

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN Sciences, LLC,
Petitioner,

v.

Tecan Genomics, Inc.,
Patent Owner.

Case IPR2025-00026

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

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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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) (“ <i>Miner 2004</i> ”)
1005	U.S. Patent Publication No. 2007/0020640 (“ <i>McCloskey</i> ”)
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1009	Authenticating affidavit of Nathaniel Frank-White from the Internet Archive, including the archived copy of <i>Illumina 2008</i>
1010	Michael L. Metzker, <i>Sequencing Technologies – the Next Generation</i> , Nature Reviews Genetics, Vol. 11 (2010) (“ <i>Metzker 2010</i> ”)
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1018	Saiki <i>et al.</i> , <i>Enzymatic amplification of β-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia</i> , <i>SCIENCE</i> 230:1350-1354 (1985) (“Saiki (1985)”)
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1022	Chamberlain <i>et al.</i> , <i>Deletion screening of the Duchenne muscular dystrophy locus via multiplex DNA amplification</i> , <i>NUCLEIC ACIDS RESEARCH</i> 16:11141-11156 (1988) (“Chamberlain (1989)”)
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1024	Grompe, <i>The rapid detection of unknown mutations in nucleic acids</i> , <i>NATURE GENETICS</i> 5:111-117 (1993) (“Grompe (1993)”)
1025	Syvänen, <i>Accessing genetic variation: genotyping single nucleotide polymorphisms</i> , <i>NATURE REVIEW GENETICS</i> 2:930-942 (2011) (“Syvänen (2001)”)
1026	Metzker, <i>Emerging technologies in DNA sequencing</i> , <i>GENOME RESEARCH</i> 15:1767-1776 (2005) (“Metzker (2005)”)
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1031	Craig <i>et al.</i> , <i>Identification of genetic variants using barcoded multiplexed sequencing</i> , NATURE METHODS 5:887-893 (2008) (“Craig (2008)’’)
1032	Li & Durbin, <i>Fast and accurate short read alignment with Burrows–Wheeler transform</i> , BIOINFORMATICS 25:1754-1760 (2009) (“Li & Durbin (2009)’’)
1033	Quail <i>et al.</i> , <i>Improved protocols for the Illumina Genome Analyzer sequencing system</i> , CURRENT PROTOCOLS IN HUMAN GENETICS 18.2.1-18.2.27 (2009) (“Quail (2009)’’)
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I. INTRODUCTION

Tecan’s Patent Owner Response (“POR”) demonstrates that there are only a handful of issues remaining in this proceeding. Tecan’s arguments focus exclusively on independent claim 1. Thus, if claim 1 is found invalid, all of the challenged dependent claims are also invalid.

Tecan disputes only two issues for Ground I. First, it alleges that the Petition impermissibly relies on disparate embodiments of *Porreca* and that *Porreca* discloses an “indexing site” only for adaptors used with molecule inversion probes (“MIPs”). In doing so, Tecan ignores *Porreca*’s express disclosures to the contrary, and its repeated teachings that the adaptors disclosed in *Porreca* can be used with any preparative method, not just MIPs. Second, Tecan argues that *Porreca* does not disclose the “identifying” limitation, but, notably, Tecan’s expert, Dr. Bustamante, does not offer opinions on this issue. Rather, Tecan relies exclusively on attorney argument to first set forth an unduly narrow claim construction and then disputes this limitation. Tecan invites error with its claim construction analysis and also ignores the clear teachings of *Porreca*, which anticipates even under Tecan’s construction.

Tecan’s arguments for Ground 2 fair no better. Tecan again disputes the “identifying” limitation, but both the POR and the Bustamante declaration fail to address paragraph 99 of *Schmitt*—a paragraph extensively cited in the Petition and

one that the Board expressly relied upon in the Institution Decision (“ID”) for the “identifying” limitation. Tecan’s failure to address paragraph 99 is fatal to its arguments. Finally, Tecan alleges that a POSA would not have been motivated to combine *Schmitt* and *McCloskey*, but, again, Tecan does so without expert testimony, and Tecan fails to address the fact that *Schmitt* expressly cites to *McCloskey 2007*, a reference by the same author as *McCloskey* and with overlapping disclosures.

The Board should reject Tecan’s arguments.

II. CLAIM CONSTRUCTION

A. “adaptor”

Tecan does not dispute that “adaptor” means “any oligonucleotide that is attached to the target sequence.” POR.13; Pet.9-10.

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

Tecan’s Proposed Construction	QIAGEN’s Proposed Construction
“identifying sequencing reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence”	Plain and ordinary meaning, which is identifying sequence reads with identical identifier and at least a portion of the target sequences as duplicates

The Board should apply the plain and ordinary meaning of this term, which is identifying sequence reads with identical identifier and at least a portion of the target sequences as duplicates. Thus, QIAGEN agrees with Tecan that both the identifier

sequence and at least a portion of the target sequence are compared to identify duplicates.

The parties disagree, however, on whether this comparison must be completed in a single step. Although not explicitly set forth in the claim construction section of the POR, Tecan interprets the phrase “a step” in its construction as requiring “a single step.” Specifically for Ground 1, Tecan argues, without the support of expert testimony, that *Porreca* does not disclose this limitation because “[t]here is no requirement in *Porreca* that the ‘collapsing differentiator tag sequences’ *is done in a single step*.” POR.29 (emphasis added). The Board should reject Tecan’s attempt to limit the “identifying” term as requiring a single step. There is nothing in the claim language that imposes the additional requirement that the comparison be done in a single step. The claim simply requires that duplicates be identified based on the identifier and target sequences. It thus covers an embodiment that makes two separate comparisons, one for the identifier and one for the target sequence, as well as an embodiment that performs a single comparison of both the identifier and the target sequence at the same time.

The specification is inconsistent with Tecan’s attempt to limit the “identifying” limitation to “a single step.” Example 1, which is titled “***Identification of Duplicate Sequencing Reads*** with NuGEN Ovation Target Enrichment Library System” (EX1002.16:47-49 (emphasis added)), presents an embodiment where

duplicates are not identified in a single step. It explains that three sequencing reads are generated: a “36 base first read, [a] 14 base second read, and [a] 24 base third read.” EX1002.17:30-31. The second read, which contains the eight base indexing site and the six base random identifier sequence, is split into two files wherein the random sequence “is set aside to further sequence parsing.” EX1002.17:33-38; EX1035.¶17. Separately, the first read, which contains a portion of the target sequence, is analyzed using “bowtie aligner” and “duplicate reads were identified by their genomic start positions.” EX1002.17:39-43; EX1035.¶18. Then, in a separate step, the random sequence was checked: “At this point, sequencing reads that started at the same genomic position were checked against the random bases file to see if they have the same or different set of random bases that were ligated to them.” EX1002.17:43-47; EX1035.¶19. The step-wise combination of these two steps determines “‘true’ duplicates”: “Where two sequences with the same starting genomic coordinate had the same set of random bases, they were considered to have come from the same initial DNA ligation event.” EX1001.Fig.5; EX1002.17:47-50; *see* EX1035.¶20. Thus, contrary to Tecan’s construction, the specification teaches identification of duplicates using more than “a single step.” EX1035.¶21.

There is nothing in either the words of the claim or the intrinsic evidence that supports Tecan’s attempt to require that the process of identifying duplicates occur in “a single step.” Indeed, the Federal Circuit has explained that “[u]nless the steps

of a method actually recite an order, the steps are not ordinarily construed to require one.” *Interactive Gift Exp., Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1342 (Fed. Cir. 2001). To the contrary, the step prior to the “identifying” step requires “produc[ing] sequencing reads” (plural), which consistent with Example 1, can most easily be analyzed in two separate steps.

III. GROUND I: *PORRECA* ANTICIPATES CLAIMS 1-3 AND 5-10

A. *Porreca* anticipates claim 1

1. *Porreca* discloses the claimed adaptor limitations

Tecan does not dispute that *Porreca* discloses limitations 1.a and 1.c. However, Tecan (at 22) argues that these elements come from “separate, incompatible embodiments” of *Porreca*. Tecan is wrong.

To anticipate a claim, a prior art reference “must not only disclose all elements of the claim...but must also disclose those elements arranged as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (citation omitted). “[A] reference can anticipate a claim even if it d[oes] not expressly spell out all the limitations arranged or combined as in the claim, if 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) (citation omitted). In other words, a prior art reference “need not always include an express discussion of the actual combination to anticipate. Instead, a reference may still anticipate if that reference teaches that the disclosed

components or functionalities may be combined and one of skill in the art would be able to implement the combination.” *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1344 (Fed. Cir. 2016) (cleaned up); *see also Hayward Indus., Inc. v. Pentair Water Pool & Spa, Inc.*, 814 F. App’x 592, 597 (Fed. Cir. 2020) (“Although Discenzo teaches optimization and the arrangement of components in different embodiments of the patent, Discenzo also explains that these features may be combined”); *Victaulic Co. v. Iancu*, 753 F. App’x 895, 900 (Fed. Cir. 2018) (“This case is distinguishable from *Net MoneyIN* because, as mentioned above, Lewis expressly contemplates the use of multiple segments, nuts and bolts, and axial insertion as required by claim 1”).

While Tecan does not dispute that *Porreca* discloses limitation 1.c, which requires “an indexing site unique to a subset of adaptors,” it alleges (at 24) that this disclosure is limited only to embodiments relating to MIPs. In doing so, Tecan fundamentally mischaracterizes the teachings of *Porreca*. *Porreca* discloses three different “preparative methods” that are used before genotyping: 1) a “circularization selection-based preparative method, e.g., molecular inversion probe capture products”; 2) “amplification-based preparative methods”; and 3) “hybridization-based preparative methods.” EX1006.¶27; EX1035.¶¶23-25. And *Porreca* makes clear that the disclosed “tagging” techniques may be used with any of the three methods: “It should be appreciated that any of the circularization,

amplification, and/or hybridization based methods described herein may be used in connection with one or more of the tiling/staggering, tagging, size-detection, and/or sensitivity enhancing algorithms described herein.” EX1006.¶31; EX1035.¶26. Thus, a POSA would have understood that *Porreca*’s teachings—specifically the tagging techniques—are broadly applicable to each of the disclosed preparative methods, not just those involving MIPs. EX1035.¶26-28.

Paragraph 149 of *Porreca* describes adaptors and teaches that “barcodes may be included, for example, to uniquely identify individual samples (e.g., patient samples) that may be mixed together.” EX1006.¶149. Tecan does not dispute that the “barcodes” are “an indexing site unique to a subset of adaptors,” but alleges that paragraph 149 relates solely to embodiments using MIPs. POR.24. According to Tecan (at 25), “[a] POSA would have understood the ligation described to [sic] 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.” But, the text of paragraph 149 refutes Tecan’s argument. The second sentence states “[a]dapters often contain PCR primer sites (for amplification or emulsion PCR) **and/or** sequencing primer sites.” EX1006.¶149 (emphasis added). By using “and/or,” this sentence expressly teaches an adaptor with **both** a PCR primer **and** a sequencing primer. EX1034.94:5-95:2; EX1035.¶29. However, as Tecan admits, MIP adaptors are ligated “**after** PCR amplification.” POR.25 (emphasis added).

Thus, adaptors used with a MIP would not include a PCR priming site because the MIP contains a PCR priming site that is used to amplify the same sample before the adaptor is ligated. *E.g.*, POR.10-11; EX1006.FIG.4a; EX1035.¶29. Indeed, Dr. Bustamante could not explain why an adaptor used with a MIP would have a PCR priming site. EX1034.95:4-97:6. A POSA reading the second sentence of paragraph 149 would thus understand that by disclosing an adaptor that can have both a PCR *and* a sequencing primer, the adaptors described in this paragraph are for more than just MIPs. EX1006.¶149; EX1035.¶29.

This conclusion is further reinforced by the fact that, after teaching that these adaptors can include “barcodes” “to uniquely identify individual samples (e.g. patient samples) that may be mixed together,” paragraph 149 cites to *McCloskey*. EX1006.¶149. *McCloskey* provides numerous details regarding design of adaptors, but none of the adaptors described in *McCloskey* are for use with MIPs. *See generally* EX1005; EX1035.¶30; EX1034.99:18-20 (“I do not believe that there is a MIPs preparative process discussed in *McCloskey*”). Thus, a POSA reading the totality of paragraph 149 would have understood that this paragraph is broadly applicable to adaptors used with any preparative process, not only adaptors used with MIPs. EX1035.¶30. Indeed, referencing paragraph 149, Dr. Bustamante admitted that “somebody could read this and understand it would apply to other methods.” EX1034.86:6-7.

Paragraph 150 also demonstrates that the teachings of paragraph 149 are applicable to all types of adaptors, not just those used with MIPs. EX1035.¶31. Paragraph 150 discloses an adaptor “arranged with the common adaptor sequence followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5’ to 3’ order).” EX1006.¶150. Notably, this adaptor is not described as being used with MIPs. Yet, as Dr. Bustamante admitted, it discloses an adaptor containing both a PCR and a sequencing primer binding site—exactly as disclosed in paragraph 149. EX1034.105:18-106:5,108:7-17. In short, a POSA reading paragraphs 149 and 150 would immediately envisage an adaptor having both a barcode and a random differentiator tag, which correspond, respectively, to the “indexing site” and “unique identifier” set forth in claim 1. EX1035.¶¶31-32.

Tecan (at 26) similarly dismisses Petitioner’s reliance on paragraph 102 by arguing that this paragraph relates to “multiplexing with MIPs,” but, again, Tecan sets forth an unduly narrowing reading of paragraph 102. The first sentence of that paragraph states “[i]t should be appreciated that aspects of the invention may be useful for high throughput, cost-effective, yet reliable, genotyping of multiple patient samples (e.g., in parallel, for example in multiplex reactions).” EX1006.¶102. That statement is not limited to MIPs. EX1035.¶33. To the contrary, as confirmed by Dr. Bustamante, the first sentence of paragraph 102 does not

mention any preparative methods and several different preparative methods are discussed in the remainder of paragraph 102. EX1034.59:17-23.

Later in paragraph 102, *Porreca* teaches 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. That sentence, like the first sentence of paragraph 102, makes no mention of MIPs. A POSA would have understood that it is applicable to multiple preparative methods, not just MIPs, especially given *Porreca*’s teaching that any of the preparative methods can be used with the tagging techniques described in *Porreca*. EX1006.¶31; EX1035.¶33. Tecan (at 26) argues that “the sentence immediately preceding the passage cited by Petitioner” refers to MIPs. But that does not mean that the sentence cited in the Petition also refers to MIPs. But Tecan ignores that both sentences begin with “[i]n some embodiments....” This indicates to a POSA that they are discussing different embodiments, and the fact that one sentence refers to a MIP embodiment does not indicate that the next sentence also refers to a MIP embodiment.

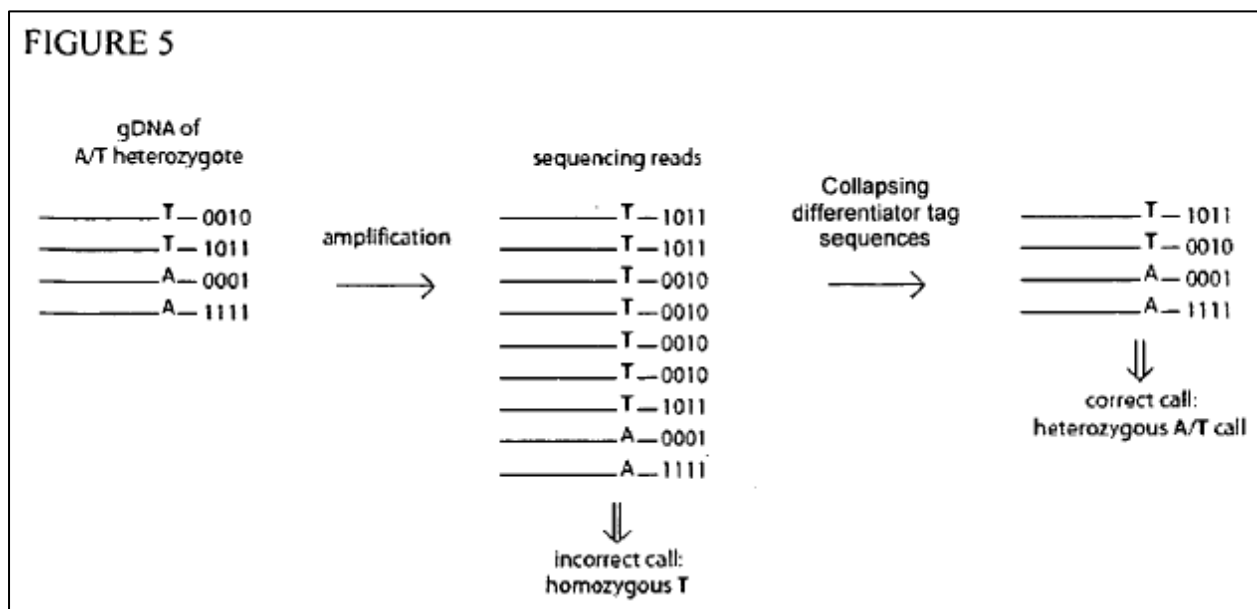
At base, Tecan inappropriately tries to cordon off *Porreca*’s teachings about adaptors to only the MIP preparative process, but that is not what *Porreca* teaches, nor is it what a POSA would understand from reading *Porreca*. *Porreca* teaches that the disclosed adaptors can be used in multiple preparative processes, not just

MIPs. The Board should find that *Porreca* discloses limitations 1.a and 1.c. EX1035.¶34.

2. *Porreca* discloses the “identifying” limitation

Without the support of Dr. Bustamante, Tecan (at 28-29) disputes that *Porreca* discloses the “identifying” limitation. Tecan’s attorney arguments are premised upon Tecan’s unduly narrow claim construction requiring that the “identifying” of duplicates occur “in a single step,” which by itself is sufficient to reject this argument. But even if “identifying” duplicates must occur “in a single step,” *Porreca* satisfies this limitation.

Figure 5 shows how this identification of duplicates is accomplished, as sequences having the same differentiator tag and target sequence are collapsed in a single step:



Pet.26 (citing Figure 5). *Porreca*’s text further confirms that sequences with identical differentiator tags and target sequences are collapsed in a single step: “[f]or any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’ into a single read before consensus basecalls are determined.” Pet.27 (quoting EX1006.¶298); *see also* EX1003.¶88.

Tecan is wrong (at 28) that “*Porreca* does not provide any disclosure for how its identification of duplicates is done.” As discussed above, the Petition and Dr. Metzker’s declaration show that *Porreca*’s Figure 5 and paragraph 298 explain exactly how the duplicate identification is performed, and they show that identification of duplicates is performed in a single step. Figure 5 shows that sequences having the same (1) target sequence and (2) differentiator tag are collapsed, or in other words, removed as duplicates in one step. Moreover, paragraph 298—which Tecan does not address at all—unambiguously discloses that target and identifier sequences that are identical are collapsed: “[f]or ***any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’*** into a single read before consensus basecalls are determined.” EX1006.¶298 (emphasis added); EX1003.¶88; ID.23-25. *Porreca* thus uses a single step to “compare[] sequences to determine if they are duplicates,” contrary to what Tecan argues (at 28).

Further, contrary to Tecan’s argument (at 28), there was no need for Dr. Metzker to elaborate during deposition on Figure 5, as it shows that the collapsing is performed in a single step based on identical target and differentiator sequences. As Dr. Metzker explained, “I think the figure clearly illustrates that it's looking at both the target sequence and the differentiator tags at the same time, to then collapse the reads into consensus sequences. So they’re removing the duplicates.” EX2108.64:11-16. Dr. Metzker did not “fill the gaps” in *Porreca*, as there are no gaps to fill. Dr. Metzker relied on *Porreca*’s express disclosures and included an explanation of how a POSA would have interpreted those disclosures. EX1003.¶87-88. This is proper expert testimony: “Our precedents establish that expert opinion may be used to interpret [an] allegedly anticipating reference and to shed light on what it would have meant to a person having ordinary skill in the art.” *Sage Prods., LLC v. Stewart*, 133 F.4th 1376, 1385 (Fed. Cir. 2025) (citation omitted).

B. *Porreca* anticipates claims 2-3 and 5-10

Tecan challenges QIAGEN’s arguments only with respect to claim 1 and offers no separate rebuttal regarding the dependent claims. As such, *Porreca* also anticipates claims 2-3 and 5-10. *See* Pet.27-33.

IV. GROUND II: CLAIMS 1-3, 5-10 WOULD HAVE BEEN OBVIOUS OVER *SCHMITT* IN VIEW OF *MCCLOSKEY*

A. Claim 1 would have been obvious over *Schmitt* in view of *McCloskey*

1. *Schmitt* discloses limitation 1.g

The Petition and the accompanying Metzker declaration cited three paragraphs of *Schmitt* that demonstrate that *Schmitt* discloses Limitation 1.g— paragraphs 85, 98, and 99. Pet.44-45; EX1003.¶¶127-28. In particular, paragraph 99 explains that following SMI tagging and amplification, both the SMI and target sequences are used to collapse the reads and generate a consensus sequence: “members of the same PCR ‘family’ are then grouped together by virtue of having a common (i.e., the same) SMI tag sequence. The *sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.*” Pet.45 (quoting EX1007.¶99) (emphasis added); EX1003.¶128. The Institution Decision not only discussed QIAGEN’s reliance on paragraph 99, ID.36, but also found it persuasive in rebutting Tecan’s preliminary arguments:

as Petitioner notes, *Schmitt* teaches reading target sequences, wherein “[t]he sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.” (**Ex. 1007 ¶99.**) We are not persuaded at this time that comparing two different methods of identifying duplicates indicates the use of SMIs excludes also using at least a portion of the target sequence.

ID.38 (emphasis added).

Despite being on notice via both the Petition and Institution Decision that paragraph 99 was a key disclosure relevant to limitation 1.g, Tecan and Dr. Bustamante fail to address paragraph 99 entirely, inaccurately declaring that “Petitioner relies on paragraphs 85 and 98 of Schmitt for disclosure of this limitation.” POR.30; EX2107.¶127; *see also* EX1034.23:18-24:20. Based on this selective recitation of the evidence relied upon in the Petition and Institution Decision, Tecan and Dr. Bustamante limited their analysis only to these two paragraphs of *Schmitt*. Tecan has waived its ability to respond to paragraph 99, which is dispositive of limitation 1.g.¹

Schmitt’s paragraph 99 by itself is sufficient to demonstrate disclosure of limitation 1.g. As noted in the Institution Decision, Paragraph 99 teaches that both the identifier—“members of the same PCR ‘family’ are then grouped together by virtue of having a common (i.e., the same) SMI tag sequence” (EX1007.¶99) and target sequences—“[t]he sequences of uniquely tagged PCR duplicates are

¹ “Patent Owner is cautioned that any arguments not raised in the response may be deemed forfeited and/or waived.” Paper 9 at 10; “Patent Owner does not contend that the remaining limitations in claim 1 are absent in Teller (see generally PO Resp.), and therefore, has waived such arguments.” *Tile, Inc. v. Linquet Techs., Inc.*, No. IPR2021-00927, 2022 WL 16973495, at *8 (P.T.A.B. Nov. 16, 2022); “Any material fact not specifically denied may be considered admitted.” 37 C.F.R. § 42.23(a).

subsequently compared in order to create a PCR consensus sequence” (*id.*)—are used to identify duplicates. ID.37-38. As Dr. Metzker explains, a consensus read means that the target sequences are the same: “One of ordinary skill in the art would have known that the target sequences in the duplicates are identical as that is required to generate a consensus read.” EX1003.¶128 (discussing *Schmitt* ¶99). Again, Tecan does not dispute any of this evidence.

While paragraph 99 discloses limitation 1.g, paragraphs 85 and 98 do so as well. *See* Pet.44-45, EX1003.¶127. Tecan’s arguments to the contrary should be rejected. First, Tecan is wrong (at 30-31) that the use of the SMI’s in these paragraphs excludes the use of the target sequence. Paragraph 85 states in part that “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...*true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence.*” EX1007.¶85 (emphases added). As Dr. Metzker explains, sequences that have “identical shear points” have identical target sequences, EX1003.¶127, meaning that the target sequence is taken into account to identify duplicates in this embodiment. The term “true PCR duplicates” additionally shows that the target sequences identified as duplicates are the same. EX1003.¶127. This paragraph thus shows that both sequences are used.

Second, Tecan is also wrong that Paragraph 98 excludes the use of the target sequence. That paragraph states in part “[e]very duplicate that arises from a single strand of DNA will have the same SMI.” EX1007.¶98. This statement merely explains how the SMI works. Because the SMI is appended to the target sequence prior to amplification, EX1007.¶85, duplicates that arise from each original DNA fragment necessarily must carry the same SMI. This statement does not mean that only the SMI is used in duplicate identification as Tecan argues. In fact, the term “duplicate” itself implies that the target sequence is the same. EX1003.¶127.

Third, Tecan mischaracterizes the deposition testimony of Dr. Metzker. Tecan (at 31-32) alleges that “Dr. Metzker could only point to Figure 3” when asked whether *Schmitt* sorted PCR duplicates by anything other than the SMI tag. While Dr. Metzker did point to Figure 3 as an example of sequences being grouped by both sequences, EX2108.70:11-72:20, Tecan never confirmed whether there was anything in addition to Figure 3 that Dr. Metzker could point to. Dr. Metzker testified that Figure 3 shows family groupings by both sequences, and that a POSA would have found it obvious that “what’s being displayed here are not just the SMI sequences but the actual target sequences themselves in showing where the sequences are identical and where the sequences differ.” EX2108.72:14-20. Tecan’s counsel did not follow up with any questions after this response.

Lastly, while Figure 3 is not necessary to demonstrate disclosure of limitation 1.g, it further supports QIAGEN’s position that *Schmitt* discloses the use of both the target and SMI to identify duplicates. *Schmitt* states that Figure 3(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. As Dr. Metzker testified, Figure 3 shows “that the reads are being sorted and characterized both by the SMI and the target sequence.” EX2108.70:17-19. The Petition relies on Figure 3 and its accompanying description to demonstrate disclosure of limitation 1.f and to show that the sequences are grouped based on the target and SMI sequences. Pet.42-43. QIAGEN can thus rely on Figure 3 for limitation 1.g as well, contrary to Tecan’s argument (at 31-32). *See Google LLC v. Ecfactor, Inc.*, No. IPR2022-00473, 2023 WL 5153642, at *11 (P.T.A.B. Aug. 1, 2023) (“the evidence and arguments were made in the Petition, just for another limitation. Our rules do not require a party to repeat the same arguments in multiple limitations of the same claim.”). Indeed, consistent with the rule, when discussing limitation 1.g, the Institution Decision stated “Patent Owner does not dispute the evidence cited by Petitioner, ***such as Figures 3a-c*** and 4 of *Schmitt* and Dr. Metzker’s supporting testimony, teach sequencing of the target sequence along with the identifier to analyze sequence reads and identify duplicates.” ID.37 (emphasis added).

2. A POSA would have been motivated to combine *Schmitt* and *McCloskey*

The Petition and Metzker declaration explain that a POSA would have been motivated to combine *Schmitt* and *McCloskey* because, *inter alia*, both references are in the same field of endeavor, are directed to solving the same problem, and because *Schmitt* cites to *McCloskey 2007*—a paper by the same author as *McCloskey* that contains overlapping disclosures as *McCloskey*. Pet.37-39, EX1003.¶¶114-16. Notably, the Institution Decision found “the citation to *McCloskey 2007* in *Schmitt* indicates to us that the ordinarily skilled artisan would have considered the teachings of *McCloskey* to be highly relevant to the teachings of *Schmitt*.” ID.32. Just as it did for limitation 1.g, Tecan ignores QIAGEN’s core arguments—the POR does not, for example, even mention *Schmitt*’s citation to *McCloskey 2007*. And like paragraph 99, Tecan has waived any argument in rebuttal to these points. *See supra* footnote 1.

Instead of engaging with the arguments in the Petition or the preliminary findings in the Institution Decision, Tecan argues (at 33), without supporting opinions from Dr. Bustamante, that “Petitioner’s argument is premised on hindsight” because “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.” This argument mischaracterizes the Petition.

As the Petition explains, the motivation to combine *Schmitt* and *McCloskey* is based on the teaching of those two references, not the claims. Pet.35-39; EX1003.¶¶109-16. *Schmitt* discloses use of an indexing site—a “fixed multiplexing barcode sequence”—to facilitate identifying the sample from which a particular sequence read originated. EX1007.¶95; Pet.36; EX1003.¶109. Indeed, a POSA would have known that an indexing site allows for multiplexed sequencing. Pet.36; EX1003.¶109. However, *Schmitt* discloses introducing the “fixed multiplexing barcode sequence” after several steps of the disclosed method had been performed. EX1007.¶95; Pet.36; EX1003.¶110. *McCloskey* discloses a “batch-stamp” that performs the same function as *Schmitt*’s “fixed multiplexing barcode sequence,” but does so in an adaptor that also contains a “barcode,” *i.e.* a unique identifier, which performs the same function as *Schmitt*’s SMI. Pet.15-16,36-37; EX1003.¶¶64,111-13. Moreover, as explained in the Petition and Metzker declaration, a POSA would have recognized that the *McCloskey* approach—both the index and identifier on one molecule—is advantageous because “append[ing] a barcode to the target sequences earlier in the process” “reduce[s] the chance of errors that may affect the analysis, such as pooling different samples together prior to labeling.” Pet.36, EX1003.¶110. These are arguments that rely exclusively on the teachings of the prior art, not the challenged claims, and are only reinforced by *Schmitt*’s citation to *McCloskey 2007*

as disclosing “techniques whereby DNA fragments to be sequenced are each uniquely tagged.” EX1007.¶6.

Rather than substantively engage with these arguments, Tecan (at 33) points to the topic sentence on page 35 of the Petition, and nothing more. That sentence states “[a] POSA would have been motivated to include the claimed indexing site in *Schmitt*’s adaptor, which is described above in Limitation 1.a.” According to Tecan, this demonstrates the use of improper hindsight. But this myopic focus on one sentence ignores Petitioner’s actual arguments. The cited sentence simply uses the shorthand “claimed indexing site” to avoid reproducing the entirety of the text of the claim limitation. It does not demonstrate that any hindsight analysis occurred. As set forth above, the remainder of this section focuses exclusively on the teachings of the prior art, not the ’357 patent or the challenged claims, to explain why a POSA would have been “motivated to combine *Schmitt* with *McCloskey*’s batch-stamp.” Pet.37.

Tecan’s reliance (at 33) on *InTouch Techs., Inc. v. VGO Commc’ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014), is also inapposite. There, the court determined that the expert “did not articulate reasons” why a POSA would have combined the references and criticized the testimony as “hindsight bias.” *Id.* at 1351-52. Unlike that case, Dr. Metzker’s motivation to combine opinions span several paragraphs and include detailed reasons why a POSA would have been motivated to include the

claimed indexing site in *Schmitt*’s adaptor, how *McCloskey* discloses such an adaptor, and why a POSA would have looked specifically to *McCloskey* to make the combination. EX1003.¶¶109-115; *see also* Pet.35-38. Dr. Metzker’s reasoned and substantive opinions stand in stark contrast to those in *InTouch*. *See, e.g., InTouch* at 1351 (“Roach discloses ‘doing things over the Internet,’ and that since ‘robots are going over the Internet too; so that applies to them as well’...She then stated that she would combine Roach with the other references to let someone who cannot get access to a robot know that it became available”). Tecan also cites (at 33) to *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991), but that case supports QIAGEN’s position. Like claim 1 of the ’357 patent, the claim elements in *Gorman* “appear in the prior art in the same configurations, serving the same functions, to achieve the results suggested in prior art.” *Id.* The court “discern[ed] all of the elements of claim 16, used in substantially the same manner, in devices in the same field of endeavor” and held the claim obvious. *Id.*

Tecan also is wrong (at 33-34) that QIAGEN “ignores” the alleged differences between the *Schmitt* and *McCloskey* adaptors. Rather, the Petition as well as Dr. Metzker’s declaration discuss both adaptors, Pet.35-37, EX1003.¶¶109-13, explain that the combination would work, and that a POSA would have known how to implement it. Pet.37-39; EX1003.¶¶114-16. Specifically, the Petition notes that *Schmitt* discloses that various sequences can be included in its adaptor, including a

“multiplexing barcode sequence.” Pet.38. And because *McCloskey* also discloses a similar sequence, a POSA would have known how to make the combination. Pet.38-39; EX1003.¶116. Notably, Tecan never argues that the combination would not work, or offer any expert testimony to that effect.

Finally, Tecan’s citation (at 34) to *Infobionic, Inc. v. Braemer Mfg., LLC*, No. IPR2015-01704, 2016 WL 1081571 (P.T.A.B. Feb. 16, 2016), is inapposite, as the quoted sentence regarding “little or no elaboration” refers to an expert’s interpretation of a claim term, and not to an expert’s testimony regarding motivation to combine. In any event, contrary to the expert testimony in *Infobionic*, Dr. Metzker provided plenty of elaboration to support his opinion. He relied on *Schmitt*’s disclosure that the *Schmitt* adaptor can include a “multiplexing barcode sequence” (the indexing site), EX1003.¶116, as well as on *McCloskey*’s disclosure of a batch-stamp (also an indexing site), EX1003.¶111-13, and elaborates across several detailed paragraphs why a POSA would have combined the two structures and would have reasonably expected success in doing so. EX1003.¶¶109-116.

* * *

The Board should reject Tecan’s arguments and hold that claim 1 would have been obvious over *Schmitt* and *McCloskey*.

B. Claims 2-3, 5-10 would have been obvious over *Schmitt* and *McCloskey*

Tecan offers arguments only with respect to claim 1 and offers no separate rebuttal regarding the dependent claims included in Ground II. As such, claims 2-3 and 5-10 would have been obvious over the combination of *Schmitt* and *McCloskey*. Pet.45-52.

V. GROUNDS III-VI

Tecan offers no arguments regarding Grounds III through VI, which address claims 4 and 7. Because Tecan has failed to show that Grounds I and II do not anticipate or render obvious claim 1, claims 4 and 7 are also invalid.

VI. TECAN DISCLAIMED CLAIMS RECITING THE SAME LIMITATIONS AS THOSE DISPUTED HERE

On September 16, 2025, then-Acting Director Stewart issued a Memorandum titled “PTAB consideration of prior findings of fact and conclusions of law,” which states that “the Board shall consider relevant materials” from other proceedings involving the same or substantially similar claims. Pursuant to the Memorandum, QIAGEN refers the Board to materials from IPR2025-00027, a proceeding involving Tecan’s related U.S. Patent No. 11,725,241. *See* IPR2025-00027, Paper 2 (“’241.Petition”). There, the Board instituted IPR on claims substantially similar to those at issue here and on grounds involving the same *Porreca* and *Schmitt* references. IPR2025-00027, Paper 7. Following institution, Tecan disclaimed all claims of the ’241 patent and jointly moved with QIAGEN for an order of adverse

judgment and termination of proceedings. IPR2025-00027, Paper 17. The Board granted the motion and entered Adverse Judgment on August 12, 2025. IPR2025-00027, Paper 19.

The Adverse Judgment is relevant here. In the ’241 patent IPR, QIAGEN asserted that *Porreca* and *Schmitt* (the same references asserted here) disclosed limitation 1.d of the ’241 patent. ’241.Petition.34-36,50-52. That limitation is identical to limitation 1.g of the ’357 patent:

’241 patent limitation 1.d	’357 patent limitation 1.g
“identifying sequence reads with identical identifier and target sequences as duplicates.”	“identifying sequence reads with identical identifier and target sequences as duplicates.”

For the ’241 patent, QIAGEN asserted that *Porreca* and *Schmitt* each disclosed “identifying sequence reads with identical identifier and target sequences as duplicates”—exactly as QIAGEN does here. ’241.Petition.34-36,50-52. The arguments and evidence asserted in both petitions are also substantially the same. *Compare* ’241.Petition.34-36 with Pet.25-27; *compare* ’241.Petition.50-52 with Pet.44-45. In other words, Tecan disclaimed claims in light of a petition that challenged the exact same limitation as the one at issue here using the same art and the same arguments. While the adverse judgment is not fully dispositive of these issues here, *see SoftView LLC v. Apple Inc.*, 108 F.4th 1366, 1372 (Fed. Cir. 2024), the Board should take the above into consideration when issuing its final written

decision, particularly given that Tecan has not provided any basis to distinguish the ’357 patent from the now-disclaimed ’241 patent.

VII. CONCLUSION

The Board should determine that all challenged claims are unpatentable.

Date: November 12, 2025

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(c) and (d), the undersigned hereby certifies that the foregoing Petitioner’s Reply to Patent Owner’s Response complies with the type-volume limitation of 37 C.F.R. § 42.24(c)(1) permitting a reply of up to 5,600 words because, exclusive of the exempted portions, it contains 5,580 words as counted by the word processing program used to prepare the paper.

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CERTIFICATE OF SERVICE

I certify that on November 12, 2025, true and correct copies of the foregoing Petitioner’s Reply to Patent Owner’s Response were served via electronic mail on the following counsel of record for the Patent Owner:

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