UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN SCIENCES, LLC,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner

Case No. IPR2025-00026
U.S. Patent No. 11,098,357

PATENT OWNER'S RESPONSE

TABLE OF AUTHORITIES

Page(s)

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780 F.3d 1376 (Fed. Cir. 2015) 23, 25, 26

Apple, Inc. v. Ameranth, Inc.,
842 F.3d 1229 (Fed. Cir. 2016) 16

BlephEx, LLC v. Myco Indus., Inc.,
24 F.4th 1391 (Fed. Cir. 2022) 22

Callicrate v. Wadsworth Mfg., Inc.,
427 F.3d 1361 (Fed. Cir. 2005) 16

In re Gorman,
933 F.2d 982 (Fed. Cir. 1991) 32, 33

Groove Digital, Inc. v. United Bank,
825 F. App'x 852 (Fed. Cir. 2020).....15

InfoBionic, Inc. v. Braemar Manufacturing, LLC,
IPR2015-01704, Paper 11 (PTAB Feb. 16, 2016).....34

InTouch Techs., Inc. v. VGO Commc'ns, Inc.,
751 F.3d 1327 (Fed. Cir. 2014) 33

Markman v. Westview Instruments, Inc.,
52 F.3d 967 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).....15

Net MoneyIN, Inc. v. VeriSign, Inc.,
545 F.3d 1359 (Fed. Cir. 2008) 22

Otonomy, Inc. v. Auris Med.,
AG, 743 F. App'x 430 (Fed. Cir. 2018) 21, 23, 27

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) (en banc) 20

Qiagen N. Am. Holdings, Inc. v. HandyLab, Inc.,
2021 WL 5024387 (Fed. Cir. Oct. 29, 2021) 31

Xerox Corp., et al. v. Bytemark, Inc.,
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Patent Owner Tecan Genomics, Inc. ("Tecan") submits this Patent Owner's Response ("POR") to respond to the Petition (Paper 2) for *inter partes* review ("IPR") of claims 1-10 (the "challenged claims") of U.S. Patent No. 11,098,357 ("the '357 patent," EX1002) filed by QIAGEN Sciences, LLC's ("Petitioner"), and the Board's institution decision, Paper 8.

I. INTRODUCTION

Petitioner's anticipation and obviousness grounds are fundamentally flawed. Petitioner's anticipation argument is legally deficient because it relies on plucking disclosures from disparate, incompatible embodiments of the prior art to allegedly meet the limitations of the challenged claims. Petitioner's obviousness argument rests on an incorrect reading of the "identifying duplicates" limitation of the challenged claims. The record, including the prosecution history, evidences that the challenged claims include a step of comparing ***both*** the identifier site ***and*** a portion of the target sequence in the process of identifying duplicates.

Petitioner's Grounds 1, 3, and 5 rely on Porreca anticipating claim 1. Petitioner, however, fails to identify any embodiment of Porreca in which an adapter that includes an indexing site is ligated to the nucleic acid fragments before the amplification step, as is required by claim 1. Petitioner relies on Porreca's embodiment of blunt-end ligation for disclosure of ligating an adapter to a fragment, but there is no disclosure in Porreca of using the embodiment with that adapter for

adding an indexing site to the nucleic acid fragments. Petitioner separately relies on Porreca's disclosure of an adaptor used in a molecular identification probe ("MIP") for inclusion of an indexing site. But Porreca's blunt-end ligation embodiment and Porreca's MIP embodiment are distinct teachings that are not compatible. Petitioner fails to provide any support for a conclusion that a combination of these embodiments would have been immediately apparent to a POSA or that a POSA would have understood these embodiments to be interchangeable. Therefore, Petitioner has failed to show that Porreca discloses all elements of claim 1 in the claimed arrangement and has, therefore, failed to prove that the challenged claims are anticipated or unpatentable under Grounds 1, 3, or 5.

Petitioner's Grounds 2, 4, and 6 rely on the combination of Schmitt and McCloskey. However, Petitioner relies only on Schmitt for the claimed step of identifying duplicates. Yet Schmitt does not disclose this limitation. Schmitt discloses that an indexing site (referred to as an SMI sequence in Schmitt) ***alone*** is used to determine whether two sequence reads are duplicates. Schmitt does not teach a process for identifying duplicates that uses anything other than the SMI sequence. Claim 1, however, requires that ***both*** the identifier ***and*** the target sequence are used to determine whether two sequence reads are duplicates. Petitioner has not pointed to any teaching or suggestion in Schmitt of using the target sequence for duplicate determination. Therefore, Petitioner has failed to show that all of the limitations are

disclosed in the prior art and has failed to prove that the challenged claims are unpatentable under Grounds 2, 4, and 6.

As such, Petitioner has not met its burden of showing that the challenged claims are unpatentable.

II. TECHNOLOGY BACKGROUND

Much of the background technology at issue in this case is not in dispute. Tecan provides some additional background here for context. The fact that a particular topic is not addressed here does not indicate that Tecan accepts Petitioner's representations.

A. Development of Sequencing Technology

Genetic sequencing, the assessment of genetic information through methods that characterize the sequence of an organism's genetic code, is essential for the understanding of biology and medicine. EX2009.0001 ("Satam 2023"). Several methods have been developed over the years to accurately and efficiently sequence DNA, starting with traditional sequencing methods that are now referred to as pre-next-generation sequencing ("NGS") technologies. *Id.*, .0002-03.

Starting in the early 2000s, the field of genetics was revolutionized by the invention of NGS. EX2004.0333 ("Goodwin 2016")[1]. Compared to traditional, pre-NGS sequencing methods, NGS sequencing utilized a new design that no longer relied on disassembling and then piecing together a single original template DNA strand. *Id.*, .0334-35. Instead, NGS sequencing now allowed for hundreds of

[1] Patent Owner cites to the native page numbers of all Exhibits that have native page numbers. *See* Paper 7, 8 n.6.

thousands of original template strands to be sequenced in the same reaction. *Id*. With NGS, a user could perform massively parallel sequencing, allowing for elements of the genome to be sequenced in a fast, scalable manner. *Id.*, .0335. As compared to pre-NGS sequencing methods, NGS was cheaper, more efficient, and capable of assessing both larger genetic samples and larger portions of the human genome in high fidelity. *Id*.; *see generally* EX2107.¶0049 ("Bustamante Declaration").

NGS systems required some amount of "library preparation" – preparation of the genetic sample after collection to generate a library of that sample for further analysis. Generally library preparation includes the steps of fragmentation, adapter ligation, and amplification. EX2155.0003-05 ("Bronner"). Fragmentation refers to a specific procedure in library preparation where larger samples are broken into smaller fragments through either physical or enzymatic means. *Id.*, .0005-06. Adapter ligation refers to attachment of adapters to the nucleic acid sample or fragments. *Id.*, .0003, 0012. Adapter ligation (or appendment via similar methods) is a critical step in library preparation as it is often used to introduce synthetic nucleotides required for compatibility with NGS platforms, such as introducing binding sites required to attached the library to the surface of the sequencing instrument. *Id.*, .0013; EX2108.0009 (31:5-32:2) ("Metzker Dep. Tr."). Adapters are also often used to facilitate amplification of the sample before sequencing.

Amplification is often used to increase the amount of sequencer-compatible genetic material. EX2155.0015. The result of this process is a sequencing library, or a collection of nucleic acid fragments prepared for sequencing on an NGS platform. EX2108.0008 (27:14-28:9); *see generally* EX2107.¶0051.

However, early NGS methods had their drawbacks. NGS was limited to shorter individual sequencing reads than those of Pre-NGS sequencing methods, which made it more difficult to map the sequence reads to a full genome. *Id.*, EX2155.0001, 0003. NGS methods also made it difficult to determine whether reads were duplicates generated during amplification, unique but identical sections of a genome, or mutated sequences of the genome. EX2001.0061 ("Alkan 2010"); *see also id.*, .0061-62; *see generally* EX2107.¶0052.

Sample amplification steps prior to NGS sequencing introduced PCR errors, which made it difficult to determine whether changes in nucleotides across similar sequences were due to mutations, or to PCR errors, and confounded the data. EX2005.0321 ("Kanagawa 2003"). There were also errors within the sequencing process, such as signal cross-talk, where signals overlap and do not accurately identify the nucleotide, leading to a sequencing read containing the wrong nucleotide. EX2010.2195-96 ("Whiteford 2009"). Lastly, errors occurred during sequencing strand synthesis, leading to sequence strands containing an incorrect

insertion or deletion of a nucleotide. EX2007.0001-02 ("Nakamura 2011"); *see generally* EX2107.¶0053.

B. Challenges With Existing Methods of NGS

Because of the errors inherent in the NGS process, identifying duplicates to accurately map the sequence reads and to distinguish between mutations versus sequencing errors, became an area of interest for both whole genome and targeted enrichment NGS applications. Beyond the scientific issues noted above, the problem of duplicates also had practical implications. For example, large numbers of duplicates in data led to unnecessarily large data sets, making it more difficult to parse the data and more expensive and burdensome to store. EX2015.0215-16 ("Mardis 2017"). Removing duplicates as much as possible would not only allow for more accurate sequencing, but would also save on the time and expense of data analysis associated with sequencing. *See generally* EX2107.¶0062.

One way to identify duplicates was to match the beginning and end of fragments to positions in the reference genome—the odds were higher that fragments with the same beginning and end sequences would be duplicates. EX2017.0012 ("the '399 patent"). But with this method, there was still a risk that naturally-occurring repetitive sequences would be improperly identified as duplicates. The identification of duplicates was particularly challenging with single primer target enrichment methods, where only the side of the fragment associated

with the primer would vary in position across the reference genome. *Id.* The end-matching method was not usable at all in instances where the reference genome was unknown. *See generally* EX2107.¶¶0062-64.

One potential solution involved the use of "barcodes" of nucleotides to tag original sequences prior to sample preparation and amplification. EX2018.0099 ("Samuels"). The presence of the barcode signaled that a fragment was part of an original sequence. *Id.* It could also be used to identify mutations present in the genome versus mutations introduced via PCR, sequencing, or sequence strand synthesis. *Id.* The barcode method, while helpful, also had downsides. Barcodes added extra nucleotides to each fragment, which increased the total number of nucleotides that needed to be sequenced and took up space on the sequence read. EX2014.0008-09 ("Wong 2013"). Shorter barcodes required less space but reduced the number of unique barcodes available and had limited value for samples that contained many unique fragments. EX2003.0041 ("Doan 2022"). As of 2013, researchers in the field struggled to find a method of identifying duplicates that improved on the accuracy of the original barcode method while still allowing for longer sequence reads. *See generally* EX2107.¶¶0065-66.

C. Capture-by-Circularization

The inherent size and complexity of the genome have presented longstanding issues when attempting genetic sequencing. Often, researchers and clinicians are

interested in select regions of the genome, such as those known to be associated with particular diseases or looking to compare a tumor DNA to normal DNA to detect changes in specific genes, that are minute in size compared to the genome as a whole. Sequencing methods can struggle to sequence smaller regions of interest in an efficient, accurate manner. EX2062.0003 ("Ernani 2009"); *see generally* EX2107.¶0067.

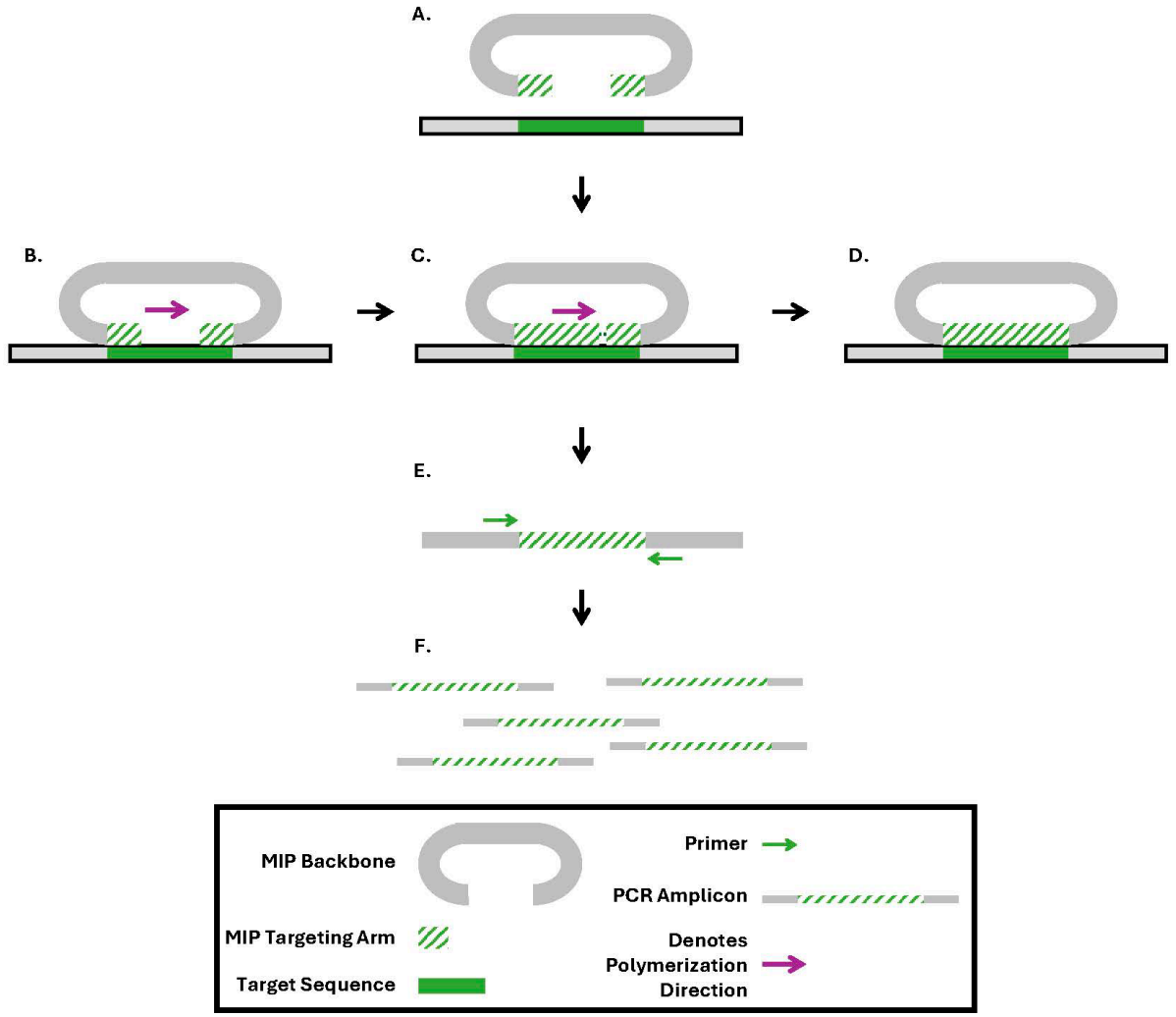
In order to minimize these issues, NGS pipelines were integrated with targeted enrichment approaches designed to enrich a genomic region of interest relative to the rest of the genome prior to sequencing. Targeted enrichment methods sought to amplify the nucleotides corresponding to the region of interest while removing or minimizing those reflecting unwanted regions of the genome, thereby enriching the amount corresponding to the signal of the region of interest relative to the rest of the genomic sample. *See generally* EX2107.¶68.

As of the priority date of the '357 patent, one of the major categories of target enrichment method was capture-by-circularization. *See* EX2016.0016 (1:39-47). These methods include molecular inversion probes or MIPs (also known as padlock probes) and targeting oligonucleotide probes. EX2006.0112, 0114 ("Mamanova 2010"); EX2153.0931 ("Porreca 2007"); *see generally* EX2107.¶0069.

Capture-by-circularization methods utilized linear nucleotide probes designed such that both ends of the probes hybridized at or near adjacent regions in a genomic

region of interest. *See* EX2016.0016 (2:11-16). The ends of the probes are often referred to as "targeting arms." EX2153.0932; *see generally* EX2107.¶0070.

As shown in the figure below, the targeting oligonucleotide probes are designed such that, when they are introduced to a sample with the genetic region of interest, each of the targeting arms will bind to that region (shown in steps A and B). *See* EX2107.¶¶0070-71); EX2016.0016 (2:11-16); EX2006.0112; EX2153.0932. When properly hybridized, the region between the hybridized regions bound by both ends of the probe could then be copied into the probe while joining the two ends of the probe to create a circle, a process termed "gap fill polymerization," shown in step C below. EX2016.0016 (2:11-16); EX2006.0112; EX2153.0932; EX2107.¶0072. Following gap fill polymerization, the 3' terminal nucleotide in the polymerized region can be enzymatically ligated to the 5' end of the adjacent targeting arm to form a circle, shown in step D below. EX2016.0016 (2:11-16); EX2006.0112; EX2153.0932; EX2107.¶0073.



EX2107.¶0075.

Probe circularization allowed for the selective enrichment of circularized probes by filtering out linear probes and probes that did not circularize properly. Then, the regions of interest copied into the circularized probes could be further amplified by PCR. *See* EX2016.0016 (2:16-18); EX2153.0932. To facilitate this process, capture-by-circularization probes were often designed with primer sequences on either sides of the targeting arms, so that the captured region could be

subsequently amplified, as shown in steps E and F above. EX2153.0932; *see generally* EX2107.¶0074.

III. THE '357 PATENT

A. Overview

The '357 patent is directed to a method of detecting and subsequently removing duplicate sequencing reads from a sample population. EX1002.0001. The claimed method is beneficial in overcoming issues related to duplication that arose in previous sequencing methods, such as the problem of distinguishing between mutations and sequencing errors, as described above. *See supra* Section II. The claimed method provides cleaner sequencing data by allowing the identification and removal of unnecessary duplicative data. This is particularly beneficial for sequencing applications where a user seeks to understand the relative amount of starting material where a scientist would want to compare the quantity of the sequenced gene in relation to another gene that might be present in the sample. In addition, as noted above, the accurate removal of duplicates can help to reduce the massive data set generated by sequencing methods, saving both time and money.

B. Level of Ordinary Skill in the Art

In its Institution Decision, the Board adopted Tecan's proposed definition of a POSA with minor modifications. Specifically, the Panel held that a person of ordinary skill in the art ("POSA") would possess the following qualifications:

> [A] person of ordinary skill would have had a Ph.D. in the field of chemistry, molecular biology, or biochemistry or a B.S. or M.S. degree with three to five years of experience working in any of those fields. The person of ordinary skill would have had experience with next generation sequencing methods and a working knowledge of how those methods functioned.

Paper 8, 8-9.

For the purposes of this proceeding, Tecan does not dispute the Board's definition of a POSA.

C. Prosecution History

During prosecution of the '357 patent, Applicants overcame multiple rejections based on the prior art references McCloskey (EX1015) and Samuels (EX2018). To overcome obviousness rejections based on McCloskey, Applicants argued that McCloskey disclosed "methods to identify redundant sequences using … a 'batch stamp,' and 'barcode,' and a target specific 'genomic target-binding site.'" EX1013.0069 ("File History for the '357 patent"). In contrast, Applicants described the claimed method as "identifying sequence reads with identical identifier and fragment sequences" to "identify redundant or duplicate sequences." *Id.*, .0069-70. Applicants further distinguished the claimed method by arguing that, "in contrast to the claimed methods, McCloskey does not use the sequence of a nucleic acid fragment to identify redundant or duplicate sequences." *Id.*

In overcoming obviousness rejections based on Samuels, Applicants distinguished the claimed method by arguing that "Samuels does not teach detecting duplicate sequence reads. Rather, Samuels reports using barcodes to differentiate sequencing errors from single nucleotide polymorphisms," thus, "Samuels fails to disclose detecting duplicate sequence reads by any means." *Id.*, .0069.

D. Claim Construction

1. "adaptor"

The Board construed the term "adaptor" as "any oligonucleotide that is attached to the target sequence." Paper 8, 9. For the purposes of this proceeding, Tecan does not dispute this construction.

2. "identifying sequence reads with identical identifier and target sequences as duplicates"

Term (Claims)	Tecan's Proposed Construction
"identifying sequence reads with identical identifier and target sequences as duplicates" ('357 patent, claim 1)	"identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence"

The term "identifying sequence reads with identical identifier and target sequences as duplicates" appears in claim 1. As the Board recognized, Tecan reserved the right to propose to identify terms and proposed constructions. Paper 8, 10. Tecan now exercises that right.

Based on a proper reading of the specification and prosecution history, the term "identifying sequence reads with identical identifier and target sequences as duplicates" should be construed as "identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence."

When construing the claims of a patent, courts consider the express language of the claims, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). "Claim terms are generally given their ordinary and customary meaning as understood by persons of ordinary skill in the art in view of the specification and prosecution history." *Groove Digital, Inc. v. United Bank*, 825 F. App'x 852, 855 (Fed. Cir. 2020) (citing *Phillips v. AWH Corp*., 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc)). Here, all intrinsic evidence supports Tecan's proposed construction.

Starting with the claim, it is clear from the claim language itself that Applicants intended that the claimed method included an independent step of identifying duplicates by using both the identifier and at least a portion of the target sequence. Each of the steps of the claimed method include specific elements necessary for that step, and the identifying step is no different. An interpretation of this term that allows the identification of duplicates with only one of the claimed elements essentially reads out the rest of this limitation. For example, if this claim

is interpreted to read on a method that includes a step of identifying duplicates using only the identifier site, the reference to the target sequence in this limitation is entirely removed from the claim. *Apple, Inc. v. Ameranth, Inc.*, 842 F.3d 1229, 1237 (Fed. Cir. 2016) (holding that, in considering the words of a claim for construction, a court should "give meaning to all of a claim's terms"). Additionally, reading this limitation expansively to include the use of the identifier site and the target sequence in different parts of the method similarly ignores the plain language of the claim that requires that both of these elements be used in the "identifying" step of the method. *See Callicrate v. Wadsworth Mfg., Inc*., 427 F.3d 1361, 1369 (Fed. Cir. 2005) (holding that it was error for the district court to read out a limitation clearly required by the claim language and specification).

The specification also supports Tecan's proposed construction of this term. For example, Example 5 of the '357 patent, "Identification of Duplicate Sequencing Reads in Determining mRNA Expression Levels," describes a process of identifying duplicate sequencing reads using both the identifier and a portion of the target sequence. Example 5 explains that each adapter contains a "unique identifier … that enables libraries made with these adapters to be distinguished." EX1002.0021 (20:19-21); EX2107.¶0094. After amplification and sequencing, "[t]he first 50 bases of the target sequence read are compared to each other. Any read that has identical sequence to any other read is identified as a duplicate." EX1002.0021

(20:58-62). Based on the structure of the adaptor used in Example 5, the "target sequence read" includes ***both*** the claimed identifier sequence and a portion of the target sequence. EX2107.¶0096. Thus, Example 5 describes a method in which the identifier and a portion of the target sequence are used together as part of a process to identify duplicates. Once a "read that has [an] identical sequence to any other read is identified as a duplicate," it is "removed from the population" such that "only a single copy is retained within the file." EX1002.0021 (20:60-62). After duplicate reads are removed, Example 5 then instructs that the 8 bases of the identifier are removed from each read, confirming that the comparison to identify duplicates used both the identifier site and a portion of the target sequence. *Id.*, 20:62-64.

The specification of the '357 patent additionally discloses that, "[if] the sequences of two libraries[2] are identical, their duplication status is unknown since this could occur by chance in any library. If an identifier sequence is used in combination with the library reads, the status can be determined (***duplicates if identical***, distinct if different)." EX1002.2020 (17:64-18:1) (emphasis added).

[2] A sequencing library refers to a collection of nucleic acid fragments to be sequenced. EX2020.0020 (¶51). A POSA would understand that one could have different sequencing libraries for nucleic acid fragments that originate from different biological samples. EX2020.0026-27 (¶61).

Thus, the specification makes clear that a critical feature of the claimed method is that both a portion of the target sequence and the identifier sequence are used together to determine whether a sequence is a duplicate.

Tecan's proposed construction is also consistent with Applicants' statements during the prosecution of the '357 patent and its predecessors. The '357 patent issued from an application that was a continuation of Application No. 15/406,002, which was a division of Application No. 14/540,917. During prosecution of the 14/540,917 application, the Examiner rejected McCloskey and Samuels. EX2021.0780-81 ("File History for the '399 patent"). McCloskey is directed to a method of identifying redundant sequences in a sequencing dataset, and discloses the use of 7-nucleotide-length "barcodes" and "batch-stamps" to do so. EX1015.0764. McCloskey further describes identification of sequence reads based only on reads that share the same "barcode" or "batch-stamp." *Id.*, .0766. Samuels is directed to a method of attaching barcodes to a nucleotide sequence to allow a user to differentiate PCR-caused errors from true single nucleotide polymorphisms. EX2018.0086-87, 94, 97, 99. Samuels further discloses amplifying the barcodes and nucleotide sequence via PCR, and sequencing the amplified products. *Id.*

Applicants overcame rejections based on McCloskey and Samuels by amending the claims to add the "identifying" limitation that is similar to that in the issued claims of the '357 patent:

1. (Currently Amended) A method for detecting a duplicate sequencing read from a population of sample sequencing reads comprising:
   a) ligating an adaptor to a 5' end of each nucleic acid fragment of a plurality of nucleic acid fragments from one or more samples, wherein the adaptor comprises:
      (i) an indexing primer binding site;
      (ii) an indexing site;
      (iii) an identifier site consisting of~~comprising at least~~ between 1 and 8 nucleotides; and
      (iv) a target sequence primer binding site;
   b) amplifying the adapter-nucleic acid fragment ligated products;
   c) generating a population of sequencing reads from amplified adapter-nucleic acid fragment ligated products; and
   d) ~~detecting~~ identifying a duplicate sequencing read as the ~~population of~~ sequencing read~~s~~ comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads~~a sequencing read with a duplicate identifier site and target sequence~~;

EX2021.0807. Applicants explained that the "identifying" step required comparison of both the identifier and a portion of the target sequence in the same identifying step. Specifically, Applicants distinguished Samuels because it "do[es] not teach (1) ***the active step*** of 'identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads.'" *Id.*, .0797-78 (emphasis added). Applicants also stated that the claimed method "is very different than the method disclosed in McCloskey" because in the claimed method "the sequence of the

identifier site and the sequence of the fragment that is amplified ***are used in combination*** to discern duplication." *Id.*, .0799 (emphasis added).

During prosecution of the application which led to the '357 patent, Applicants overcame similar rejections based on Samuels and McCloskey by clarifying that the claimed method was directed to "using the identifier and fragment sequence to identify duplicate reads … ***[T]he fragment sequence is used in conjunction with the identifier*** to find duplicates." EX1013.0070. When an inventor has asserted that the invention does or does not include a particular aspect, that intention "is regarded as dispositive." *Phillips*, 415 F.3d at 1316. Thus, a POSA would understand from the statements made during prosecution that Applicants were directing the claims at a method that includes a step in which duplicates are identified using a combination of the identifier site and at least a portion of the target sequence.

Thus, the claim language, the specification, and the prosecution history all support a conclusion that the term "identifying sequence reads with identical identifier and target sequences as duplicates" means "identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence."

IV. THE ASSERTED GROUNDS

Petitioner asserts that the challenged claims are unpatentable based on the following grounds:

Ground	Challenged Claims	References
1	1-3, 5-10	Porreca (35 U.S.C. §102)
2	1-3, 5-10	Schmitt and McCloskey (35 U.S.C. §103)
3	4	Porreca and Illumina 2008 (35 U.S.C. §103)
4	4	Schmitt, McCloskey, and Illumina 2008 (35 U.S.C. §103)
5	7	Porreca and Illumina 2008 (35 U.S.C. §103)
6	7	Schmitt, McCloskey, and Illumina 2008 (35 U.S.C. §103)

V. GROUND I: PORRECA DOES NOT ANTICIPATE ANY CHALLENGED CLAIM

Petitioner's arguments for Ground 1 fail because the Petition does not point to any embodiment in Porreca that includes all the limitations of claim 1 as arranged in the claim. Instead, Petitioner's arguments require a POSA to "pick[], choos[e], and combin[e] various disclosures not directly related to each other," which is not anticipation. *Otonomy, Inc. v. Auris Med.*, AG, 743 F. App'x 430, 439 (Fed. Cir. 2018) "[I]t is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to

achieve the claimed invention." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). For example, when "two separate protocols" were disclosed in a prior art reference, yet "[n]either of these protocols contain[ed] all five links arranged or combined in the same way as claimed," the Federal Circuit has confirmed that the reference could not anticipate the claimed system. *Id.* Here, the Petitioner attempts to cobble together "distinct teachings" from Porreca to reach claim 1. This is improper.

A. Petitioner Relies on Separate, Incompatible Embodiments for Limitations 1.a and 1.c

Limitation 1.a requires the step of "ligating an adaptor to each of a plurality of nucleic acid fragments," and limitation 1.c requires that the adaptor include "an indexing site unique to a subset of the adaptors." The claim further requires that the adaptor-ligated fragments are amplified, meaning that the claimed adaptor must be ligated to the fragment before amplification. Petitioner fails to identify a disclosure in Porreca of ligating an adaptor that includes an indexing site (or barcode) to the nucleic acid fragments prior to amplification. Instead, contrary to Federal Circuit precedent, Petitioner combines elements from distinct teachings within the reference to make its anticipation argument, but the embodiments that Petitioner attempts to combine are incompatible. *See*, *e.g.*, *Net MoneyIN,* 545 F.3d at 1371; *BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1400 (Fed. Cir. 2022) (holding that anticipation based on two figures in a prior art reference was not established because the figures

showed separate embodiments); *Otonomy, Inc. v. Auris Med.*, AG, 743 F. App'x 430, 439 (Fed. Cir. 2018) (holding that in order for distinct embodiments in a reference to be combined for anticipation the reference must provide "guidance in the disclosure to link them together.") To establish anticipation with aspects of different embodiments, Petitioner must show that a "person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015). Here, Petitioner has not established that the elements of the challenged claims would be immediately apparent to a POSA. Instead, Petitioner relies on distinct teachings that employ ligation in fundamentally different ways and cannot be combined. As such, Petitioner has failed to show that the challenged claims are anticipated.

For limitation 1.a, Petitioner relies on Porreca's only adaptor ligation embodiment, shown in Figure 4C. It is not disputed that Figure 4C of Porreca discloses ligating an adaptor to a nucleic acid fragment. Paper 2, 18-19. Figure 4C shows what is known as blunt-end ligation of an adaptor to a nucleic acid fragment (Porreca's "molecule of interest"). EX2108.0016 (59:5-11). Dr. Metzker describes Figure 4C as "showing a very common method called ligation of an adapter to the end of a fragment." EX2108.0011 (40:19-21). Petitioner further points to paragraph 150 of Porreca that discloses inclusion of a differentiator tag (or identifier site) in an

adaptor that is ligated. Paper 2, 18. Petitioner does not identify any disclosure in Porreca that describes using an indexing site with the embodiment of Figure 4C.

Petitioner instead relies on descriptions related to MIPs (paragraph 149 and 102 of Porreca) for the disclosure of the indexing site required by limitation 1.c. Paper 2, 20. Paragraph 149 describes the use of what is known as a molecular inversion probe or MIP. The first sentence of paragraph 149 provides that "[t]he skilled artisan will appreciate that as part of a ***MIP library preparation process***, adapters may be ligated onto the ends of the molecules of interest." EX1006.0033 (¶[0149]). Petitioner's expert, Dr. Metzker, confirmed that this paragraph refers to the process shown in Figure 4A, which Dr. Metzker referred to as a "padlock probe." EX2108.0015 (53:18-54:13).

As described above, a MIP, or padlock probe, is a specialized tool that is designed to hybridize with target sequences in a sample and create a circular oligonucleotide that can be amplified. Dr. Metzker explained that a "padlock probe… has two targeting arms….[that] are connected by an adaptor." EX2108.0012 (41:12-22). The targeting arms are designed to bind to region of interest in a sample. EX2016.0016 (2:11-16). EX2006.0112; EX2153.0932. The targeting arms will hybridize to a nucleic acid fragment in the sample and the ends of the targeting arms (or extensions of the targeting arms to fill the sequence between) can be ligated together to form a circular oligonucleotide. *Id*.;

EX2108.0012 (43:11-13) ("a ligase can then ligate the padlock probe that has the adapter based on hybridization to the target.").

Unlike the blunt end ligation process of Figure 4C, a POSA would have understood that in the MIP process, the adaptor is never ligated to the nucleic acid fragment/molecule of interest in the sample and no adaptor-ligated fragments are amplified. EX2107.¶¶0117, 120. Rather, any pre-amplification ligation of the adaptor, if performed, would be to attach the adaptor to the targeting arms of the probe. EX2107.¶¶0073, 117. To the extent Petitioner relies on the ligation performed to circularize the MIP after the targeting arms are bound to the target sequence in the sample, for example as discussed by Dr. Metzker at his deposition (EX2108.0012 (42:11-44:17)), this also does not meet the limitation of the claims. Any ligation to circularize the MIP would be connecting the two targeting arms or connecting portions of the target sequence that has been extended from the targeting arms—not ligating the claimed adaptor to a nucleic acid fragment in a sample. EX2107.¶¶0073, 117.

A POSA would have understood the ligation described to in paragraph 149 refers to adapters that can be ligated to the molecule of interest for purposes of sequencing ***after*** the MIPs are circularized and after PCR amplification. EX2107.¶¶0117-19 (citing paragraphs 252, 294, and 380 of Examples 1, 2, and 6 of Porreca, respectively, as examples of this post-PCR ligation). As Dr. Bustamante

explains, in Example 1 for example, Porreca describes a method in which the capture probes (MIPs) targeting sequences in a sample are allowed to hybridize with sample nucleotides. EX2107.¶0118. The MIPs that bound to portions of the sample are circularized and then amplified. *Id.* The amplified products are purified and mechanically sheared, and only then are the adaptors necessary for NGS sequencing ligated to the amplified fragments. *Id.* Thus, a POSA would have understood the statement regarding ligating adaptors in paragraph 149 of Porreca to be describing the process of adding sequencing adaptors after the MIP is used to amplify portions of the sample, as in, e.g., Example 1. *Id.*

Petitioner also points to paragraph 102 of Porreca which discusses the concept of multiplexing reactions, specifically with reference to multiplexing with MIPs. EX2107.¶0212; Paper 2, 20-21. For example, the sentence immediately preceding the passage cited by Petitioner states that "in some embodiments a plurality of capture reactions (e.g., using different capture probes for different target loci) may be performed in a single multiplex reaction on a single patient sample. EX1006.0028 (¶[0102]). The reference to "capture reactions" and "capture probes" clearly refers to the MIP process and not blunt-end ligation since there is no probe or capture reaction when using a ligated adaptor. EX2107.¶0212. For example, Porreca consistently uses "capture probes" and "capture reactions" in relation to the MIP process or some other similar circularization process. EX1006.0025 (¶[0068])

("Circularization selection-based preparative methods include molecular inversion probe capture reactions and 'selector' capture reactions."); .0053 (Example 3 (titled "Differentiator Tag Sequence Design for MIP Capture Reactions")); *see also* EX2107.¶0212 (explaining that a POSA would understand "captured nucleic acids" to refer to library preparation method such as capture-by-circularization).

A POSA would have understood that the embodiments in Figure 4A and 4C are not compatible with one another and could not be combined. EX2107.¶0122. Specifically, the ligation steps in these embodiments are fundamentally different, connect different elements of the tools, and occur at different steps of the process. EX2107.¶¶0117-19. A POSA would not have envisioned an embodiment that both ligated an adaptor to a nucleic acid fragment and used a MIP with an indexing site. EX2107.¶0122.

Here, Petitioner points to two distinct, incompatible teachings in Porreca for disclosure of an adaptor with an indexing site that is ligated to a nucleic acid fragment in a sample. Petitioner fails to identify any guidance, let alone "specific guidance," that would lead a POSA to link the two teachings together. *See Otonomy*, 743 F. App'x at 439 ("anticipation requires that the reference provide specific guidance that would lead a person of ordinary skill to an embodiment within the claim"). Petitioner has thus failed to meet its burden to show that Porreca anticipates claim 1.

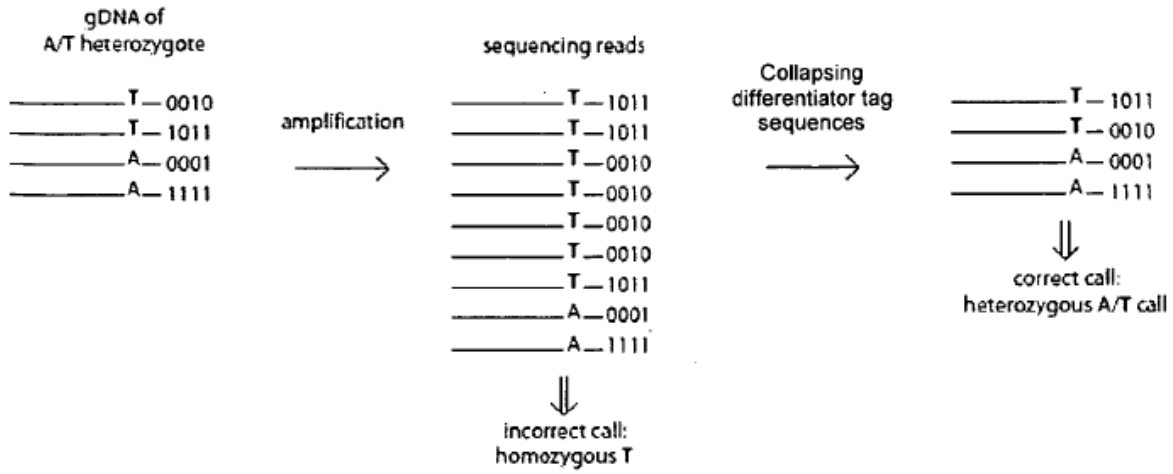
B. Porreca Also Fails to Disclose Limitation 1.g

Limitation 1.g requires the step of "identifying sequence reads with identical identifier and target sequences as duplicates." As properly, construed this limitation requires "identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence." Porreca does not provide any disclosure for how its identification of duplicates is done, and therefore, does not disclose this step as claimed.

Petitioner relies exclusively on Figure 5 of Porreca as allegedly "demonstrat[ing] that sequences having the same target nucleic acid sequence and differentiator tag are identified and collapsed." Paper 2, 26. However, when asked to explain where Porreca explains how the collapsing is done, Dr. Metzker could point only to Figure 5 itself. EX2108.0017 (64:8-19). Additionally, when asked if Porreca explains Porreca compares sequences to determine if they are duplicates, Dr. Metzker could only respond that Figure 5 "speaks for itself." Such a disclosure is insufficient. As discussed above, the challenged claims require a specific process of using both the identifier site and the target sequence to identify duplicates.

Figure 5, shown below, simply includes an arrow with the notation "[c]ollapsing differentiator tag sequences."

FIGURE 5



EX1006.0006 (Fig. 5). There is no requirement in Porreca that the "collapsing differentiator tag sequences" is done in a single step. There simply is no information on how Porreca proposes that this comparison be done. For example, the method could first compare differentiator tags in a first step and then compare target sequences in a second step. Petitioner relies exclusively on conclusory expert testimony to fill the gaps in Porreca, which is improper. *Xerox Corp., et al. v. Bytemark, Inc*., IPR2022-00624, Paper 12 at 5 (PTAB Feb. 10, 2023).

C. Porreca Fails to Disclose Dependent Claims 2-3 and 5-10

Claim 1 is the only independent claim in the '357 Patent, from which all other challenged claims depend. As explained above, the Petitioner fails to show that Porreca anticipates claim 1 because the prior art lacks disclosure of required elements of the claims. Therefore, the Petition similarly fails to show anticipation of any of the dependent claims.

VI. GROUND 2: CLAIM 1 IS NOT RENDERED OBVIOUS BY THE COMBINATION OF SCHMITT AND MCCLOSKEY

As properly construed, limitation 1.g requires "identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence." Petitioner relies exclusively on Schmitt for this limitation, but Schmitt does not use a combination of the identifier site and the target sequence to identify duplicates. Schmitt only discloses identifying duplicates using the identifier alone. Accordingly, the combination of Schmitt and McCloskey cannot render claim 1 obvious. Moreover, there is insufficient motivation to combine the two references.

A. The Combination of Schmitt and McCloskey Fails to Disclose Limitation 1.g

Limitation 1.g requires "identifying sequence reads with identical identifier and target sequences as duplicates." This limitation requires "identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence." Petitioner fails to identify such a step in Schmitt or McCloskey.

Petitioner relies on paragraphs 85 and 98 of Schmitt for disclosure of this limitation. Paper 2, 44. Paragraph 85 provides "***the SMI adaptor molecules*** may be used in methods for unambiguous identification of PCR duplicates." EX1007.0029 (¶[0085]). The paragraph further provides 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***." EX1007.0030 (¶[0085]). As such, Schmitt teaches that duplicates are "unambiguously identified" through comparison of the SMI tags alone, without reference to the target sequence. EX2107.¶¶0127-28. Paragraph 98 reiterates that the SMI is used to determine duplicates by stating that "[e]very duplicate that arises from a single strand of DNA will have ***the same SMI***." EX1007.0034 (¶[0098]). The SMI tag is the claimed identifier and does not include the target sequence. Paper 2, 34 ("Schmitt's SMI adaptor molecule satisfies the claimed 'unique identifier.'). There is simply no disclosure in Schmitt of using the target sequence in any manner to determine whether two sequences are duplicates.

Moreover, Dr. Metzker confirmed that there is no disclosure in Schmitt of using the target sequence to for duplicate determination. When asked to "point to anything in the description that explains that sequence reads are grouped into paired families by anything other than the SMI tags," Dr. Metzker could only point to Figure 3 of Schmitt. EX2108.0019 (71:16-72:5). As an initial matter, the Petition does not rely on Figure 3 as disclosing anything in relation to this limitation. Paper 2, 44-45. Therefore, any such argument should be deemed waived. *See*, *e.g.*, *Qiagen N. Am. Holdings, Inc. v. HandyLab, Inc.*, 2021 WL 5024387, at *3 (Fed. Cir. Oct. 29, 2021) (citing PTAB Consolidated Trial Practice Guide). In any event, any

reliance on Dr. Metzker's testimony regarding what Figure 3 discloses would be improper as expert testimony cannot be used to fill gaps in the prior art *Xerox Corp., et al. v. Bytemark, Inc*., IPR2022-00624, Paper 12 at 5 (PTAB Feb. 10, 2023).

Accordingly, Petitioner cannot meet its burden of showing that the combination of Schmitt and McCloskey renders claim 1 obvious.[3]

B. Petitioner's Motivation to Combine Schmitt and McCloskey Is Also Deficient

Even assuming that Petitioner adequately explained how the prior art disclosed all limitations of the challenged claims (which it has not), Petitioner fails to show that a POSA would have been motivated to combine Schmitt and McCloskey to arrive at the challenged claims with a reasonable expectation of success. Petitioner relies on improper hindsight and the conclusory testimony of an expert witness to support its allegations, and the Board should reject these arguments. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991).

As an initial matter, Petitioner's argument is premised on hindsight. Rather than starting with the prior art, Petitioner's argument is based on a POSA being "motivated to add ***the claimed indexing site*** to *Schmitt's* adaptor." Paper 2, 35. This

[3] Schmitt and McCloskey fail to render claim 1 obvious under any reasonable construction of limitation 1.g since the claim language itself clearly requires using more than just the identifier to identify duplicates.

is quintessential hindsight. Petitioner improperly works backwards from the claim limitations to match the prior art to the claimed adaptor, using the claimed adaptor elements as a roadmap for its obviousness arguments. *In re Gorman*, 933 F.2d at 987 ("It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps."); *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing finding of obviousness and criticizing expert for "rel[ying] on the [challenged] patent itself as her roadmap for putting what she referred to as pieces of a 'jigsaw puzzle' together.").

Finding the claimed indexing site in McCloskey, Petitioner claims that a POSA would have been motivated to start with the adaptor of Schmitt and add the indexing site of McCloskey. Petitioner makes no effort to explain why a POSA would have looked to the McCloskey adaptor specifically to modify the adaptors in Schmitt. Instead, Petitioner argues that a "POSA would have known that it would be beneficial to append a barcode to the target sequence," and would have thus added the barcode disclosed in McCloskey to the adaptor disclosed in Schmitt. Paper 2, 36. Petitioner ignores the differences between the structure of the Schmitt and McCloskey adaptors and how they might, or might not, work if combined. Petitioner's arguments merely cherry-pick a single disclosure from McCloskey and argue that a POSA would have combined it with Schmitt to arrive at the claimed

adaptor. Paper 2, 37-39. The only support to which Petitioner points is *ipse dixit* expert testimony without any underlying factual support. Petitioner further fails to include any of this hindsight-heavy expert analysis in the Petition itself, and therefore, it should be disregarded. *InfoBionic, Inc. v. Braemar Manufacturing, LLC*, IPR2015-01704, Paper 11 at 6 (PTAB Feb. 16, 2016) (denying institution because expert testimony "offer[ed] little or no elaboration" to support Petitioner's arguments).

As a result, the Petition lacks any prior art evidence that a POSA would have been motivated to combine the indexing site of McCloskey with Schmitt to arrive at the claimed invention with a reasonable expectation of success. The hindsight-driven combination of these two references to achieve the claimed adaptor is unsupported by any contemporaneous evidence and should be rejected. Further, the combination of the two references fails to disclose the limitation requiring identification of duplicate sequence reads based on ***both*** the identifier and target sequence. Petitioner has, therefore, failed to meet its burden of showing claim 1 obvious.

C. The Combination of Schmitt and McCloskey Fails to Render Obvious Dependent Claims 2-3 and 5-10

Claim 1 is the only independent claim, from which all other challenged claims depend. As explained above, the Petition fails to show that the prior art renders

claim 1 obvious, and therefore, the Petition similarly cannot establish any of the dependent claims are obvious.

VII. GROUNDS 3 AND 5: PETITIONER HAS NOT SHOWN THAT ANY CHALLENGED CLAIM IS OBVIOUS OVER THE COMBINATION OF PORRECA AND ILLUMINA 2008

In Grounds 3 and 5, Petitioner relies exclusively on Illumina 2008 for disclosure of limitations in the challenged dependent claims 4 and 7. Paper 2, 52-58. As established above, Porreca fails to disclose elements of claim 1. Accordingly, Illumina 2008's alleged disclosures of elements of claims 4 and 7 cannot cure the deficiencies of Porreca with respect to claim 1. Therefore, Petitioner has failed to show that claims 4 and 7 are rendered obvious by the combination of Porreca and Illumina 2008.

VIII. GROUNDS 4 AND 6: PETITIONER HAS NOT SHOWN THAT ANY CHALLENGED CLAIM IS OBVIOUS OVER THE COMBINATION OF SCHMITT, MCCLOSKEY, AND ILLUMINA 2008

In Grounds 3 and 5, Petitioner relies exclusively on Illumina 2008 for disclosure of limitations in the challenged dependent claims 4 and 7. Paper 2, 52-58. As established above, the combination of Schmitt and McCloskey fails to render claim 1 obvious. Accordingly, Illumina 2008's alleged disclosures of elements of claims 4 and 7 cannot cure the deficiencies of Schmitt and McCloskey with respect to claim 1. Therefore, Petitioner has failed to show that claims 4 and 7 are rendered obvious by the combination of Schmitt, McCloskey, Illumina 2008.

IX. CONCLUSION

For at least the reasons set forth above, Petitioner's proposed grounds of unpatentability fail, and Tecan respectfully requests that the Board find all Challenged Claims patentable.

Dated: August 20, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Response** complies with the type-volume limitation of 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(b)(1). The Response contains 7,239 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system use to prepare the Response.

Dated: August 20, 2025

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on August 20, 2025, a copy of the foregoing **Patent Owner's Response** and all supporting documents were served on the counsel of record for Petitioner by delivering a copy via electronic mail to the following addresses:

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