” EX1003.¶¶120-21. *Porreca* teaches that amplicons comprising a differentiator tag appended to a target nucleic acid molecule (*see* §IX.B.1(b)) are sequenced, and that the resulting sequencing reads contain both

differentiator and target sequences. “[E]ach 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. “The sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence.” EX1006.¶150; *see also* EX1006.¶138.

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.

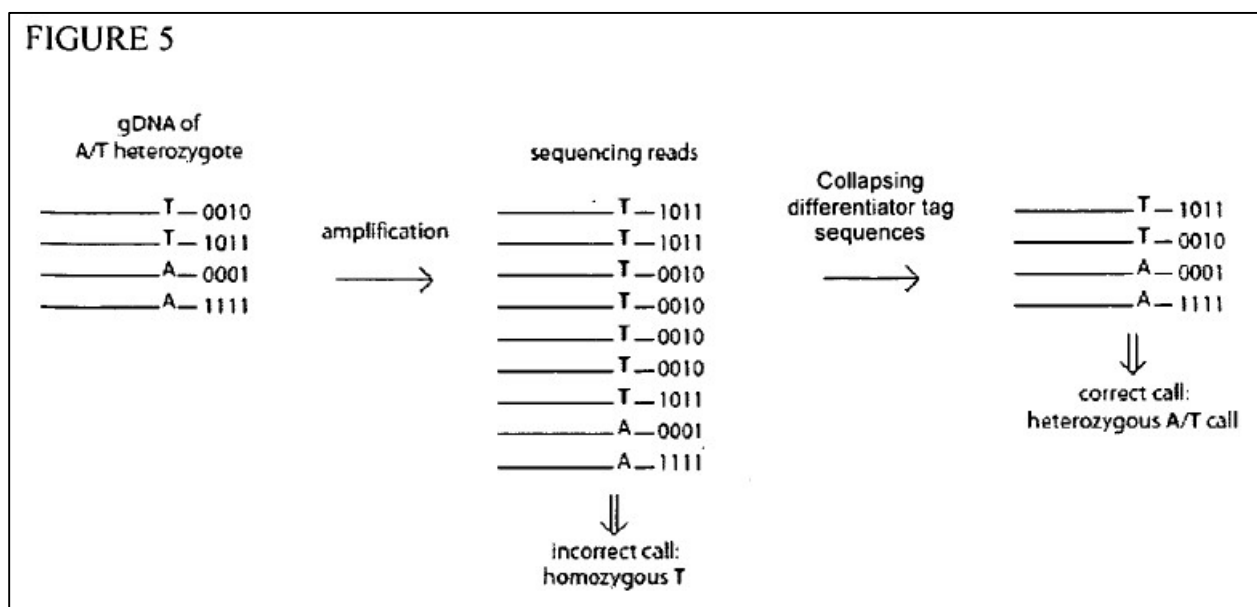
(e) Limitation 1.d

Porreca discloses “identifying sequence reads with identical identifier and target sequences as duplicates.” EX1003.¶¶122-24. *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. *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:



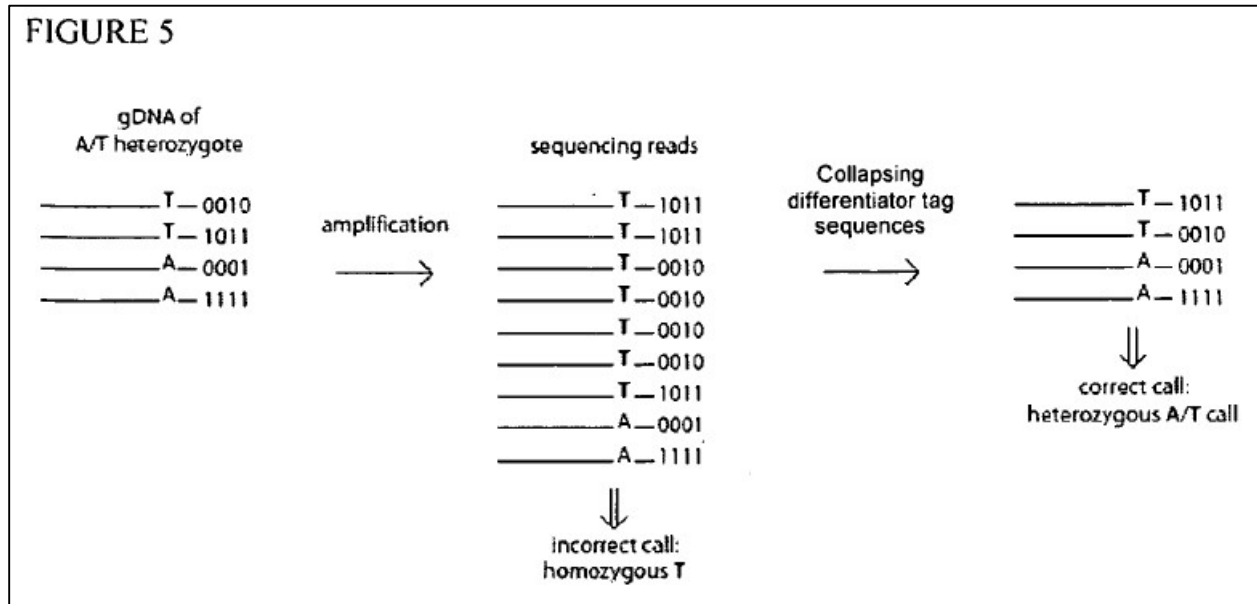
EX1006.Fig.5. *Porreca* explains that Figure 5’s identification and collapsing of duplicate sequencing reads occurs after both the target and differentiator tag sequences are sequenced. “FIG. 5 depicts a non-limiting method for genotyping based on target and differentiator tag sequences. Sequencing reads 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.¶¶122-24.

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.¶¶122-24; *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 “removing a duplicate read from the sequence reads.” EX1003.¶¶125-26. As explained above, §IX.B.1(e), *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.¶¶125-26. 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. 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. 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.¶¶125-26. Indeed, the ’241 patent also acknowledges that duplicates “may be collapsed down to a single read, thus reducing the number of sequencing reads used in final analysis.” EX1001 at 1:41-45. The ’241 patent thus acknowledges that

collapsing sequencing reads removes duplicates from the analysis. EX1003.¶¶125-26.

3. Claim 3

Porreca discloses “wherein the identifier site is sequenced with the target sequence.” EX1003.¶127. *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 “wherein the amplicons include amplified fragments of cDNA.” EX1003.¶128. *Porreca* explains that its disclosed methods can be applied to the analysis of various types of nucleic acids, including 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; *see also* EX1006.¶150 (“This

allows the differentiator tag sequence to be incorporated directly at the cDNA level”).

5. Claim 6

Porreca discloses “wherein the amplicons include amplified fragments of genomic DNA.” EX1003.¶129. *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); *see also* EX1006.¶147.

6. Claim 7

Porreca discloses “wherein each adaptor includes a primer binding site.” EX1003.¶¶130-31. *Porreca* teaches that adaptors can include primer binding sites. “Adapters often contain PCR primer sites (for amplification or emulsion PCR) and/or sequencing primer sites.” EX1006.¶149. *Porreca* also teaches the use of a “common adaptor,” EX1006.¶150, 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.¶¶130-31.

7. Claim 8

Porreca discloses “wherein the primer binding site is a universal target sequencing primer binding site.” EX1003.¶¶130-33. For example, *Porreca*

discloses “sequencing primer sites,” which a POSA would understand to satisfy this limitation. EX1003.¶¶130-33. “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,” EX1006.¶150, 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.¶¶130-33.

8. Claim 9

Porreca discloses “wherein each unique identifier is at least 6 nucleotides in length.” EX1003.¶134. *Porreca* teaches differentiator tag sequences having a variety of nucleotide lengths, including those with at least 6 nucleotides. “Differentiator tag sequences may be... up to 6...or more nucleotides in length.” EX1006.¶141 (emphasis added).

9. Claim 10

Porreca discloses “wherein the adaptors have been appended to the fragments using a ligation reaction or a priming reaction.” EX1003.¶¶135-36. *Porreca* teaches a ligation reaction: “[t]he actual incorporation of the random differentiator tag sequences can be performed through various methods known in the art. For example,

nucleic acids comprising differentiator tag sequences may be incorporated by ligation.” EX1006.¶150. “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; *see also* EX1006.Fig.4c. *Porreca* teaches a priming reaction as well: “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).” EX1006.¶150.

10. Claim 11

Porreca discloses “wherein each unique identifier is at a junction between the adapter and the nucleic fragment.” EX1003.¶137. *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.¶137.

11. Claim 13

Porreca discloses “wherein each adaptor further comprises an indexing site.” EX1003.¶¶138-40. *Porreca* teaches adaptors may 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. *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 and that all nucleic acids from the same sample would have an identical barcode. 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 ’241 patent’s “indexing site” limitation. EX1003.¶¶138-40; *see also* EX1001 at 4:35-44.

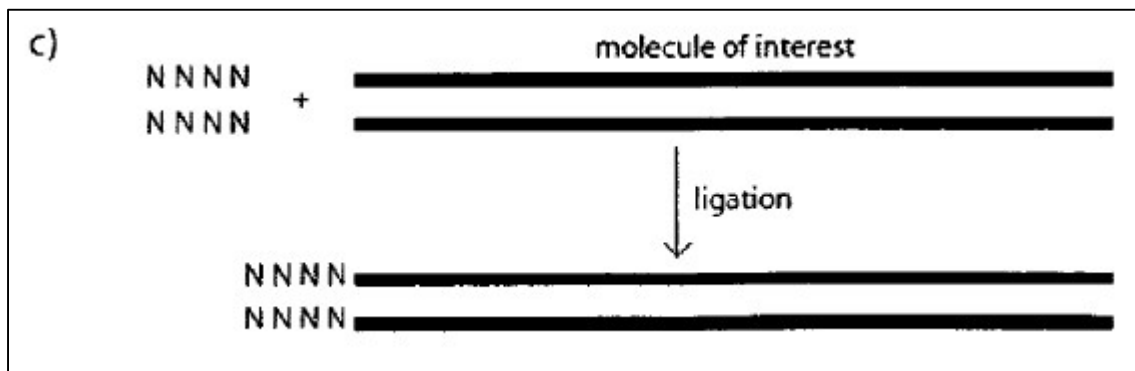
12. Claim 14

Porreca discloses “wherein each identifier site is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length.” *See* §IX.A.7; EX1003.¶¶141.

13. Claim 15

Porreca discloses “obtaining a sample comprising the nucleic acid, fragmenting the nucleic acid to yield the fragments of nucleic acid, appending the adaptors to the fragments of nucleic acid, and performing an amplification reaction to obtain the amplicons.” EX1003.¶¶142-43. *Porreca*’s disclosure of amplicons, *see* §IX.B.1(b), which are generated from nucleic acid fragments satisfies this claim.

Porreca’s Figure 4C shows that the differentiator tag is ligated to a “molecule of interest”:



EX1006.Fig.4C. It further discloses that “FIG.4A-C depict various non-limiting examples of methods for combining differentiator tag sequence and target sequences.” EX1006.¶140. A POSA would have understood that “molecule of interest” and “target sequences” refer to nucleic acid fragments. EX1003.¶¶142-43. Moreover, a POSA would have understood that fragmenting was necessary, as NGS

reactions have a limit on the size of the analyzed nucleic acid. EX1003.¶¶142-43. Indeed, *Porreca* contains several examples where nucleic acid was fragmented by shearing, the resulting fragments were appended to adaptors, and the resulting products were amplified. EX1006.¶¶293,379.

14. Claim 16

Porreca discloses “wherein the amplicons include amplified fragment of a nucleic acid from a first sample with an appended adaptor that includes a first index and amplified fragment of a nucleic acid from a second sample with an appended adaptor that includes a second index, and the method includes separating sequence reads by sample based on the first or second index.” EX1003.¶¶144-46. As described above, *see* §IX.B.11, *Porreca*’s barcode satisfies the claimed indexing site.

Porreca further discloses the analysis of nucleic acids from different samples. For example, it teaches that “nucleic acids are analyzed in biological samples obtained from a plurality of different subjects,” EX1006.¶57, and that “[i]n some embodiments, 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. It also discloses that “barcodes may be included, for example, to uniquely identify individual samples (e.g., patient samples) that may be mixed together.” EX1006.¶149.

A POSA would have known that nucleic acids containing different subject-specific tags (or a barcode in other words) originated from different samples. A POSA would have further known that the steps of this claim are necessarily performed in order to assign “the information from each product” “to an identified subject.” EX1006.¶102. *Porreca*’s disclosure of tagging samples from different subjects and subsequently assigning information from each product to an identified subject satisfies this claim. EX1003.¶¶144-46.

C. Ground III: Claims 1-3, 5-12, and 14-15 Are Anticipated by *Schmitt*⁸

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.¶148. *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. EX1007.¶104.

(b) Limitation 1.a

Schmitt discloses “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor.” EX1003.¶¶149-152. *Schmitt*

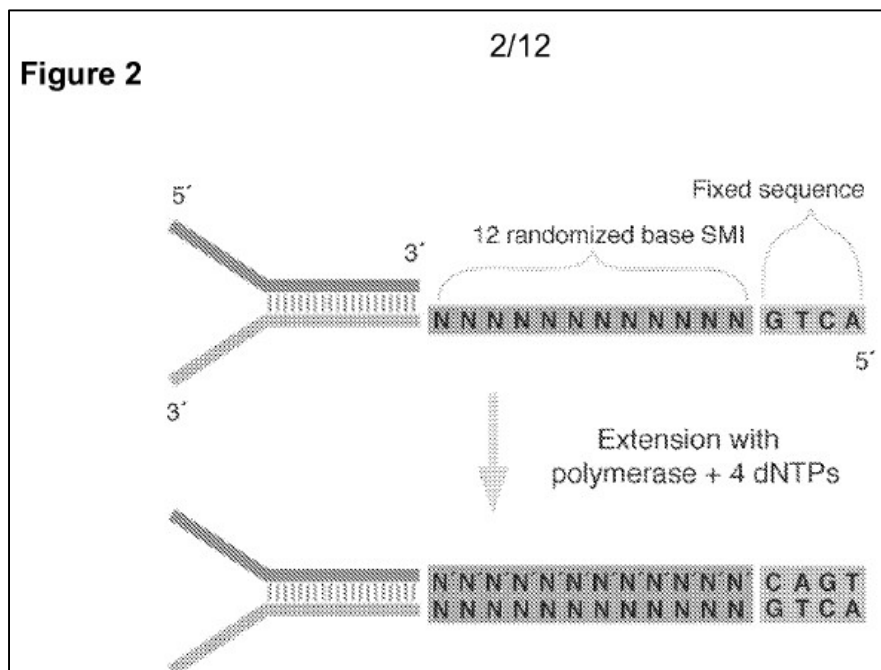
⁸ EX1003.¶¶42-43,147-182.

discloses attaching an SMI adaptor molecule to a target nucleic acid and amplifying 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. *Schmitt*’s Example 1 additionally discloses the claimed amplicons. EX1007.¶98; *see also* EX1007.¶¶89-95.

(c) Limitation 1.b

Schmitt discloses “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment.” EX1003.¶¶153-56. *Schmitt*’s SMI adaptor molecule satisfies the claimed “identifier site.” *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,” and that in one embodiment, a “12 nucleotide SMI n-mer sequence that is ligated to each end of a target nucleic acid molecule, as described in the Example below, results in generation of up to 4^{24} (i.e., 2.8×10^{14}) distinct tag sequences.” EX1007.¶26. Figure 2 shows an exemplary 12 nucleotide SMI from Example 1:



EX1007.Fig.2 (excerpt).

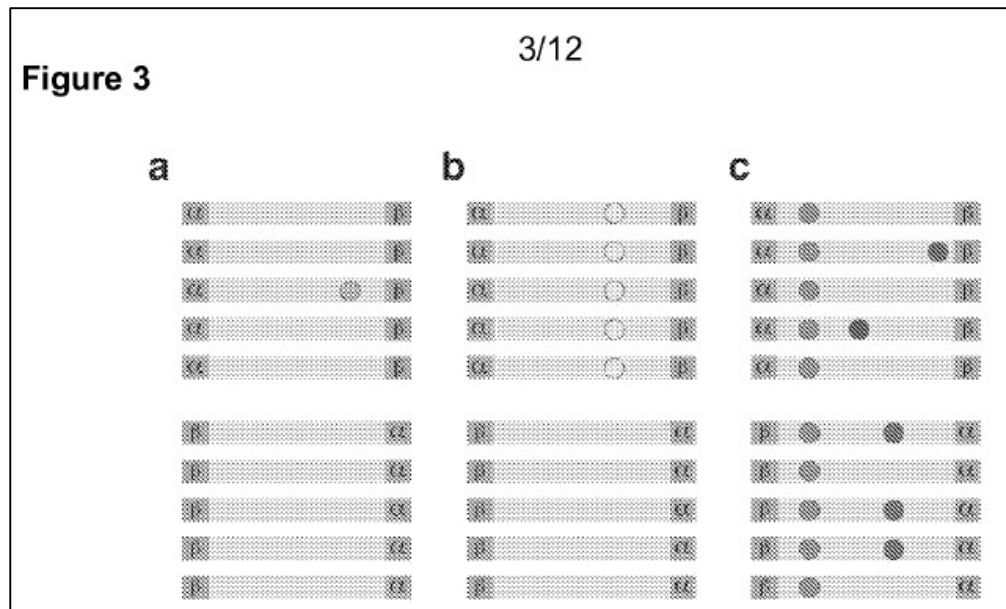
Other disclosures in *Schmitt* further emphasize that every DNA fragment bears its own unique SMI. Regarding Figure 1’s embodiment, *Schmitt* states that “every adaptor contains a unique, double-stranded, complementary n-mer random tag on each end (n-mer = 12 bp according to one embodiment), every DNA fragment becomes labeled with two distinct SMI sequences.” EX1007.¶12. *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. *Schmitt*’s discussion of Example 1 also discloses this limitation. See EX1007.¶¶88-95,98-99,101,104.

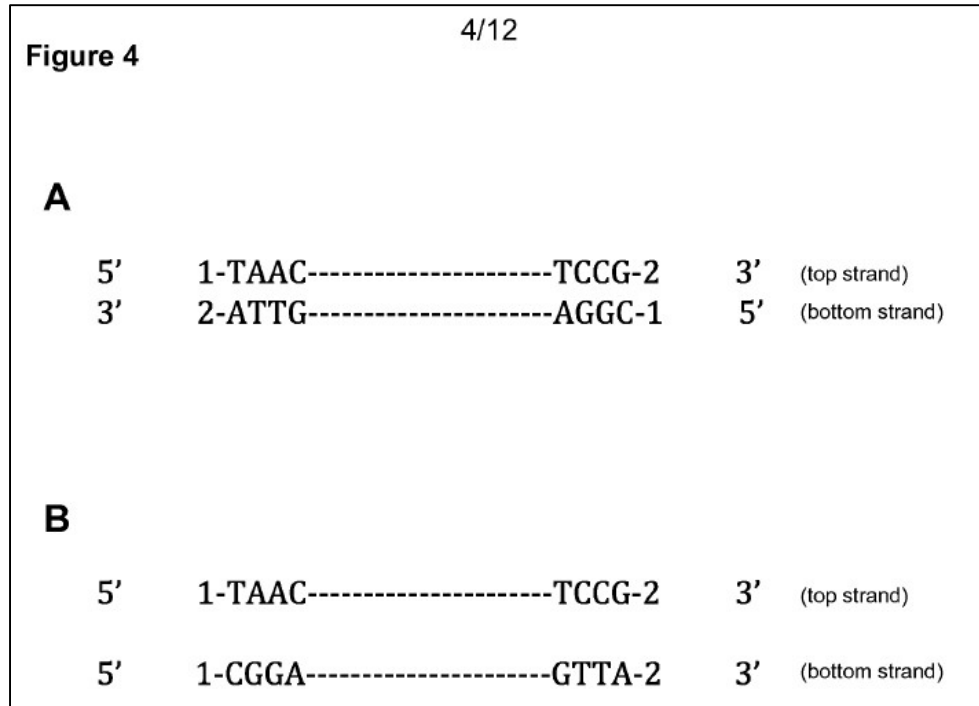
(d) Limitation 1.c

Schmitt discloses “sequencing the amplicons to generate sequence reads that include identifier and target sequences.” EX1003.¶¶157-60. *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....” 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 (excerpt); *see also* 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; EX1003.¶¶157-60.

(e) Limitation 1.d

Schmitt discloses “identifying sequence reads with identical identifier and target sequences as duplicates.” EX1003.¶¶161-62. *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 duplicate sequence reads will have identical identifier and target sequences.:

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 duplicates have identical SMIs and target sequences (*i.e.*, identical shear points):

However sequence reads with identical shear points can also reflect distinct molecules because there are a limited number of possible shear points at any given genomic location, and with increasing sequencing depth, recurrent shear points are increasingly likely to be seen. Because the use of SMI tags (or ‘double-stranded SMI sequences’) allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (*i.e.*, the same or identical) SMI sequence.

EX1007.¶85.

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.¶¶161-62.

2. Claim 2

Schmitt discloses “removing a duplicate read from the sequence reads.” EX1003.¶¶163. *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.¶¶163. Indeed, the ’241 patent also discloses that collapsing duplicate reads “reduce[s] the number of sequencing reads,” *i.e.*, removes duplicates from the analysis. EX1001 at 1:41-45; *see also* §IX.B.2; EX1003.¶¶163.

3. Claim 3

Schmitt discloses “wherein the identifier site is sequenced with the target sequence.” EX1003.¶¶164-66. *Schmitt*’s duplex consensus sequencing method

involves “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.¶¶164-66. The embodiments shown in Figures 3 and 4 also satisfy this limitation. EX1003.¶¶164-66.

Schmitt further discloses regarding Example 1 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* additionally 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.¶¶164-66

4. Claim 5

Schmitt discloses “wherein the amplicons include amplified fragments of cDNA.” EX1003.¶167. *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.

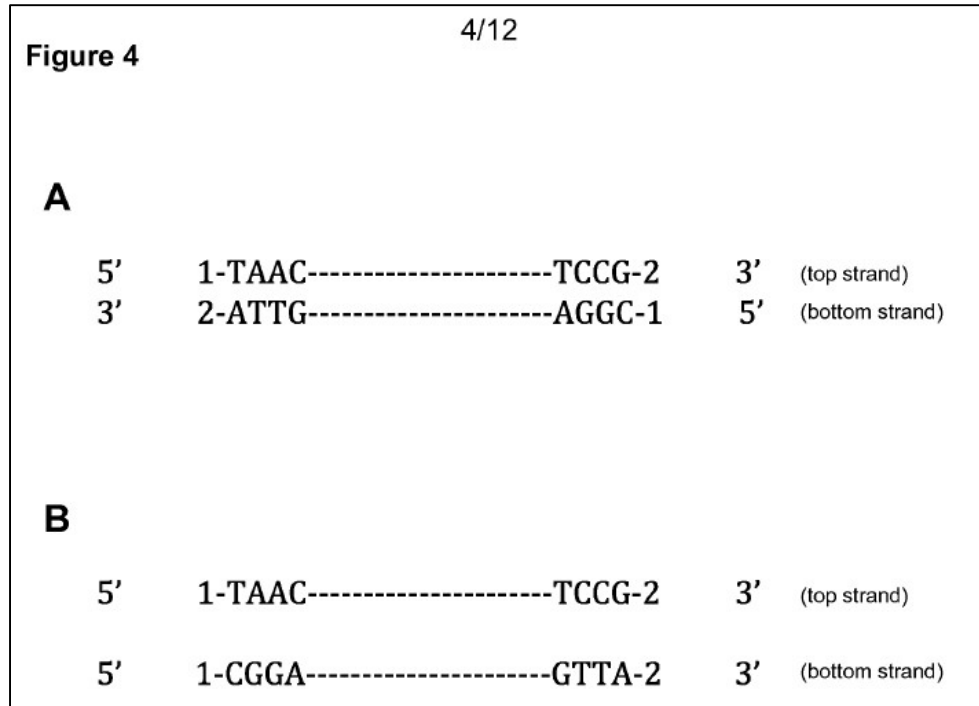
Schmitt further discloses that a ligated RNA molecule “may be reverse transcribed into DNA, and then sequenced as a double-stranded target DNA molecule.” EX1007.¶72. A POSA would have known that reverse transcribing RNA results in cDNA, and thus amplifying this product would have produced “amplified fragments of cDNA.” EX1003.¶167.

5. Claim 6

Schmitt discloses “wherein the amplicons include amplified fragments of genomic DNA.” EX1003.¶168. *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...”).

6. Claim 7

Schmitt discloses “wherein each adaptor includes a primer binding site.” EX1003.¶¶169-70. *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...both the top and bottom strands have binding sites for PCR primers FC1 and FC2 as shown in the examples below.” EX1007.¶23; *see also* 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.” 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.

7. Claim 8

Schmitt discloses “wherein the primer binding site is a universal target sequencing primer binding site.” EX1003.¶¶171-73. *Schmitt* teaches a sequencing primer binding site that satisfies the claimed “universal target sequencing primer binding site.” EX1003.¶¶171-73. “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: “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.

8. Claim 9

Schmitt discloses “wherein each unique identifier is at least 6 nucleotides in length.” EX1003.¶174. *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. Example 1 involves the use of “a 24-nucleotide SMI” that “consists of two 12-nucleotide sequences that can be designated XY.” EX1007.¶100.

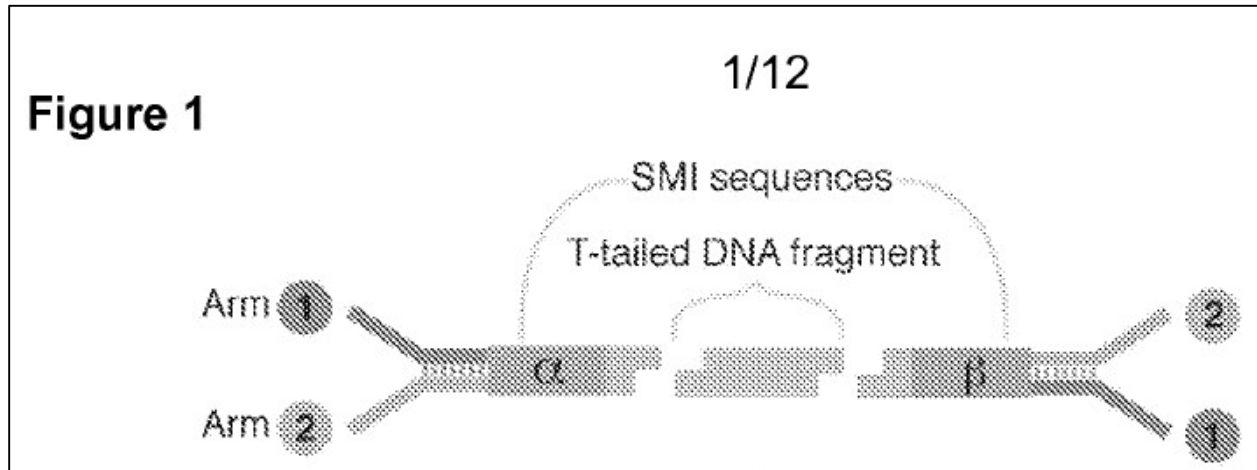
9. Claim 10

Schmitt discloses “wherein the adaptors have been appended to the fragments using a ligation reaction or a priming reaction.” EX1003.¶¶175-76. *Schmitt* teaches the claimed ligation reaction: “SMI adaptor molecule includes a single molecule identifier (SMI) sequence which comprises a degenerate or semi-degenerate DNA sequence; and an SMI ligation adaptor that allows the SMI adaptor molecule to be ligated to the double-stranded target nucleic acid sequence.” EX1007.¶9. *Schmitt* further discloses a duplex consensus sequencing method that “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.” EX1007.¶10. “In some embodiments, the SMI adaptor molecules are ligated to both ends of a target nucleic acid molecule.” EX1007.¶28; *see also* EX1007.¶¶72,74. The SMI adaptor in Example 1 was also ligated to the target nucleic acid sequence. “The custom adaptors were ligated by combining 750 ng of T-tailed DNA with 250 pmol adaptors in a reaction....” EX1007.¶92.

10. Claim 11

Schmitt discloses “wherein each unique identifier is at a junction between the adapter and the nucleic fragment.” EX1003.¶¶177-78. During prosecution of the related ’357 patent, 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); *see also* EX1007.¶12. The SMI sequence (α and β) is located on the adaptor in between sequences 1, 2 and the t-tailed DNA fragment. It is thus located at a “junction between the adapter and the nucleic fragment.”

11. Claim 12

Schmitt discloses “further comprising determining the genomic start position for each sequencing read.” EX1003.¶¶179-80. *Schmitt*’s Example 1 involves aligning the sequencing reads to the human genome, which results in a determination of the genomic start position for each sequencing read. EX1003.¶¶179-80. “Reads were aligned to the human genome with the Burrows-Wheeler Aligner (BWA)...10. Align reads to the human genome.” EX1007.¶96. The BWA alignment tool is a

widely used program that maps NGS reads to a reference genome. EX1003.¶¶179-80.

The *Li & Durbin* reference⁹ explains that the “Burrows-Wheeler Alignment tool (BWA)” was “a new read alignment package” that can “efficiently align short sequencing reads against a large reference sequence such as the human genome.” EX1032.Abstract. It further explains that the authors “simulated reads from the human genome using the wgsim program that is included in the SAMtools package and ran the four programs [including BWA] to map the reads back to the human genome. As we know the exact coordinate of each read, we are able to calculate the alignment error rate.” EX1032.0005.

Schmitt additionally discloses the use of “samtools rmdup, a standard tool,” EX1007.¶103, which was similarly well-known in the field and that also provided the genomic start position for each sequencing read. For example, *Li 2009* discloses the steps of “(a) Alignments of one pair of reads and three single-end reads. (b) The corresponding SAM file. . . . The coordinate shown in SAM is the position of the

⁹ “Extrinsic evidence may be used to interpret the allegedly anticipating reference and [to] shed light on what it would have meant to [a PHOSITA].” *Monsanto Technology LLC v. El DuPont de Nemours and Company*, 878 F.3d 1336, 1345 (Fed. Cir. 2018) (alteration in original) (citation omitted).

first aligned base.” EX1011.2079. *Schmitt*’s disclosure of “align[ing] reads to the human genome” with commonly used tools BWA, EX1007.¶96, and disclosure of samtools, EX1007.¶103, discloses this limitation. EX1003.¶¶179-80.

12. Claim 14

Schmitt discloses “wherein each identifier site is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length.” *See* IX.C.8; EX1003.¶¶181

13. Claim 15

Schmitt discloses “further comprising obtaining a sample comprising the nucleic acid, fragmenting the nucleic acid to yield the fragments of nucleic acid, appending the adaptors to the fragments of nucleic acid, and performing an amplification reaction to obtain the amplicons.” EX1003.¶¶182-83. *Schmitt* discloses a duplex consensus sequencing method that includes the following steps: “[s]heared double-stranded DNA that has been end-repaired and T-tailed is combined with A-tailed SMI adaptors and ligated according to one embodiment...After size-selecting for appropriate length fragments, PCR amplification with primers containing Illumina flow-cell-compatible tails is carried out to generate families of PCR duplicates.” EX1007.¶12. A POSA would have understood that shearing a nucleic acid molecule generates fragments of that molecule. EX1003.¶182. *Schmitt* discloses other embodiments that meet this limitation as well. *See* EX1007.¶¶68,73-74.

Example 1 further teaches this limitation. Example 1’s method includes the following steps: “3 micrograms of DNA was diluted...and was sheared on the Covaris AFA system...” EX1007.¶¶92; “The custom adaptors were ligated...” EX1007.¶¶92; “375 ng adaptor-ligated DNA was PCR amplified...” EX1007.¶¶93.

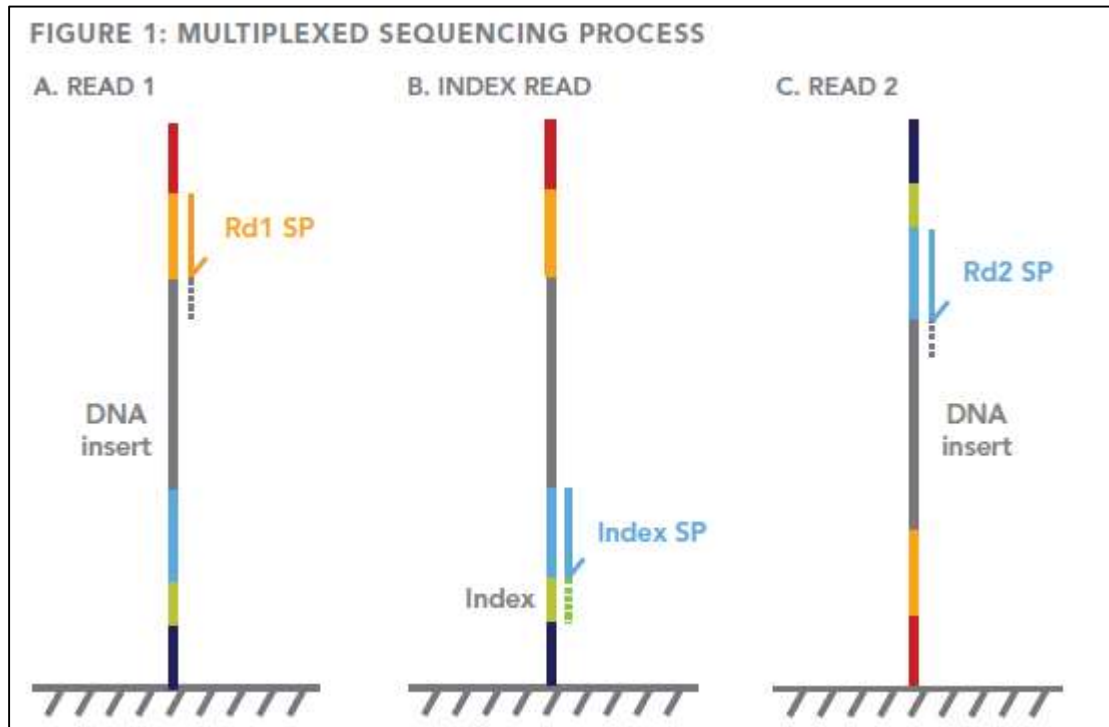
D. Grounds IV and V: Claim 4 Would Have Been Obvious Over *Porreca* In View Of *Illumina 2008* And Over *Schmitt* In View Of *Illumina 2008*¹⁰

Claim 4 recites “wherein the identifier site is sequenced separately from the target sequence.” A POSA would have been motivated to sequence the identifier site separately from the target sequence in both *Porreca*’s and *Schmitt*’s systems. EX1003.¶¶184-85. 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.¶¶184-85. 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.¶¶184-85.

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

¹⁰ EX1003.¶¶44-46,184-85.

'241 patent. EX1003.¶185. 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.¶184-85. 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.¶184-85.

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. EX1003.¶184-85. 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.

E. Grounds VI and VII: Claim 8 Would Have Been Obvious Over *Porreca* In View Of *Illumina 2008* And Over *Schmitt* In View Of *Illumina 2008*¹¹

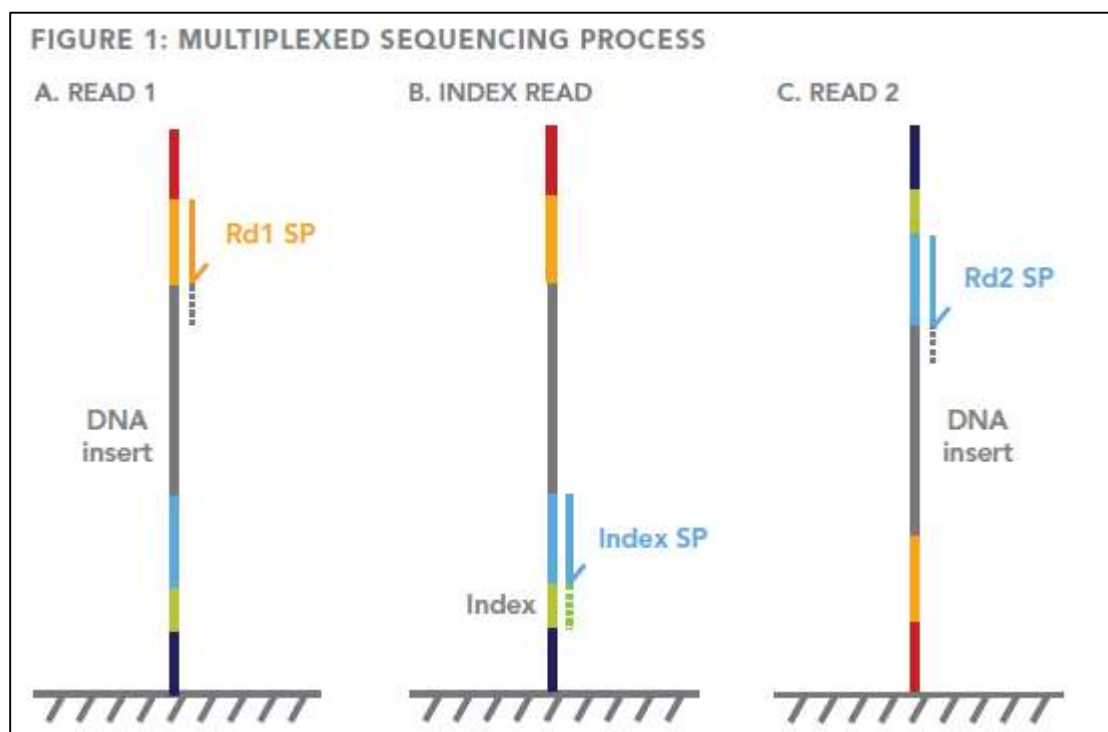
As discussed above in Grounds II and III, both *Porreca* and *Schmitt* disclose this claim. See §§IX.B.7, IX.C.7. To the extent Patent Owner contends that *Porreca*’s “sequencing primer site,” *Porreca*’s “common adaptor sequence,” or *Schmitt*’s “sequencing primer binding site” fail to disclose the 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.¶¶186-90. A POSA 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.¶¶186-90. 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.¶¶186-90.

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 ’241 patent. EX1003.¶¶185. 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

¹¹ EX1003.¶¶44-46, 186-90

the adaptors and are universal target sequencing primer binding sites.

EX1003.¶¶187. *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.¶¶186-88.

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.

EX1010.0032 (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. See §IX.D; EX1003.¶¶186-90.

F. Ground VIII: Claim 12 Would Have Been Obvious Over *Porreca* In View Of *Li 2009*¹²

Claim 12 recites “[t]he method of claim 1, further comprising determining the genomic start position for each sequencing read.” In light of *Li 2009*, in combination with *Porreca*, it would have been obvious to a POSA to perform the method of claim 1 and to further determine the genomic start position for each sequencing read. EX1003.¶¶191-96. *Li 2009* discloses the limitation “determining the genomic start position for each sequencing read.” It describes an alignment format called

¹² EX1003.¶¶44-46,191-96.

“Sequence Alignment/Map (SAM)” and discusses the “SAMtools” software package that provides universal tools for processing read alignments. EX1011.0001 SAMtools was a well-known tool that provides a common alignment format for NGS sequence reads mapped to a reference genome sequence, EX1003.¶¶191-96, and was even explicitly referred to in *Schmitt* as a standard tool: “PCR duplicates were filtered out with samtools rmdup, **a standard tool** which uses the shear points of DNA molecules to identify PCR duplicates, as molecules arising from duplicated DNA will have shared shear points.” EX1007.¶103 (emphasis added).

Li 2009’s Figure 1 shows a Compact Ideosyncratic Gapped Alignment Report (CIGAR) and the corresponding SAM file in Figure 1(b). *Li 2009* explains that “[t]he coordinate shown in SAM is the position of the first aligned base. The CIGAR string for this alignment contains a P (padding) operation which correctly aligns the inserted sequences.” EX1011.0002. A POSA would understand this disclosure to meet the limitation requiring “determining the genomic start position for each sequencing read.” EX1003.¶¶191-96.

A POSA would have been motivated to combine the methods disclosed in *Porreca* with the SAMtools alignment tool disclosed in *Li 2009*. EX1003.¶¶191-96. As discussed above, SAMTools was a well-known tool for aligning NGS sequences and was described in *Schmitt* as being a “standard tool.” EX1007.¶103. A POSA would have been motivated to use the alignment and analysis techniques

disclosed in *Li 2009* because *Porreca* is directed to NGS methods and SAMtools was commonly used in such analysis. EX1003.¶¶191-96.

A POSA also would have been motivated to combine the two references because SAMtools, and thus *Li 2009*, offers features that are beneficial to *Porreca*'s methods. EX1003.¶¶191-96 For example, *Porreca* states that its invention is useful for detecting and removing PCR duplicates. EX1006.¶24; *see also* §§IX.B.1(e), IX.B.2. SAMtools also allows for the removal of PCR duplicates: "SAMtools is a library and software package for parsing and manipulating alignments in the SAM/BAM format. It is able to convert from other alignment formats, sort and merge alignments, remove PCR duplicates, generate per-position information in the pileup format (Fig. 1c)...and show alignments in a text-based viewer." EX1011.2078. Both references are thus clearly in the same field of endeavor and are complementary to one another in solving the same problem, i.e., removing PCR duplicates from DNA sequencing reads to improve the accuracy of data analysis. EX1003.¶¶191-96.

A POSA also would have reasonably expected success in combining the references. As explained above, SAMtools is a "standard tool," EX1007.¶107, and well-known in the art, and a POSA would have known how to use its features to carry out the methods disclosed in *Porreca*. EX1003.¶¶196.

G. No Secondary Considerations of Nonobviousness

Grounds 4-8 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 '241 patent. These factors thus weigh against discretionary denial. As explained above in §V.C, the examiner issued no rejections during prosecution of the '241 patent, so the examiner did not expressly address any prior art reference during prosecution. *McCloskey, Porreca, Schmitt*, and *Li 2009* were never before the Patent Office. And while *Illumina 2008* was listed on the face of the '241 patent, it was never expressly assessed by the examiner and did not form the basis for any rejections, and thus does not weigh in favor of discretionary denial. *See, e.g., Lifecore Fitness v. Woodway USA*, IPR2024-00083, Paper 13 at 22 (May 17, 2024). *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.¹³

¹³ *Illumina 2008* was substantively considered by the examiner during prosecution of the '357 patent, which is the parent patent of the '241 patent. EX1013.0079-81. However, the examiner considered *Illumina 2008* in conjunction with the Samuels reference, which is not at issue here. The examiner never considered *Illumina 2008*

Petitioner additionally notes that *McCloskey* is different from and contains substantially more material than the “*McCloskey 2007*”¹⁴ paper that is cited on the face of the patent, 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 relied upon by Petitioner here that were not included in the *McCloskey 2007* paper. For example, *McCloskey* discloses the hairpin linker adaptor, §IX.A.1, sequencing data from the disclosed examples, §§IX.A.1(d),IX.A.1(e), and data analysis techniques, §§IX.A.1(e),IX.A.2, that are all missing from the *McCloskey 2007* paper. These two references are thus not cumulative of each other. And similar to *Illumina 2008*, the *McCloskey* paper was never substantively addressed by the examiner.

in conjunction with *Porreca* and *Schmitt*, which were also not before the patent office during prosecution of the ’357 patent, and certainly never considered the arguments that Petitioner makes here.

¹⁴ “McCloskey, 2007, Encoding PCR products with batch-stamps and barcodes, *Biochem Genet* 45:761-767” (EX1015) is cited at EX1001.page.5.

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).

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 ’241 patent. Every aspect of the claimed invention was already known in the art, and none of *McCloskey*, *Porreca*, *Schmitt*, or *Li 2009* 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 '241 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 13,705 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. 11,725,241 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. 11,725,241 as evidenced on the Patent Office’s public Patent Center system:

21710 - BROWN RUDNICK LLP
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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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