

Case IPR2024-00965
U.S. Patent No. 11,768,200

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA INC.,
Petitioner

v.

MOLECULAR LOOP BIOSCIENCES, INC.,
Patent Owner

Case IPR2024-00965

U.S. Patent No. 11,768,200

PATENT OWNER'S RESPONSE

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<i>Samsung Elecs. Col., Ltd. v. Infobridge Pte. Ltd.</i> , 929 F.3d 1363 (Fed. Cir. 2019)	19, 20
<i>Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.</i> , 97 F.4th 882 (Fed. Cir. 2024)	43, 44

All citations to 35 U.S.C. §§102 and 103 in this paper refer to the pre-AIA statute.

All emphases are added unless otherwise noted.

PATENT OWNER'S EXHIBIT LIST

Ex. #	DESCRIPTION
2001	Declaration of Viktor Adalsteinsson, Ph.D.
2002	Deposition Transcript of Paul T. Spellman, Ph.D., April 9, 2025
2003	Illumina White Paper – Effects of Index Misassignment on Multiplexing and Downstream Analysis, Illumina (2018), available at https://www.illumina.com/content/dam/illumina-marketing/documents/products/whitepapers/index-hopping-white-paper-770-2017-004.pdf
2004	Kircher et al., <i>Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform</i> , Nucleic Acids Research 40(1):e3 (2011).
2005	Lefrancois et al., <i>Efficient yeast ChIP-Seq using multiplex short-read DNA sequencing</i> , BMC Genomics 10:37 (2009).
2006	Illumina Application Note – High-Speed Multiplexed 16S Microbial Sequencing on the MiSeq® System, Illumina (2011), available at https://www.illumina.com/documents/products/appnotes/appnote_miseq_16S.pdf
2007	Illumina Sequencing - Multiplexed Sequencing with the Illumina Genome Analyzer System (2008), available at https://www.illumina.com/documents/products/datasheets/datasheet_sequencing_multiplex.pdf
2008	<i>Microbiome profiling by Illumina sequencing of combinatorial sequence-tagged PCR products</i> , arxiv.org/abs/1007.5075 (as archived December 12, 2020, at https://web.archive.org/web/20201212073547/https://arxiv.org/abs/1007.5075)
2009	Maughan et al., <i>SNP Discovery vis Genomic Reduction, Barcoding, and 454-Pyrosequencing in Amaranth</i> , The Plant Genome 2:260-270 (2009).
2010	Meyer et al., <i>Targeted high-throughput sequencing of tagged nucleic acid samples</i> , Nucleic Acids Research 35(15): e97 (2007).
2011	Wang et al., <i>A Low-Cost Library Construction Protocol and Data Analysis Pipeline for Illumina-Based Strand-Specific Multiplex RNA-Seq</i> , PLoS One 6(1): e26426 (2011)
2012	Kenny et al., <i>Multiplex Target Enrichment Using DNA Indexing for Ultra-High Throughput SNP Detection</i> , DNA Research 18:31-38 (2010).

All citations to Exhibits refer to stamped exhibit page numbers.

I. Introduction

U.S. Patent No. 11,768,200 (the “’200 Patent”) covers significant advances in next-generation sequencing (“NGS”) and multiplexing technologies. Multiplexing involves pooling nucleic acid templates from many different samples and amplifying the pooled nucleic acid templates, improving efficiency by allowing simultaneous sequencing of amplicons from multiple samples and eliminating the need for individual sequencing reactions for each sample. Prior to the ’200 Patent, errors were often introduced during multiplexing after the samples were pooled together due to amplification mechanisms that formed chimeric molecules. However, the errors from these chimeric molecules were not recognized at the time of the ’200 Patent invention, leading to incorrect sample assignment and causing flawed analysis of some sequences in multiplexing reactions.

The ’200 Patent inventors discovered this issue and worked against conventional wisdom to develop a novel sequencing approach that would reduce these errors and ensure accurate sample assignment while still being scalable and cost-effective, contributing to the commercial appeal of NGS and its later widespread adoption in the industry. Specifically, the inventors found that adding identifier sequences unique to each sample prior to pooling and amplification allowed downstream errors to be more easily recognized and corrected during data analysis, increasing sample assignment accuracy. *See, e.g.*, EX1001, 2:12-29. For

example, with their method the inventors were able to detect and discard chimeric molecules formed during cluster amplification before performing subsequent analyses. In the years following the advancement of the '200 Patent, its methods have proven to be an efficient solution to a problem that was unrecognized throughout the industry at the time of the invention.

Petitioner cannot prevail on any of its grounds. For Ground 1 that relies on anticipation by Gloor and Ground 2 that relies on anticipation by Parameswaran, Petitioner fails to show that either Parameswaran or Gloor discloses all limitations of the claims. And for Ground 3 that relies on the combination of Parameswaran and Gloor, Petitioner fails to show that a POSA would have been motivated to combine Parameswaran's pyrosequencing method with Gloor's flow-cell sequencing method, or that a POSA would have had a reasonable expectation of success of achieving the claimed invention. Furthermore, Petitioner fails to show that Gloor was prior art as of the priority date used in the Petition (Paper 1, "Pet.") for the '200 Patent.

For Ground 4 that relies on the combination of Parameswaran and Binladen, Petitioner again fails to show that a POSA would have been motivated to combine the references, and additionally fails to show that the combination discloses or renders obvious all limitations of the claims. And for Ground 5 that adds Bentley to the combination, Petitioner similarly fails to show that a POSA would have been motivated to make the combination.

Accordingly, Petitioner cannot prevail on any of Grounds 1-5, and claims 1-6 (“Challenged Claims”) are patentable.

II. Background

A. Overview Of The '200 Patent Technology

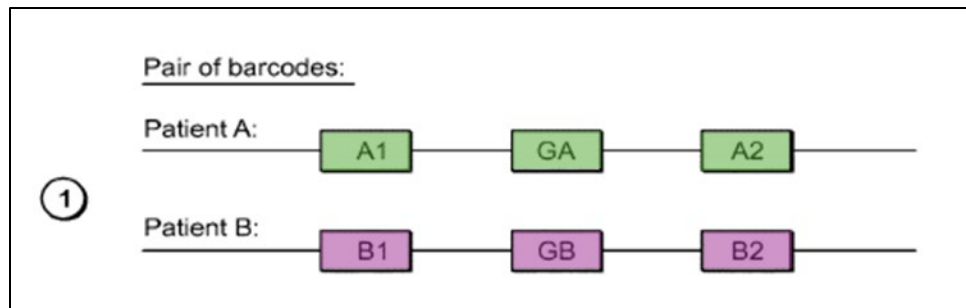
The '200 Patent describes “maintaining the integrity and identification of a nucleic acid template in a multiplex sequencing reaction.” EX1001, 1:19-21; EX2001, ¶¶25-26. As the '200 Patent recognizes, “molecular overlap can lead to apparent high quality, but incorrect sequence data” during amplification after the samples have been pooled together in multiplex sequencing, leading to error. EX1001, 4:17-20, 4:46-52; EX2001, ¶33. For example, the overlap and resulting high-quality signal can cause data to “be assigned to the wrong sample,” an issue that was not remedied by earlier approaches. EX1001, 4:60-63; EX2001, ¶¶34-35. At the time, others did not fully appreciate these problems, including the prevalence of sequence misassignment caused by chimeric molecules created during cluster amplification, nor were existing methods sufficient for accurate data analysis. EX1001, 4:53-63, 6:17-20, 7:20-23, Figure 3; EX2001, ¶34.

However, as others eventually came to recognize after the '200 Patent, chimeric molecules formed after sample pooling during amplification in NGS workflows can have a significant impact on accurately tracing sequences back to the correct sample. EX2004; EX2003; EX2001, ¶¶33-37. Thus, finding a solution was

crucial to improving multiplexing, and the '200 Patent provided that solution by recognizing that downstream sample identification would be more accurate if sequences were identified with multiple identifier sequences that were unique to each starting template. EX1001, 7:24-38; EX2001, ¶37.

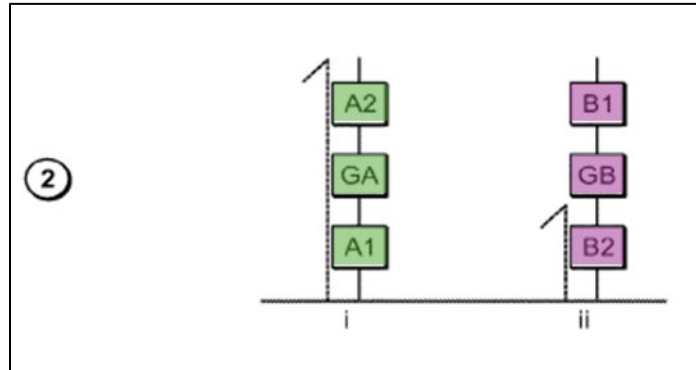
The '200 Patent provided its novel solution for addressing this issue with a method to identify and discard invalid sequence reads attributable to the chimeric molecules that arise during amplification. *See* EX1001, 5:55-58, 6:53-55; EX2001, ¶¶31, 37-41. As the '200 Patent explains, although previous barcode identifiers were used in an attempt to assign sequencing data to samples, they still could not accurately detect the cross-over errors from chimeric sequences between different templates that formed during amplification, especially when formed during an early amplification cycle. EX1001, 4:53-63; EX2001, ¶¶31, 36-37. By requiring detection of the multiple identifier sequences, the solution reduced “false positive and/or false negative results.” EX1001, 2:4-11, 2:16-18 (“The invention is based upon using ***two or more identifiers***, such as nucleic acid barcodes that are uniquely associated with an analyte to be detected.”), 7:37-38. And by using at least two identifiers for each template (e.g., for each sample), the '200 Patent increased the ability to detect and eliminate error because a “template containing only one identifier or an incorrect pair (i.e., a pair or more of identifiers not associated with the same template) will be excluded from analysis.” *Id.*, 2:23-25; EX2001, ¶37.

The ability to detect cross-over error by using multiple identifiers is shown in Figure 2 of the '200 Patent. As illustrated, when samples have been collected from a patient A and a patient B, each template from each patient will have a pair of sequence identifiers specific to that patient (e.g., A1 and A2 for patient A; B1 and B2 for patient B) that flank a gene fragment (e.g., GA for patient A; GB for patient B). EX1001, 5:22-27; EX2001, ¶¶27, 38.



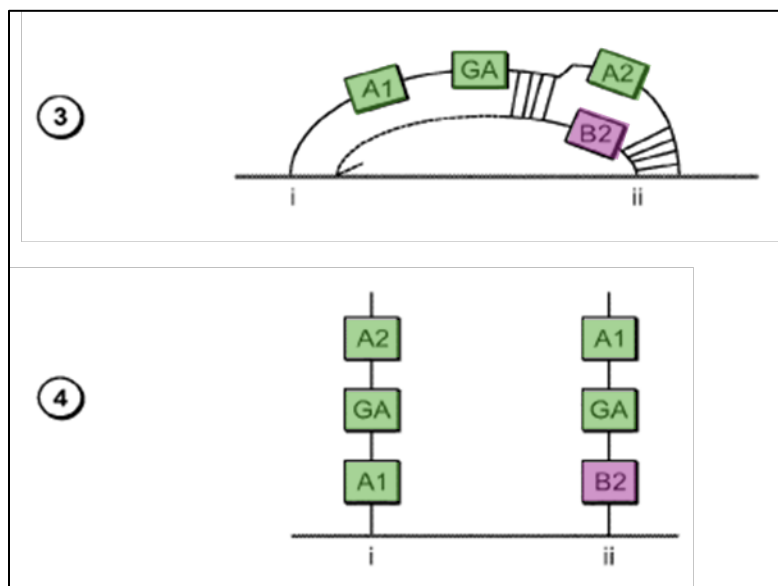
EX1001, FIG. 2(1) (annotated).

After various tagged nucleic acid samples are pooled together, “the samples are then hybridized to primers at discrete locations on a flow cell” for subsequent amplification and sequencing. *Id.* at 5:28-29; EX2001, ¶¶28-30, 39. In some instances, “the nucleic acid from patient A and the nucleic acid from patient B land within a cluster radius” on the surface of the flow cell, and the proximity permits improper overlap between them when the primer of one template (e.g., from patient B) is only partially extended and thus incorporates one identifier sequence but not the other. EX1001, 5:28-40; EX2001, ¶39.



EX1001, FIG. 2(2) (annotated).

After extension, the template-primer duplex will be denatured and re-annealed for another amplification cycle on the surface of the flow cell. Subsequent polymerase extension of the template amplicons will result in a chimeric molecule containing one of patient B's barcodes (e.g., B2 in Fig. 2(3)-(4) below), one of patient A's barcodes (e.g., A1 in Fig. 2(3)-(4) below), and the gene fragment from patient A. *Id.*, 5:41-55; EX2001, ¶¶30, 40-41.



EX1001, FIG. 2(3)-(4) (annotated).

The chimeric molecule that forms on the surface of the flow cell includes an incorrect pair of barcodes (i.e., one from patient A and one from patient B), allowing the chimeric molecule to be identified as error and discarded instead of being incorrectly attributed to patient B in the analysis. *Id.*, 5:55-58; EX2001, ¶¶32, 40-41. “While each barcode sequence [A1 and B2] on its own is a valid barcode sequence, taken together, the two barcode sequences do not form a valid barcode sequence pair.” EX1001, 5:62-65; EX2001, ¶41. Even though “[d]uring the sequencing process, this would yield a high-quality signal,” sequencing data resulting from the improper molecule that was formed during amplification can still be detected and excluded because “during data analysis the molecules would be recognized as invalid” due to their invalid barcode pair. EX1001, 5:65-6:6; EX2001, ¶41.

By increasing the ability to detect and exclude errors, the inventive methods of the '200 Patent “dramatically reduce false positives in a multiplex sequencing reaction” and provide a solution to problems that previously hampered next-generation multiplex sequencing reactions and were not recognized by others until several years later. EX1001, 6:53-57, 7:24-38, Figure 3; *see also* EX2004; EX2003; EX2001, ¶¶ 33-42.¹

¹ Petitioner’s assertions that the inventions in the '200 Patent were copied from others are not well taken. *See* Pet., 20. Petitioner does not contend that the detailed

B. Overview Of The '200 File History

The '200 Patent's application was filed on June 4, 2021 as Application No. 17/339,527, claiming priority to December 23, 2010. EX1001, Cover. Petitioner applies December 23, 2010, as the effective priority date of the '200 Patent for purposes of the Petition. Pet., 17; EX2001, ¶43.

In an Office Action dated June 1, 2023, the Examiner rejected the pending claims on the ground of nonstatutory double patenting. EX1007, 272-276. In response, Applicant filed a terminal disclaimer. EX1007, 371-382. The Examiner then deemed the claims to be allowable. A Notice of Allowance was issued on July 27, 2023, stating that “no references were found teaching or suggesting claims 66-71 [issued claims 1-6].” EX1007, 395, 399-401; EX2001, ¶¶44-45.

description and figures showing the invention are copied from any other publications. *Id.* (citing EX1001, 1:25-31; 3:37-43; 7:45-20:62), *id.*, 42-43. And Petitioner's overstated accusations of “copying” refer only to text discussing general considerations relevant to the invention that are incorporated into the '200 Patent from prior publications that were cited to the Patent Office, including some that are incorporated by reference in their entirety into the patent's specification.

III. Overview Of The References

A. Gloor (EX1005)

Gloor discusses a “low-cost, high-throughput microbiome profiling method that uses combinatorial sequence tags.” EX1005, 1; EX2001, ¶61. Gloor developed a “low-cost high throughput” method that allowed it to sequence “272 clinical samples by a single Illumina paired-end sequencing run.” EX1005, 1, 3; EX2001, ¶67. Gloor explained a recent study had reported that sequences reported as “rare microbiota” were actually caused by pyrosequencing errors. EX1005, 12; EX2001, ¶62. Gloor found that with Illumina sequencing and combinatorial dual indexes (“CDIs”), it could sequence “much greater depth at a much lower cost than is possible with current pyrosequencing technology.” EX1005, 23; EX2001, ¶65. Because Gloor averaged “20-fold greater sequence coverage” using Illumina sequencing platforms, Gloor concluded that the “higher fidelity Illumina sequencing may have resulted in fewer [species] because of a lower error rate contributing to fewer ‘rare microbiome’ [species].” EX1005, 23.

Gloor explained that “[c]ombinatorial sequence tagging can be used to examine hundreds of samples with far fewer primers than is required when sequence tags are incorporated at only a single end.” *Id.*, 1. Such combinatorial sequence tagging uses fewer primers to tag a greater number of samples than single indexes or unique dual indexes (“UDIs”) because each unique tag requires its own primer.

EX2001, ¶¶61-67. Gloor reported that only 34 unique barcodes (and thus 34 primers) were needed to sequence 272 samples when using combinatorial sequence tagging. EX1005, 6 (Table 2); EX2001, ¶65.

B. Parameswaran (EX1004)

Parameswaran presented pyrosequencing-based methods for multiplex sequencing. EX1004, 1 (“A *pyrosequencing-tailored nucleotide barcode design* unveils opportunities for large-scale sample multiplexing.”). Parameswaran explained that constraints in its sequencing, such as physical space segregation, previously limited the maximum number of samples that could be multiplexed to 16 independent samples. *Id.*, 1-2. Parameswaran introduced a method that pooled samples together for sequencing instead of “relying on physical separators,” therefore “maximiz[ing] sequence space and multiplex capabilities.” *Id.*, 2. Parameswaran provided a method that allowed “up to 48 different samples” to be unambiguously assigned and highlighted the viability of sequencing even more samples with combinatorial tagging. *Id.*, 1, 8 (“The low misassignment rate also indicates the potential utility of combinations of forward and reverse barcodes to generate up to 48^2 (= 2304) combination barcodes for this set of sequences.”); EX2001, ¶¶57, 60.

Parameswaran designed its “barcoding approach to substantially enhance the scope and capacity of multiplexed high-throughput pyrosequencing.” EX1004, 4.

Because Parameswaran identified known errors in pyrosequencing technologies, it designed its barcodes to minimize those pyrosequencing-specific errors. *Id.*; EX2001, ¶¶46-53. For example, Parameswaran “expected to minimize errors related to pyrosequencing” with its barcoding method and claimed to minimize the “errors most frequently observed for pyrosequencing.” EX1004, 7; EX2001, ¶¶49-50.

Parameswaran’s methods isolated RNA from individual samples and converted it to cDNA for sequencing. EX1004, 2. Parameswaran then amplified the DNA with two rounds of PCR with barcoded primers creating a library of barcoded PCR products. *Id.*, 3-4; EX2001, ¶54. Parameswaran pooled barcoded libraries from 25 samples and ran the pooled samples through pyrosequencing. EX1004, 4. Parameswaran analyzed “all sequences with a match to *one of the two expected*” barcodes, which it considered as “true members of the corresponding dataset.” *Id.*, 8. Parameswaran found it could “unambiguously assign 99.8% of obtained barcoded sequences by bioinformatically probing for an error-free barcode *at either end of the sequence of interest.*” *Id.*, 2; EX2001, ¶¶54-57.

C. Binladen (EX1029)

Binladen describes the use of “tagged primers to generate homologous DNA amplification products from multiple specimens” that are sequenced by pyrosequencing. EX1029, 1. Binladen describes multiplex sequencing reactions using DNA from thirteen species and attributes observed errors to “artefacts of the

current GS20 pyrosequencing chemistry,” “errors in the original primer synthesis process,” “contamination arising during the extraction or PCR setup,” and “the fact that many species are closely related in the targeted 16S mtDNA region.” *Id.*, 6, 8; EX2001, ¶¶76-77.

D. Bentley (EX1006)

Bentley sought to develop an approach “for accurate, rapid and economical whole-genome” sequencing. EX1006, 1. Bentley explains that previous methods, such as capillary sequencing, took multiple years and millions of dollars to sequence one individual human genome. *Id.* However, Bentley used massively parallel sequencing on Illumina Genome Analyzers to sequence one human genome and “determined an accurate whole human genome sequence in 8 weeks” with an approximate cost of \$250,000. *Id.*, 3, 5.

Bentley sequences a single sample and therefore does not sequence, or suggest sequencing, more than one sample at once in a multiplex reaction, or using any sample indexes to do so. EX2001, ¶¶78-82.

IV. The Level Of Ordinary Skill In The Art

Petitioner proposes a level of ordinary skill in the art as a person having either “(i) a Ph.D. in molecular biology, genetics, bioinformatics, or a related field and at least two years of experience in high-throughput sequencing technologies or (ii) a Master’s degree in one of the same fields with at least four years of experience in

high-throughput sequencing technologies.” Pet., 18. Patent Owner² adopts Petitioner’s proposal for a POSA for purposes of this proceeding. EX2001, ¶¶20-23.

V. Claim Construction

A. “Homopolymer Region” (Claim 5)

Petitioner and Dr. Spellman claim to apply the plain and ordinary meaning of each claim term in the Petition. Pet., 24; EX1003, ¶133. But Dr. Spellman admitted that the term “homopolymer region” in Claim 5 is given a “controlling definition” in the specification and changed his opinion regarding that claim term. EX2002, 64:17-65:8, 67:3-18, 95:23-97:15. Specifically, the ’200 Patent states “the barcode sequences can be designed to have minimal or no homopolymer regions, i.e., *2 or more of the same base in a row such as AA or CCC*, within the barcode sequence.” EX1001, 9:6-10. The term “homopolymer region” in Claim 5 should thus be construed as “two or more of the same base in a row.” EX2001, ¶24.

VI. Ground 1: The Challenged Claims Are Patentable Over Gloor.

A. Gloor Does Not Disclose All Limitations Of Claim 1.

Claim 1 recites “detecting the presence of *two or more identifier sequences that are uniquely associated with the nucleic acid analyte of interest*.” EX1001,

² As indicated in the Updated Mandatory Notices filed February 27, 2025 (Paper 11), the Patent Owner in this proceeding is Molecular Loop Innovations LLC.

21:5-7. That element is missing in Gloor. EX2001, ¶¶83-85. As Petitioner recognizes (Pet., 7), Gloor uses a ***combinatorial*** sequence tagging method, ***not*** a method where identifier sequences are uniquely associated with a nucleic acid template. Gloor’s method instead allows identifier sequences to be used across multiple different samples and thus cannot meet this claim limitation. EX2001, ¶¶84-85.

The plain language of Claim 1 requires “identifier sequences ***that are uniquely associated*** with the nucleic acid of interest.” That requirement means that any identifier sequence can be used with only one template nucleic acid of interest. EX2001, ¶83-85. Once an identifier sequence has been used with one nucleic acid analyte of interest, it cannot be used with another—otherwise it would no longer be “uniquely” associated with the nucleic acid of interest. EX2001, ¶¶83-85. Claim 1 does ***not*** say that it is a “pair” or “distinct pair” of sequences that is uniquely associated with the nucleic acid of interest, instead it requires that the ***identifier sequences*** themselves are “uniquely associated.”

The additional limitations of Claim 1 are consistent with that interpretation, because it allows validating the sequence of a nucleic acid analyte of interest by “excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect pair of identifiers” as claimed. EX1001, 22:2-6. One would not be able to discern whether pairs of identifiers were “incorrect” if identifier sequences were used across different nucleic acids of interest. EX2001, ¶85. That

understanding is also consistent with the specification, which explains that identifiers are “uniquely associated with an analyte of interest, such that the identifiers will only be present when the analyte of interest is detected.” EX1001, 2:5-8.

Petitioner cannot dispute that Gloor’s CDI method re-used identifiers across samples. Dr. Spellman admits that “*Gloor repeated individual identifier sequences across multiple samples,*” such that “each *pair* of identifiers”—*not* each identifier sequence itself—“was uniquely associated with nucleic analytes of interest from a single sample.” EX1003, ¶26. Thus, Gloor does not disclose the claimed step of “detecting the presence of two or more identifier sequences that are uniquely associated with the nucleic acid of interest.” EX2001, ¶85.

B. Gloor Does Not Disclose The Additional Limitations Of Claim 5.

Claim 5 recites “t[he] barcode sequences are designed to have no homopolymer regions.” EX1001, 22:13-14. Contrary to Petitioner’s assertion (Pet., 33), Gloor does not anticipate Claim 5 because Gloor does not disclose barcode sequences designed to have no homopolymer regions. EX2001, ¶¶86-88.

Gloor’s discussion of its sequence tag design contains *no discussion* of homopolymer regions. EX2001, ¶87. Gloor explains that it chose the sequence tags “to ensure all 4 nucleotides were represented in each of the first four positions of the primers using parameters similar to those in the barcrawl program.” EX1005, 5.

Gloor additionally explains that the sequence tags were chosen “to ensure that they would not induce primer-dimer formation.” *Id.*, 6. Primer-dimer formation is unrelated to homopolymer regions. EX2001, ¶¶87. Gloor neither discloses nor suggests limitations for the remaining nucleotides that could instruct a POSA to exclude homopolymer regions. EX2001, ¶¶86-87.

Petitioner relies on Table 2 of Gloor, arguing that “Gloor anticipates claim 5 because its barcode sequences lack homopolymer regions.” However, Gloor’s incidental lack of homopolymer regions in its chosen sequence tags does not show any teaching that “[he] barcode sequences are *designed* to have no homopolymer regions.” EX2001, ¶88.

Accordingly, Gloor does not disclose “[he] barcode sequences are designed to have no homopolymer regions.”

C. Petitioner Did Not Prove That Gloor Is Prior Art. (All Claims)

Petitioner fails to carry its burden to prove by a preponderance of the evidence that Gloor qualifies as a prior art printed publication. *See Hulu, LLC, v. Sound View Innovations, LLC*, IPR2018-01039, Paper 66, 22 (PTAB Oct. 5, 2021). To demonstrate that Gloor is a printed publication, Petitioner must show that Gloor was “‘sufficiently accessible to the public interested in the art’ before the critical date.” *Align Tech., Inc. v. Dental Monitoring SAS*, IPR2023-01369, Paper 42, 25 (PTAB Mar. 3, 2025) (quoting *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989)).

Petitioner fails to show that Gloor was publicly accessible before December 23, 2010 for three reasons. **First**, the scant evidence Petitioner relies upon to show public accessibility—a declaration and exhibits submitted by Dr. Gloor (EX1002), one of the authors of the Gloor reference—shows at best that Gloor may have been **submitted** to arXiv.org by July 28, 2010, but does not show that Gloor was actually disseminated or accessible to the public on July 29, 2010. **Second**, Petitioner does not point to any evidence to support Dr. Gloor’s proclaimed speculative belief that Gloor was accessible on arXiv.org or by any other means at any point in 2010. **Third**, there is no reliable evidence regarding arXiv.org’s policies or business practices at the time Gloor was allegedly submitted that could make up for the deficient direct evidence regarding Gloor’s alleged accessibility on arXiv.org. Because Petitioner’s evidence fails to show that Gloor was publicly accessible, Petitioner fails to show that Gloor qualifies as a prior art printed publication.

First, Petitioner’s evidence shows, at best, that Gloor was **submitted** on July 28, 2010, but does not show that Gloor was disseminated or otherwise made available at that time. *Jazz Pharm., Inc. v. Amneal Pharms., LLC*, 895 F.3d 1347, 1355-56 (Fed. Cir. 2018) (“A reference is considered publicly accessible upon a satisfactory showing that such document **has been disseminated or otherwise made available** to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.”). For example, Dr.

Gloor states that he **submitted** his paper on July 28, 2010 (EX1002, ¶16), with “the **intention** of making its findings accessible to the public” (*id.*, ¶18), but does not show that he or anyone else could confirm that arXiv.org actually published it on July 29, 2010.

The exhibits to the Gloor declaration similarly show that Dr. Gloor might have submitted the article on July 28, 2010, but they do not show that it was ever actually disseminated or otherwise made available to the public. Exhibit A is a copy of the Gloor paper itself—it lacks any disclosure or date showing when it was **published**. Exhibits B and C show the “**Submission** History” of Gloor showing it was submitted on July 28, 2010, but do not provide any disclosure or date when it was **published**. Exhibit E is an email Dr. Gloor received that states his paper was submitted and provides a link to Dr. Gloor himself where the article might be available, but neither Exhibit E nor Dr. Gloor says that the link was actually disseminated or accessible to the public on July 29, 2010. And Exhibit E is insufficient in any event because it shows only that Dr. Gloor might have been able to access the paper. A reference is “**not** publicly accessible if the only people who know how to find it are the ones who created it.” *Samsung Elecs. Col., Ltd. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1372 (Fed. Cir. 2019).

Second, there is no evidence that Gloor actually was disseminated or made available in 2010. Both the Gloor declaration and the accompanying exhibits lack

any actual announcement, email, webpage capture, or any other evidence showing that the arXiv.org link was actually announced and made available to the public in 2010. For example, Exhibit E states that the Gloor **abstract**—not the full paper—“**will** appear in today’s mailing.” EX1002, Ex. E, 1. Petitioner does not provide that mailing. Similarly, Exhibit F, an email Dr. Gloor received on March 21, 2024, not in 2010, states that the Gloor paper was submitted on July 28, 2010, and states (with no supporting explanation) that “[i]t **would** have been announced on Thursday, July 29, 2010.” Petitioner does not provide that announcement. What is left is Dr. Gloor’s uncorroborated speculation that he “**believe[s]** arXiv.org sent email alerts to subscribers on July 29, 2010, announcing that *Gloor* was publicly accessible,” with no evidence supporting that speculative belief. That is insufficient; “the Board is not obligated to accept a witness’s speculation as true.” *See Samsung Elecs. Co., Ltd. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1372 n.3 (Fed. Cir. 2019) (affirming Board finding that a reference published on a website was not publicly accessible where the petitioner “did not offer evidence, apart from the **speculation** of [the author], that a person of ordinary skill, exercising reasonable diligence, would have located the [allegedly public website] or even known to look for it.”).

Further, Dr. Gloor’s alleged recollection that he presented **findings** from his paper to attendees of the Human Microbiome Research Conference in August and September 2010 does not demonstrate that the Gloor **reference** was publicly

accessible before December 23, 2010. Critically, Dr. Gloor does not even claim he presented all details (e.g., background, methods, results, discussion) of the Gloor reference itself. Instead, he merely claims to have given a poster presentation summarizing findings: “I presented a *poster describing the findings* reported in Gloor (Exhibit H) to attendees of the Human Microbiome Research Conference held between August 31 and September 2, 2010.” EX1002, ¶18. And that poster merely cited the Gloor reference and another paper. EX1002, Ex. H (excerpted below):

References

Hummelen, R., Fernandes, A.D., Macklaim, J.M., Dickson, R.J., Chantalucha, J., Gloor, G.B., and Reid, G. (2010). Deep sequencing of the vaginal microbiota of women with HIV. PLoS One 5, e12078.

Gloor, G.B., Hummelen, R., Macklaim, J.M., Dickson, R.J., Fernandes, A.D., MacPhee, R., and Reid, G. (2010). Microbiome profiling by Illumina sequencing of combinatorial sequence-tagged PCR products. ArXiv e-Prints. arXiv:1007.5075v1 [q-bio.GN]

But a presentation made *after* the alleged date of public accessibility that merely refers to Gloor does not show that Gloor itself was publicly accessible. *See In re Klopfenstein*, 380 F.3d 1345, 1349 (Fed. Cir. 2004) (“[T]he mere presentation of slides accompanying an oral presentation at a professional conference is not per se a ‘printed publication’ for the purposes of § 102(b).”).

Third, Petitioner fails to provide evidence of arXiv.org’s policies or business practices *in 2010* to support Dr. Gloor’s speculation that the Gloor reference was made available before December 23, 2010. For example, Exhibits C and D to the Gloor declaration detail arXiv.org’s submission policies *in 2024*—the date of their

capture—but there is no evidence tying those policies to the alleged publication *fourteen years earlier* in 2010. And Dr. Gloor cannot provide authoritative testimony regarding arXiv.org’s publication policies or practices in 2010. Though Dr. Gloor claims he is “familiar with arXiv.org as a user of the system and a registered author of seven articles available from the system” (EX1002, ¶12), he admits that he did not become a registered member of arXiv.org until July 28, 2010—the same day he allegedly submitted his paper. Dr. Gloor describes no personal experience or firsthand knowledge with arXiv.org, let alone its policies and practices, at the time he submitted his paper (as a brand new user) on July 28, 2010. Accordingly, Dr. Gloor cannot backfill the lack of evidence showing that the Gloor reference was actually announced, disseminated, or otherwise made available to the public in 2010.

Petitioner’s deficient evidentiary record here falls far short of the kind of evidence necessary to prove public accessibility. For example, in *Align Tech. Inc. v. Dental Monitoring SAS*, the petitioner similarly relied on a paper published via arXiv.org before a July 21, 2017 priority date. But there, unlike here, the petitioner provided corroborative evidence establishing public accessibility, including (a) a declaration providing “personal knowledge of arXiv.org’s *routine business practice in the 2017 timeframe*”; (b) WayBack Machine archived copies of arXiv.org *from 2016 and 2017* reflecting arXiv.org’s publication policies at that time; (c) a

declaration reviewing metadata of the reference in question showing it was created and last modified before the priority date; and (d) a declaration from the Records Request Processor at the Internet Archive explaining the functioning of the WayBack Machine. *Align Tech.*, IPR2023-01369, Paper 42, 29-32 (PTAB Mar. 3, 2025). Based on the entirety of the evidentiary record presented in *Align Tech.*, the Board found Petitioner had carried its burden to prove public accessibility. *Id.*, 33.

Petitioner provided none of that evidence here. Dr. Gloor did not have personal knowledge of arXiv.org's business practices and policies before July 29, 2010, because he admits that he only became a registered user the day before. EX1002, ¶12. Petitioner provided no archived copies of arXiv.org's policies in 2010—Petitioner relies on evidence from **2024**. EX1002, Exs. C, D, F. Petitioner fails to show that the arXiv.org link was created or last modified in July 2010—and in fact, the earliest WayBack Machine capture of that link dates only to 2020. EX2008. And Petitioner provides no declarations from any employee of arXiv.org or any other archival organization showing that the Gloor reference was actually published on arXiv.org in 2010.

Accordingly, Petitioner has failed to show that Gloor was publicly accessible before December 23, 2010 to qualify as a prior art printed publication.

VII. Ground 2: The Challenged Claims Are Patentable Over Parameswaran.

A. Parameswaran Does Not Disclose All Limitations Of Claim 1.

Claim 1 recites “excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect pair of identifiers from sequence analysis of the multiplex sequencing reaction.” EX1001, 22:2-6. Parameswaran does not disclose that claimed step. EX2001, ¶¶89-91. Petitioner appears to argue that because Parameswaran perceived sequences with mismatched barcode motifs or one perfect barcode motif and one imperfect barcode motif, it necessarily disclosed excluding those sequences to assign samples more accurately. Pet., 40-41. But Parameswaran disclosed no such discarding, nor would it be inherent in Parameswaran’s disclosure because Parameswaran did the opposite and *included* those sequences in its analysis. EX2001, ¶¶89-91.

Parameswaran includes the sequences in its dataset that Petitioner alleges Parameswaran somehow excluded. EX1004, 8 (“For our purposes, all sequences with a *match to one of the two expected sequence motifs* were considered as true members of the corresponding dataset.”); EX2001, ¶¶90-91. By doing so, Parameswaran states that it was able to “unambiguously assign 99.8% of obtained barcoded sequences by bioinformatically probing for *an error-free barcode* at *either end of the sequence of interest*.” EX1004, 2; *see also id.*, 1 (“[W]e found that over 99.8% of obtained sequences could be assigned to 25 independent, uniquely

barcoded libraries *based on the presence of either a perfect forward or a perfect reverse barcode.*”). EX2001, ¶¶90-91.

Parameswaran’s data emphasizes that it included both sequences with only one identifier and sequences with an incorrect pair of identifiers in its analysis. EX2001, ¶¶90-91. The only sequences that Parameswaran explains were actually excluded from its analysis were *sequences containing zero matches to any identifier*. EX2001, ¶¶90-91; EX1004, 8 (“*[A]ll sequences with a match to one of the two expected sequence motifs were considered as true members* of the corresponding dataset. Run I (0.13%) and run II (0.17%) of sequences had *no perfect matches to any of the sequence motifs (forward or reverse), and were discarded.*”). Parameswaran makes no such statement regarding exclusion for the “perfect, unexpected” barcode motifs it found in its data. And in its data summary (Table 3), Parameswaran shows that sequences were included as long as there was a match to at least one barcode motif, including sequences having incorrect pairings, such as duplicate motifs and pairs of one perfect motif and one imperfect motif. EX1004, 7 (Table 3); EX2001, ¶¶90-91. Parameswaran again included all of those sequence in its analysis, contrary to the claim, as *only sequences containing zero matches to any identifier* were discarded. EX2001, ¶¶90-91; EX1004, 8.

Accordingly, Parameswaran does not disclose “excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect

pair of identifiers from sequence analysis of the multiplex sequencing reaction” as claimed.

B. Parameswaran Does Not Disclose The Additional Limitations Of Claim 5.

Claim 5 recites “[he] barcode sequences are designed to have no homopolymer regions.” EX1001, 22:13-14. Contrary to Petitioner’s assertion (Pet., 42-43), and as Petitioner’s expert now admits, not only do Parameswaran’s barcodes include homopolymer regions, but *every* barcode in Parameswaran includes homopolymer regions. EX2002, 67:3-18 (“[Q.] So as it’s referred to in the Molecular Loop patents, for homopolymers, *there are two homopolymers in every bar code in Parameswaran, true? A. That is correct.*”), 96:6-10.

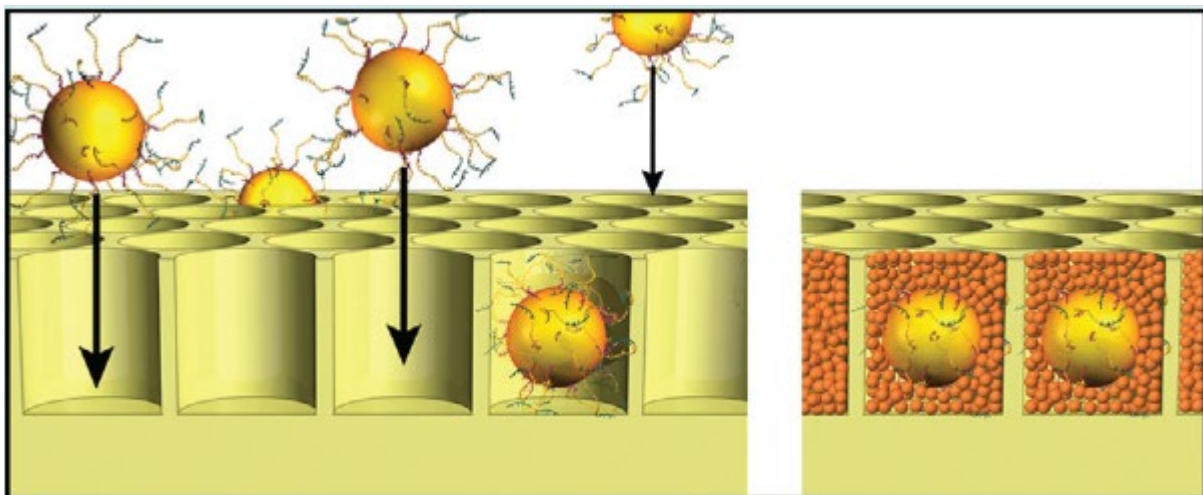
Parameswaran specifically designed *every one* of its barcodes to *include* two homopolymer regions. EX2001, ¶¶92-96. The ’200 Patent defines “homopolymer region” as “*2 or more of the same base in a row.*” EX1001, 9:6-10; EX2001, ¶93; EX2002, 67:3-13. Parameswaran designs its barcodes to do exactly that, purposefully including in its guidelines that “[e]ach barcode has two distinct dinucleotide pairs,” which Parameswaran describes as “*homopolymeric* dinucleotides.” EX1004, 4, Table 1, Table 2 (showing that every barcode contains at least one homopolymer region); EX2001, ¶¶93-95.

Therefore, Parameswaran does not disclose “t[he] barcode sequences are designed to have no homopolymer regions.”

C. Parameswaran Does Not Disclose The Additional Limitations Of Claim 6.

Claim 6 recites “the nucleic acid analyte of interest is on the surface of a flow cell.” EX1001, 22:15-16. Petitioner incorrectly asserts that Parameswaran teaches “the nucleic acid analyte of interest is on the surface of a flow cell.” Pet., 43 (*citing* EX1028, 6-8); EX2001, ¶¶97-100.

In Roche 454 pyrosequencing used in Parameswaran, the analyte of interest is not *on the surface* of the flow cell, but suspended above the flow cell. EX2001, ¶¶99-100. As shown below, the analyte of interest is bound to a bead and deposited into a flow cell.



EX1028, Fig. 5, Fig. 8; EX1003, ¶190.

Depositing analyte-bound beads into wells was used in Roche 454 sequencing because it permits the beads to be free floating and surrounded by reagents to provide light to read the analyte of interest. EX2001, ¶¶99-100; *see also* EX1011, Figure 3c; EX1010, 4 (“The beads are incubated with a polymerase and single-strand binding proteins and, together with smaller beads carrying the ATP sulfurylases and luciferases, gravitationally deposited in the wells.”). Therefore, a POSA would understand that the nucleic acid analytes bound to the beads are not “on the surface of a flow cell” as claimed because the nucleic acids are attached to beads that are free floating so that they can be surrounded with reagents and allow enough light to be produced. EX2001, ¶¶98-100.

Therefore, Parameswaran does not disclose “the nucleic acid analyte of interest is on the surface of a flow cell.”

VIII. Ground 3: The Challenged Claims Are Patentable Over Parameswaran And Gloor.

A. Petitioner Fails To Show A Motivation To Combine. (All Claims)

1. Petitioner Improperly Cherry-Picks Portions Of Parameswaran and Gloor Without Considering The Full Context Of The References And The State Of The Art.

Petitioner argues that a POSA would have been motivated to combine Parameswaran and Gloor. Pet., 48-51; EX2001, ¶101. Petitioner consistently ignores context, fails to consider the references together, and fails to consider significant reasons why a POSA would not make that combination. *Arctic Cat Inc. v.*

Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1363 (Fed. Cir. 2017) (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”). A POSA would not have been motivated to combine Parameswaran’s unique dual indexes (“UDIs”) and pyrosequencing with Gloor’s CDIs and Illumina sequencers because a POSA (1) would appreciate that the pyrosequencing-specific problems for which Parameswaran’s barcodes were tailored had not hampered Illumina sequencers as used in Gloor, (2) would heed Gloor’s warning that pyrosequencing methods were often unsuitable for Illumina sequencers, and (3) would not have any reason to use the UDIs from Parameswaran to replace Gloor’s disclosed CDI sequencing method.

First, a POSA in December 2010 would not have thought that Parameswaran’s barcoding methods would have utility in Gloor’s Illumina sequencers because Illumina sequencers did not have the same needs of pyrosequencing that guided the design of Parameswaran. EX2001, ¶¶102-105. Parameswaran in 2007 expressed the view that “multiplexed high-throughput pyrosequencing is currently limited in complexity (number of samples sequenced in parallel), and in capacity (number of sequences obtained per sample),” and sought to allow for “pooling and sequencing of DNA from independent samples, and to facilitate subsequent segregation of sequencing capacity.” EX1004, 1. Parameswaran explains that the utility of its barcoding approach was “to

substantially enhance the scope and capacity of multiplexed high-throughput pyrosequencing” because it “allows for the unambiguous assignment of nucleic acid sequences from a mixture of libraries from up to 48 different samples.” *Id.*, 4, 8.

But by the time of the invention in 2010, as Petitioner’s expert recognizes, it was already “standard to sequence many samples in parallel referred to as ‘multiplex’ sequencing.” EX1003, ¶67. Indeed, Gloor used Illumina sequencers for 272 clinical samples, over five times the sequencing capability taught in Parameswaran, and achieved about 12 million useable reads. EX1005, 2. Gloor also explains that it found “an exceedingly low error rate.” *Id.* Accordingly, a POSA in 2010 would not have seen utility in applying Parameswaran’s methods to Illumina sequencers at least because Gloor claimed to achieve the high complexity and capacity at a low error rate that previously escaped pyrosequencing, and for which Parameswaran’s barcoding method was tailored for pyrosequencing applications. EX2001, ¶¶102-108.

Second, a POSA would not have been motivated to use Parameswaran’s “***pyrosequencing-tailored*** nucleotide barcode design” (EX1004, 1 (Title)) with Gloor, because Gloor ***warns against*** applying pyrosequencing approaches to Illumina sequencers. Gloor stated “we found that methods used to analyze pyrosequencing microbiome data were ***often unsuitable for reads generated by Illumina sequencing***, and we present a workflow that can be used for rapid and

robust generation of the relative abundance of organisms in each sample.” EX1005, 2. And Parameswaran emphasizes that its methods were specifically designed for pyrosequencing. EX1004, 1 (“A *pyrosequencing-tailored nucleotide barcode design* unveils opportunities for large-scale sample multiplexing.”), 4 (“Specifications for the barcodes are *based on details of pyrosequencing error characteristics*.”). A POSA would not seek to introduce Parameswaran’s “often unsuitable” (in Gloor’s words) pyrosequencing methods into a workflow specifically designed for Illumina sequencers, which was already thought to be “rapid and robust.” EX2001, ¶¶104-105; *Arctic Cat*, 876 F.3d at 1363 (one must consider evidence that “suggests reasons that a skilled artisan would be discouraged from pursuing such a combination,” even when not rising to the level of teaching away).

Third, a POSA would not have had a reason to use the UDI methods disclosed in Parameswaran to replace Gloor’s CDI method. *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 69 F.4th 1341, 1351 (Fed. Cir. 2023) (requiring motivation to incorporate a specific feature of one art into another based on what a POSA would have understood were the benefits of that feature). Parameswaran concluded that near-perfect assignment was achieved “based on the presence of *either* a perfect forward *or* a perfect reverse barcode.” EX1004, 1. Based on that conclusion, as Dr. Spellman admits, Parameswaran actually espoused CDIs for increasing sample capacity, with “the potential utility of combinations of forward and reverse barcodes

to generate up to 48^2 (= 2304) combination barcodes for this set of sequences.” *Id.*, 8; EX2002, 147:9-148:3. And Gloor already used CDI methods, which Parameswaran encouraged, to sequence 272 samples and achieve an apparent “exceedingly low error rate.” EX1005, 2.

Neither Gloor nor Parameswaran provided any indication that UDIs would improve the sequencing using an Illumina sequencer over the CDI method disclosed in Gloor. EX2001, ¶¶58-60, 106-108. To the contrary, Parameswaran suggests the opposite (EX1004, 8), and Gloor touts that its use of “the *combination* of sequence tags at each end of the overlapped reads *allowed us to use a small number of primers to uniquely tag a large number of samples*” (EX1005, 2). A POSA would also recognize that using UDIs would require *more* primers and barcodes than CDIs. EX2001, ¶¶106-107. And Gloor taught that using combinatorial indexes on Illumina sequencers allowed “much greater depth at a much lower cost than is possible with current pyrosequencing technology.” EX1005, 23. Accordingly, a POSA viewing the references in full context would have no reason to use UDIs instead of Gloor’s CDIs in view of the increased complexity and cost required for essentially no reward. EX2001, ¶¶102-108; *see Arctic Cat*, 876 F.3d at 1363 (“evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine”).

2. Petitioner’s Proffered Reasons Fail To Show A Motivation To Combine Parameswaran’s Unique Dual Indexes With Gloor’s Illumina Sequencer.

i. Petitioner Does Not Show That A Desire To “Reduce Technical Error” Or Gain “Methodical Advantages,” Including Efficiency And Cost Considerations, Would Have Motivated The Proposed Combination.

Petitioner argues a desire to “reduce technical error” or achieve “methodological advantages,” along with efficiency and cost considerations, would have motivated a POSA combine Parameswaran and Gloor (Pet., 48-49, 50), but in doing so does not sufficiently explain why a POSA would implement Parameswaran’s UDIs in Gloor’s sequencing in view of those considerations or to achieve those alleged advantages. When evaluating efficiency and cost considerations, a POSA would have understood that Gloor’s CDIs—*not* Parameswaran’s UDIs—provided the cheaper and more efficient approach. EX2001, ¶¶65-67, 107, 109-111. Indeed, both Parameswaran and Gloor highlighted that benefit of CDIs. EX1004, 1 (“[C]ombinations of forward and reverse barcodes may be used to sequence from as many as n^2 independent libraries for each set of ‘n’ forward and ‘n’ reverse barcodes, for each defined set of cloning-linkers.”); EX1005, 1 (“Combinatorial sequence tagging can be used to examine hundreds of samples with far fewer primers than is required when sequence tags are incorporated at only a single end.”).

In view of Gloor touting the cost-effective nature of its approach, a POSA would not be motivated to replace its CDIs with UDIs because such modification would run counter to Gloor's touted benefits. EX2001, ¶¶109-111. In particular, a POSA would appreciate that using UDIs with Gloor would be *more costly* than the CDIs Gloor was already using. For example, UDIs require more barcodes per sample than CDIs. EX2001, ¶¶65-67, 107, 109-111. Parameswaran noted it could sequence more samples with fewer unique barcodes if it used combinatorial tagging. EX1004, 1, 8; EX2001, ¶111. Indeed, Gloor was able to sequence 272 samples with only 34 unique barcodes (18 left barcodes and 16 right barcodes). EX1005, 6. But for Petitioner's combination, a POSA would be required to design and use 544 unique barcodes (272 pairs)—*16 times more* barcodes than Gloor used—to sequence the same sample set. EX2001, ¶111. Thus, a cost-sensitive and efficiency-focused POSA would steer clear of the combination because UDIs would be more expensive and less efficient than combinatorial indexes, which provide economies of scale with increased simplicity and savings as the number of samples increases.

A POSA would further understand that the unnecessary introduction of additional unique barcodes could lead to more errors. EX2001, ¶¶112-114. For example, Parameswaran observed errors related to barcode design that resulted in sequences with error-free mismatched barcode motifs. EX2001, ¶¶112-113. Some of Parameswaran's forward barcodes were reverse complements of reverse

barcodes, or vice versa, and Parameswaran attributed the most sequences with mismatched barcode motifs to those reverse complement barcodes, requiring the analysis of additional nucleotides from the cloning linkers. EX1004, 7 (“Since six of the forward barcodes are exact reverse complements of six reverse barcodes, we added a number of adjoining nucleotides in the Cloning-Linker (0-17) to the barcode query to reduce ambiguity while segregating the sequences into independent datasets.”); EX2001, ¶¶112-114. Thus, a POSA would understand that barcode design, particularly when the number of barcodes requires designing the barcodes to be too similar to one another, could lead to more errors, and thus that challenges and potential errors related to barcode design increase with the number of unique barcodes required to be designed. EX2001, ¶¶112-114.

Petitioner argues that a POSA “would have been motivated to combine the dual indexing methods disclosed in Parameswaran and Gloor to reduce technical errors that occur during multiplex sequencing” (Pet. 49), but ignores that the references claimed to have already addressed any such “technical errors.” Parameswaran reports that “over 99.8% of obtained sequences could be assigned,” and that “false discovery rate ... was estimated to be <0.005%.” EX1004, Abstract. Parameswaran “expected to *minimize errors related to pyrosequencing*,” and indeed found that the “observed error spectrum appeared most closely to match that *expected as a result of known imprecisions in the chemical synthesis of DNA*

primers used in standard PCR reactions.” EX1004, 7. Parameswaran thus touted its method’s ability to already address any appreciated “sequencing error” in pyrosequencing. EX2001, ¶¶58-60, 112-113.

To the extent a POSA might have sought to further reduce “technical errors” on Parameswaran’s pyrosequencers or on Gloor’s Illumina sequencers, the references suggest any such error came from PCR methods, not from sequencing. EX2001, ¶¶112-114. Parameswaran and Gloor, after touting their near perfection, both attribute any miniscule remaining error to steps separate from sequencing, such as PCR amplification. EX1004, 7 (“rare coincidental sequence matches (due to multiple fortuitous errors during barcode synthesis or sequencing)”, “contamination in PCR primer stocks”, and “cross-contamination of template DNAs in the second round of PCR”); EX1005, 2 (“the majority of errors arise during the PCR amplification step”). A POSA following those threads certainly would not have looked to Parameswaran’s method, which included a second round of PCR that potentially led to cross-contamination of template DNA. EX1004, 7; EX2001, ¶¶112-114.

Accordingly, “technical errors” and “methodological advantages,” along with associated efficiency and cost considerations, would have led a POSA away from implementing unique dual indexing in Gloor’s Illumina sequencing, not toward such combination. *Arctic Cat*, 876 F.3d at 1363.

ii. Petitioner Does Not Show That A Desire To “Efficiently Identify And Discard Chimeric Sequences” Would Have Motivated The Proposed Combination.

Petitioner incorrectly argues that a POSA would have combined Parameswaran and Gloor due to a general desire to “efficiently identify and discard chimeric sequences” formed during NGS workflows. Pet., 49. Petitioner’s argument fails because “it improperly rel[ies] on hindsight in formulating the problem to be solved,” as a POSA at the time of the invention would not have understood chimeric sequences giving rise to such errors, such as the cross-over error discussed throughout the ’200 Patent, to be a problem in pyrosequencers like Parameswaran’s or Illumina sequencers like Gloor’s. *Purdue Pharma L.P. v. Depomed, Inc.*, 643 F. App’x 960, 965 (Fed. Cir. 2016); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (no motivation to combine where POSA would have had to recognize the problem solved by combining two references in order to be motivated to combine them).

Petitioner overstates the awareness of problems arising from chimeric sequences, such as cross-over error, prior to the invention. At the time of the ’200 Patent, a POSA would not have known that cross-over error was problematic for NGS, particularly for the pyrosequencer in Parameswaran or the Illumina sequencer in Gloor. EX2001, ¶¶58-60, 65-75, 115-127. Petitioner cites references that

generally discuss chimeric molecules (Pet., 6), but none of those actually discusses any issues of cross-over error caused by chimeric sequences formed between samples. EX2001, ¶¶115-120. Instead, they discuss only potential chimeras formed *within samples* (e.g., during standard PCR), do not utilize any tagged nucleic acids, and/or generally provide only potential mechanisms that could create chimeras in standard PCR. EX2001, ¶¶115-120; EX1017, 5 (“[c]apturing the full diversity *within a sample*”); EX1018, 3-4; EX1019, 1; EX1020, 1. And those references addressing standard PCR do not discuss NGS systems like Parameswaran’s pyrosequencer or Gloor’s Illumina sequencer; most of the references predate NGS by *more than a decade*. See EX1018 (dated 1990); EX1019 (dated 1989); EX1020 (dated 1995). The two references Petitioner cites that actually address NGS similarly do not discuss cross-over error or chimeric sequences giving rise to such error. EX2001, ¶¶121-126; EX1033, 9 (hypothesizing chimeras are “caused by problems in library preparation” or “the result of poor sequencing library preparation”); EX1034, 10. To the contrary, literature at the time of the patented invention taught that cross-over error for NGS, and particularly on flow-cell based machines like Illumina’s, was not a problem. EX2005, 4 (“Thus, analysis of different ChIP samples with distinct barcodes indicates that *signal from one barcoded library does not crossover to those of other barcoded libraries.*”).

Petitioner argues that a POSA would have known that the dual indexing methods in Parameswaran and Gloor would allow a POSA “to efficiently identify and discard chimeric sequences” (Pet., 49), but that argument incorrectly presupposes the POSA was aware of the cross-over problem being caused by chimeric sequences on Parameswaran’s and Gloor’s sequencers. A POSA would understand instead that Parameswaran’s mismatched barcode motifs were **not** cross-over error. EX2001, ¶¶58, 126-132. Parameswaran reported sequencing runs in which the perceived “mismatched” motifs were corrected by adding nucleotides from the cloning linkers to the analysis. EX1004, 7 (Table 3). A POSA would not have appreciated from that disclosure that there was any remaining cross-over error in need of correcting. EX2001, ¶¶126-132. Instead, as Dr. Adalsteinsson explains, and Dr. Spellman agreed, Parameswaran’s data suggested that the mismatched motifs were caused by “sequencing error” that the linker nucleotides solved (leading Parameswaran to claim a resulting lack of sequencing error), **not** by actual barcode swapping leading to cross-over error. EX2001, ¶126; EX2002, 168:6-17. If the mismatched barcode motifs were a source of cross-over error in Parameswaran, a POSA would not expect the number of mismatched barcode motifs to decrease at all with the inclusion of additional nucleotides from the cloning linkers in the “search motif” used to distinguish sequences from various independent experiments or samples. EX2001, ¶¶126; EX1004, 7 (Table 3). Instead, a POSA would expect cross-

over error to remain steady no matter how many cloning linkers are included in the search motif. EX2001, ¶126. But in Parameswaran, the inclusion of additional cloning linkers in the search motif significantly reduced the instances of “error-free mismatched barcodes” to the point where Parameswaran was comfortable highlighting that its approach might not even need UDIs and could sequence far more samples (“ n^2 ” rather than $n/2$) with CDIs. EX1004, 1; *id.*, 8.

Parameswaran posits three potential sources of its mismatched barcode motifs, none of which are a cross-over problem caused by chimeric sequences in the NGS workflow. EX1004, 7 ((1) “rare coincidental sequence matches (due to multiple fortuitous errors during barcode synthesis or sequencing)”, (2) “contamination in PCR primer stocks”, and (3) “cross-contamination of template DNAs in the second round of PCR”).

First, Parameswaran’s mention of rare coincidental sequence matches due to errors in barcode synthesis and sequencing cannot be cross-over error because they are errors in the barcodes themselves (or reads of the barcodes) that would cause all template DNA from one sample to have barcodes corresponding to two different samples from the start. That is not a cross-over error because it is not caused by a chimeric molecule with template nucleic acids from two different samples, much less one formed during amplification. EX2001, ¶¶58, 128-130. A POSA would have understood that the coincidental sequence matches are a product of barcode design

itself, not any potential cross-over error during the sequencing workflow EX2001, ¶¶58, 128-130.

Second, Parameswaran’s mention of contamination in PCR primer stock cannot be cross-over error because PCR primers are added *prior to* any pooling, amplification, or sequencing step in a nucleic acid workflow. EX2001, ¶¶131-132. Contamination in Parameswaran’s PCR primers would lead to mis-labeling, with the wrong primer permeating all template nucleic acid from one sample, creating template nucleic acid molecules with barcodes associated with two different samples. EX2001, ¶¶131-132. A POSA concerned with contamination in PCR primer stocks would thus have no inkling of cross-over errors.

Third, Parameswaran’s mention of cross-contamination in the second round of PCR occurs *before any samples are pooled together*, amplified, or sequenced. Petitioner provides no explanation how a POSA could thus understand cross-contamination in the second round of PCR to create chimeric sequences between two template nucleic acids from different samples. EX2001, ¶¶114, 131-132. And Dr. Spellman explained that contamination in Parameswaran would result from problems such as “pipette errors” or “aerosols” occurring prior to amplification—*not* cross-over error. EX2002, 137:22-139:9. Furthermore, a POSA could simply avoid the second round of PCR to deal with that contamination. EX2009, 2, 3, 5; EX2001, ¶¶114, 131-132.

Gloor similarly does not instruct a POSA that it suffered from cross-over error caused by chimeric sequences. As Petitioner recognizes, Gloor's use of combinatorial indexes meant that its method could not have unearthed the cross-over error that Petitioner alleges a POSA would seek to reduce. Pet., 48-49; EX2001, ¶¶68-75, 133. To the extent chimeric sequences are discussed in Gloor, Gloor expressed no concern about them. Gloor found such a low rate of chimeric sequences through alternative testing, that "the dataset was used *without further regard to chimeric sequences.*" EX1005, 8. Petitioner provides no reason why a POSA implementing Gloor's sequencing would seek to reduce any issue caused by chimeric sequences when such an occurrence was determined to be insignificant and not worthy of further consideration.

Researchers in the field around the time of the invention determined a single error-free index was sufficient to address any false assignment rate of next generation sequencers, further confirming that a POSA would not have known that cross-over error was an issue for next generation sequencers, and specifically flow-cell based sequencers, even with the existence of dual-indexing methods such as Parameswaran's and Gloor's. EX2010, 3; EX1029, 1; EX2011, 2, 6; EX2012, 1; EX2001, ¶¶116, 121-124, 134-137. Indeed, Illumina's own documents at the time touted the use of single indexes with its sequencing systems. EX2006; EX2007. It

was not until around 2017 that Illumina acknowledged cross-over error on its sequencers, and moved toward UDIs. EX2004; EX2003; EX2001, ¶¶137-138.

Petitioner's attempt to read the cross-over errors addressed by the '200 Patent into the prior art is the type of hindsight that the Federal Circuit has warned against. *Mintz v. Dietz & Watson*, 679 F.3d 1372, 1377-78 (Fed. Cir. 2012) (impermissible hindsight arises when motivation is based on a problem a POSA would not have recognized, because "when someone is presented with the identical problem and told to make the patented invention, it becomes virtually certain that the artisan will succeed in making the invention"); *Purdue Pharma.*, 643 F. App'x at 963 ("[T]o the extent that [Petitioner] relied on the nature of the problem to be solved to supply a reason to combine the prior art, it improperly used hindsight by defining the problem with a recitation of the challenged claims."). Because there was no awareness that cross-over error was an issue for NGS systems like Parameswaran's and Gloor's at the time of the invention, a POSA would not have recognized it as a problem nor sought to solve such a problem through the use of UDIs.

iii. Petitioner Does Not Show That Parameswaran's Speculation Regarding Other Sequencers Would Have Motivated The Proposed Combination.

Petitioner argues that Parameswaran and Gloor provide express motivation by mentioning each other's sequencing platforms, and that such mention would motivate implementing Parameswaran's indexing method on Gloor's Illumina

platform. Pet., 50-51. But Petitioner mischaracterizes Parameswaran, which only states that its “pyrosequencer-tailored *barcodes*”—and specifically its individual “barcode specification”—might be compatible with other platforms, not the entire pyrosequencing-tailored unique dual indexing approach. EX1004, 8. Parameswaran thus suggests that its individual barcode blueprint might provide a starting point for barcodes to enable multiplexing in other sequencing platforms, and that “the precise structure of the barcodes might need to be revised to reflect sequencing error profiles of various systems.” *Id.*

Moreover, Parameswaran only *speculates* that its barcodes *might* be compatible with other sequencing platforms. Such mere speculation, without explaining why a POSA would *want* to add one part of Parameswaran’s barcode method (specifically the unique dual indexes) to Gloor is insufficient. Even if Parameswaran’s speculation were to lead one to *consider* other sequencing platforms, the Federal Circuit requires more than just consideration and possibility. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (“The obviousness inquiry *does not merely ask whether a skilled artisan could combine the references*, but instead asks whether ‘they would have been motivated to do so.’”).

Petitioner further argues it “would at the very least have been obvious for a POSA to try Parameswaran’s unique dual-indexing method with one of the other two sequencing platforms in place of Roche 454 sequencing, as Parameswaran

suggests.” Pet., 50-51 (citing *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007)). But “KSR did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is ‘obvious to try,’ without considering the nature of the science of technology.” *Leo Pharm.*, 726 F.3d at 1357 (quoting *Abbott Labs. V. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008)); *Purdue Pharma.*, 643 F. App’x at 965 (“Indeed, it remains important to identify a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way* the claimed new invention does.”) (emphasis in original). Instead, *KSR* requires “a design need or market pressure to ***solve a problem***” and a “finite number of identified, predictable solutions” to satisfy the motivation to combine requirement. 550 U.S. at 421. The mere identification of other alternative methods in a prior art reference cannot itself satisfy the motivation to combine. *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 888 (Fed. Cir. 2024) (“***It does not suffice to simply be known.*** A reason for combining must exist.”). Thus, Petitioner’s argument that it would have been obvious to try Parameswaran’s UDIs on Gloor’s sequencers simply because they were known fails.

Moreover, Petitioner fails to consider that there were downsides to simply adding UDIs to Gloor’s sequencing with CDIs on an Illumina sequencer. As just one example, and as explained above, using UDIs on Gloor’s 272 samples would have required the creation of far more unique barcodes, whereas Gloor was able to

sequence all of its samples with “exceedingly low error” using “far fewer primers than is required for single-end bar-code sequencing.” *Supra*, Section VIII.A.1. Petitioner provides no reason why a POSA would have gone through that trouble, and extra cost, without any suggestion that UDIs would reduce error in Gloor’s sequencing, simply because it was “obvious to try.” And although Petitioner claims other researchers had used unique dual-indexing (Pet., 51 (citing EX1038)), Petitioner merely points to an indexing method that sequenced and analyzed a single barcode with each sequence. EX2001, ¶140; EX1038, 5-6. Even ignoring the apparent downsides to UDIs, at best a POSA would have seen UDIs as simply another alternative, which does not create motivation to combine. *Virtek*, 97 F.4th at 886 (finding no motivation to combine where the prior art “disclosures ... do not provide any reason why a skilled artisan would use the claimed alternative instead of another,” because “it does not suffice to meet the motivation to combine requirement to recognize that two alternative arrangements ... were both known in the art”).

B. Petitioner Fails To Show A Reasonable Expectation of Success. (All Claims)

Petitioner fails to show that a POSA would have “reasonably expected that the sequences of nucleic acid analytes of interest in a multiplex sequencing reaction would be successfully validated” by combining Parameswaran with Gloor. Pet., 51-

53. As explained above in Section VIII.A, a POSA at the time of the invention would not have understood there to be issues with nucleic acid sequence validation in Illumina sequencers like Gloor's based on chimeric molecules formed between two samples. A POSA, having no knowledge that such an issue was even a problem for NGS, and particularly for Illumina sequencers like Gloor's, would not understand sequences containing only one identifier or an incorrect pair of identifiers to give rise to validation issues. A POSA would therefore have no expectation that incorporating Parameswaran's UDIs into Gloor's Illumina sequencer approach and excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect pair of identifiers from sequence analysis would successfully validate sequences of nucleic acid. EX2001, ¶141.

Thus, nothing that Petitioner puts forth shows any reason why a POSA would have a reasonable expectation of success in combining Parameswaran and Gloor.

C. Petitioner Fails To Show That The Combination Discloses Or Renders Obvious The Limitations Of Claim 5.

As explained above in Sections VI.B and VII.B, neither Parameswaran nor Gloor discloses "t[he] barcode sequences are designed to have no homopolymer regions." Petitioner does not argue that this limitation would have been obvious in the combination, instead citing only to its deficient assertions that the limitation is

disclosed in the references. Pet., 55. Petitioner thus fails to show Claim 5 would have been obvious for the combination. EX2001, ¶¶86-88, 92-96, 142.

D. Petitioner Did Not Prove That Gloor Is Prior Art. (All Claims)

As explained above in Section VI.C for Ground 1, Petitioner failed to establish Gloor as printed publication prior art prior to December 23, 2010. For those same reasons, Petitioner's Ground 3 also fails.

IX. Ground 4: The Challenged Claims Are Patentable Over Parameswaran And Binladen.

A. Petitioner Fails To Show That The Combination Discloses Or Renders Obvious The Limitations Of Claim 1.

Claim 1 recites “analyzing both identifiers and excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect pair of identifiers from sequence analysis of the multiplex sequencing reaction.” EX1001, 22:2-6. Petitioner argues that each of Parameswaran and Binladen include this step (Pet., 60-62), but neither does. EX2001, ¶¶143-145. Parameswaran does not disclose this limitation for the reasons explained above in Section VII.A, and Binladen fails to disclose the limitation for the reasons explained below.

Binladen does not analyze *both identifiers* and exclude sequences as required by claim 1. EX2001, ¶¶144-145. Instead, Binladen simply tags a template DNA with two of the same sequence tags to ensure one of the sequence tags is read, because the full sequence length of the template DNA in Binladen exceeded the approximate

read length for its sequencers. EX1029, 3 (“GS20 sequencing reads are limited to approximately 120 bases, thus in this experiment the full sequence (133-141 bp including primer species dependent) was not returned and our analyses were limited to simply *discriminating using the primer at the sequence end of the product.*”). Indeed, Binladen includes and assigns all sequences based on the presence of only one primer sequence because *it only sequences one primer sequence* in each read. *Id.*, 2 (Figure 1 showing tags assigned and analyzed based on the presence of one dinucleotide tag), 3, 5 (“Initially, we discarded all sequence reads without an exact match to *any* of the primers used in the studies.”); EX2001, ¶¶144-145. Petitioner acknowledges Binladen ‘discarded all sequence reads without an exact match to *any* of the primers used in the studies’ so that “only sequence reads with *an appropriate sequence identifier* were further analyzed.” Pet., 61. A POSA would therefore understand that Binladen does not analyze both identifiers and exclude sequences based on that analysis as claimed, because Binladen did not even sequence both identifiers in its reads. EX2001, ¶¶144-145.

Petitioner hints at inherency, arguing that Binladen “necessarily” meets this limitation by “discarding reads without *an exact forward or reverse tag.*” Pet., 61. But because Binladen only sequences and analyzes one primer sequence in each read, a POSA would understand that Binladen cannot meet this step, either explicitly or inherently. EX2001, ¶¶144-145.

Petitioner does not argue that this limitation would have been obvious in the combination, asserting only that the limitation is disclosed in the references. Pet., 61-62. Petitioner thus fails to show Claim 1 would have been obvious for the combination.

B. Petitioner Fails To Show That The Combination Discloses Or Renders Obvious The Limitations Of Claim 5.

Neither Parameswaran nor Binladen discloses “t[he] barcode sequences are designed to have no homopolymer regions.” Parameswaran does not disclose this limitation for the reasons explained above in Section VII.B, and Binladen fails to disclose the limitation for the reasons explained below.

Binladen’s identifier tags include homopolymer regions. As explained above, the ’200 Patent explicitly defines a homopolymer region as “2 or more of the same base in a row such as AA or CCC.” EX1001, 9:6-10. A number of Binladen’s dinucleotide tags were homopolymeric, as shown in Binladen’s Table 3 (including tags “AA,” “CC,” “GG,” and “TT”). EX1029, 7 (Table 3); EX2001, ¶¶146-150.

Petitioner ignores Binladen’s homopolymeric dinucleotide sequences, arguing instead that a narrow subset of Binladen’s identifiers—“Binladen’s pairs of 4-nucleotide tags” (Pet., 65)—lacked homopolymers. But Binladen only designed “three further unique primer pairs”—in addition to its primers containing dinucleotide tags (including at least four homopolymeric dinucleotides)—“that

contain tetranucleotide tails ... to investigate whether an increased tail length affects the efficiency of the method.” EX1029, 3; EX2001, ¶¶147-150. The majority of the 5’ primer tags utilized and analyzed in Binladen’s experiment were the dinucleotide tags—including the homopolymer tags. EX1029, 3 (Table 1).

Petitioner provides no reason why a POSA would ignore Binladen’s dinucleotide tags. To the contrary, a POSA would be wary of discarding that disclosure because although the “*limited number of tetranucleotide tags*” left them “unable to investigate the effect of the identity of the 3rd and 4th position nucleotides,” Binladen found that the “performance of the tetranucleotide tagged primers *was less efficient than predicted.*” EX1029, 7; EX2001, ¶149. Petitioner cannot ignore Binladen’s teachings as a whole and cherry-pick only the few tetranucleotide sequences in Binladen’s experiment from the majority of the tags used (including the homopolymers). *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449-49 (Fed. Cir. 1986) (finding it is error to fail to consider a prior art reference in its entirety and to ignore portions of the reference that lead away from obviousness).

Additionally, Binladen does not disclose barcodes *designed to* exclude homopolymer regions as claimed, nor suggest the utility of designing barcodes in such a way, because it does not contain *any* discussion of homopolymer regions. EX2001, ¶150. At best, Binladen suggests using longer sequence tags, but is silent

as to whether homopolymer regions should be avoided or would otherwise have any effect for such longer tags. *See* EX1029, 8 (“our limited observations are that increased length reduces the competitive binding efficiency of the PCR product (against shorter tags)”). A POSA would have no reason to conclude from Binladen’s passing mention of longer tags that barcodes should be designed to exclude homopolymer regions. EX2001, ¶150.

Petitioner does not argue that this limitation would have been obvious in the combination, asserting only that the limitation is disclosed in the references. Pet., 65. Petitioner thus fails to show Claim 5 would have been obvious for the combination.

C. Petitioner Fails To Show That The Combination Discloses Or Renders Obvious The Limitations Of Claim 6.

Petitioner asserts that both Parameswaran and Binladen disclose “the nucleic acid analyte of interest is on the surface of a flow cell.” Pet., 65-66. Parameswaran does not disclose this limitation for the reasons explained above in Section VII.C. And Petitioner acknowledges that Binladen uses the same pyrosequencing as Parameswaran, in which on places “bead-bound nucleic acid analytes into a flow cell for sequencing.” Pet., 66. Binladen’s pyrosequencing fails to meet this claim limitation for the same reasons discussed above for Parameswaran’s identical pyrosequencing methods. *See supra* Section VII.C; EX2001, ¶¶97-100, 151.

Petitioner does not argue that this limitation would have been obvious in the combination, asserting only that the limitation is disclosed in the references. Pet., 65-66. Petitioner thus fails to show Claim 6 would have been obvious for the combination.

D. Petitioner Fails To Show A Motivation To Combine. (All Claims)

Petitioner argues that a POSA would have combined Parameswaran and Binladen (Pet., 56, 62-64) but fails to “explain how specific references could be combined, which combination(s) of elements in specific references would yield a predictable result, or how any specific combination would operate or read on the asserted claims.” *See ActiveVideo Networks, Inc. v. Verizon Commc’ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (argument that fails to explain how two prior art references would be combined is conclusory and insufficient to support a motivation to combine). Petitioner frames its combination with the assertion that “Parameswaran and Binladen illustrate that a POSA would have been able to ‘implement a predictable variation’ of a known dual-indexing method to arrive at the claimed subject matter, rendering it obvious.” Pet., 56. But Petitioner’s conclusory framing does not create a motivation to combine. *See ActiveVideo*, 694 F.3d at 1327 (explaining that “a conclusory statement that a person of ordinary skill in the art would have known, based on the ‘modular’ nature of the claimed components, how to combine any of a number of references to achieve the claimed

inventions ... is not sufficient and is fraught with hindsight bias”). Indeed, Petitioner does not even explain whether it is relying on Parameswaran or Binladen for the “known dual-indexing method” in the combination or what “predictable variation” a POSA would make to arrive at any of the claimed subject matter.

A POSA would not have “‘implemented a predictable variation’ of a known dual-indexing method to arrive at the claimed subject matter” with the combination of Parameswaran and Binladen. EX2001, ¶¶152-154. As Petitioner acknowledges, “Parameswaran studied the dual-indexing methods used in Binladen.” Pet., 56. Parameswaran found that “the barcodes used in [Binladen’s and others’] experiments are too short to allow for massively parallel runs involving large numbers of sample libraries.” EX1004, 8. Petitioner does not explain why a POSA would look to incorporate Binladen’s methods into Parameswaran’s multiplexing methods—essentially what Parameswaran taught would be a step backwards, highlighting that Binladen’s chosen identifiers were too short to run large numbers of samples. *See* Pet., 62-63; EX2001, ¶¶152-154; *Arctic Cat*, 876 F.3d at 1363 (Fed. Cir. 2017) (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”).

Binladen likewise does not suggest its methods would improve Parameswaran’s barcoding method. EX2001, ¶¶152-153. Instead, Binladen calls itself an initial study, and “caution[s] that while we demonstrate the overall

efficiency of this method, future studies are required to confirm the global extent of our observations on the primer efficiencies.” EX1029, 7; *see also id.*, 8. A POSA would understand that Parameswaran, published after Binladen, evaluated those preliminary results and determined that its longer barcodes were better. EX2001, ¶¶152-153. Indeed, Parameswaran explained that “shorter barcodes also have a steeper trade-off between number of possible barcodes and the minimum number of nucleotide differences between individual barcodes,” which both Parameswaran and a POSA would deem less suitable for multiplexing than Parameswaran’s barcoding method. EX2001, ¶¶152-154; EX1004, 2.

Accordingly, Petitioner does not show motivation to combine Parameswaran and Binladen to arrive at the claimed invention.

X. Ground 5: The Challenged Claims Are Patentable Over Parameswaran, Binladen, And Bentley.

A. Petitioner Fails To Show A Motivation To Combine. (All Claims)

Petitioner argues that a POSA would have combined Parameswaran, Binladen, and Bentley, relying on the same arguments for the combinations in Grounds 3 and 4. *See* Pet., 66-67 (citing Pet., Sections VIII.B-C and IX.A-C). For the reasons explained above in Sections VIII.A-B and IX.D, those arguments fail. Petitioner does not provide any additional support or argument specific to this combination, and thus fails on Ground 5 as well. EX2001, ¶155.

XI. Conclusion

For the foregoing reasons, the Challenged Claims are patentable.

Dated: April 17, 2025

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Case IPR2024-00965
U.S. Patent No. 11,768,200

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that this paper, excluding the portions exempted under 37 C.F.R. § 42.24(a), has 11,748 words as counted by Microsoft Word 365, the word-processing system used to prepare this paper.

Dated: April 17, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on April 17, 2025, a complete copy of the foregoing was served on counsel of record for Petitioner by filing this document through P-TACTS and by sending this document via electronic mail to the following addresses:

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