

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.
Petitioner,

v.

UNIVERSITY OF WASHINGTON,
Patent Owner.

Case No. IPR2022-00817
Patent No. 10,760,127

PATENT OWNER'S SUR-REPLY

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PATENT OWNER'S UPDATED EXHIBIT LIST

Exhibit No.	Description
2001	Eid, J., et al., "Real-Time DNA Sequencing from Single Polymerase Molecules," <i>Science</i> 323:133-138 (2009)
2002	Niedringhaus, T.P., et al., "Landscape of Next-Generation Sequencing Technologies," <i>Anal. Chem.</i> 83:4327-4341 (2011)
2003	Thompson, J.F. and Milos, P.M., "The Properties and Applications of Single-Molecule DNA Sequencing," <i>Genome Biology</i> 12:217 (2011)
2004	Stranneheim, H. and Lundeberg, J., "Stepping Stones In DNA Sequencing," <i>Biotechnol</i> 7:106-1073 (2012)
2005	Quail, M.A., et al., "A Tale of Three Next Generation Sequencing Platforms: Comparison of Ion Torrent, Pacific Biosciences and Illumina Miseq Sequencers," <i>BMC Genomics</i> 13:341 (2012)
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2013	McCloskey, M.L., et al., “Encoding PCR Products with Batch-stamps and Barcodes,” <i>Biochem Genet</i> 45:761-767 (2007)
2014	Declaration of Rahul Satija, D.Phil. in Support of Patent Owner Response
2015	Complaint, <i>Twinstrand Biosciences, Inc. v. Guardant Health, Inc.</i> , Case No. 1:21-cv-01126-UNA (D. Del.), filed Aug. 3, 2021
2016	Decision Denying Institution, <i>Guardant Health, Inc. v. University of Washington</i> , Case No. IPR2022-00816 (P.T.A.B.), Paper No. 16, filed Oct. 13, 2022
2017	Johne, R., et al., “Rolling-Circle Amplification Of Viral DNA Genomes Using Phi29 Polymerase,” <i>Trends in Microbiology</i> , 17(5):205-11 (2009)
2018	Report and Recommendation, <i>Twinstrand Biosciences, Inc. v. Guardant Health, Inc.</i> , Case No. 1:21-cv-01126-UNA (D. Del.), filed Dec. 29, 2022
2019	Guardant Health, Inc. Response to Notice of Opposition, European Patent No. 2,893,040, filed May 29, 2020

Exhibit No.	Description
2020	Prosecution History of U.S. Patent No. 10,760, 127 (“127 Prosecution History”)
2021	“Single Molecule Real Time (SMRT™) DNA Sequencing,” Technology Backgrounder, <i>Pacific Biosciences</i> (2009)
2022	Fichot, E. B. and Norman, R. S, “Microbial Phylogenetic Profiling With The Pacific Biosciences Sequencing Platform,” <i>Microbiome</i> 1(10):1-5 (2013)
2023	Shadt, E. E., et al., “A Window Into Third-Generation Sequencing,” <i>Pacific Human Molecular Genetics</i> , 19(2):R277-R240 (2010)
2024	Liu, L., et al., “A Brief Utilization Report On The Illumina Hiseq 2000 Sequencer,” <i>Mycology</i> , 2(3):169-91 (2011)
2025	Koren, S., et al., “Hybrid Error Correction And <i>De Novo</i> Assembly Of Single-Molecule Sequencing Reads,” <i>Nature Biotechnology</i> (2012)
2026	Eid, J, et al., “Supporting Online Material for: Real-Time DNA Sequencing from Single Polymerase Molecules,” <i>Science</i> (2008)
2027	Gupta, P. K., “Single-Molecule DNA Sequencing Technologies For Future Genomics Research,” <i>Trends in Biotechnology</i> , 26(11):602-11 (2008)
2028	Zhang, X., et al., “Improving Genome Assemblies By Sequencing PCR Products With Pacbio,” <i>BioTechniques</i> , 53(1):61-2 (2012)
2029	Levene, M. J., et al., “Zero-Mode Waveguides For Single-Molecule Analysis At High Concentrations,” <i>Science</i> , 299:682-86 (2003)

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2030	Korlach, J., et al., “Selective Aluminum Passivation For Targeted Immobilization Of Single DNA Polymerase Molecules In Zero-Mode Waveguide Nanostructures,” <i>PNAS</i> , 105(4):1176-81 (2008)
2031	McCarthy, A., “Third Generation DNA Sequencing: Pacific Biosciences’ Single Molecule Real Time Technology,” <i>Chemistry & Biology</i> , 17:675-76 (2010)
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2035	Ozsolak, F., “Third Generation Sequencing Techniques and Applications to Drug Discovery,” <i>Expert Opinion on Drug Discovery</i> , 7(3):231-43 (2012)
2036	Demidov, V. V., “Rolling-Circle Amplification In DNA Diagnostics: The Power Of Simplicity,” <i>Expert Review of Molecular Diagnostics</i> , 2(6):542-48 (2002)
2037	Liu, D., et al., “Rolling Circle DNA Synthesis: Small Circular Oligonucleotides as Efficient Templates for DNA Polymerases,” <i>Journal of American Chemical Society</i> , 118:1587-94 (1996)
2038	Lizardi, P. M., et al., “Mutation Detection And Single-Molecule Counting Using Isothermal Rolling-Circle Amplification,” <i>Nature Genetics</i> , 19:225-32
2039	Smith, D. E., et al., “Dynamical Scaling of DNA Diffusion Coefficients,” <i>Macromolecules</i> , 29:1372-73 (1996)

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2040	Robertson, R. M., “Diffusion Of Isolated DNA Molecules: Dependence On Length And Topology,” <i>Proceedings of the National Academy of Sciences</i> , 103(19):7310-14 (2006)
2041	Grosberg, A. Y. and Rabin, Y., “DNA Capture Into A Nanopore: Interplay Of Diffusion And Electrohydrodynamics,” <i>The Journal of Chemical Physics</i> , 133: 165102-1-15 (2010)
2042	Coupland, P., et al., “Direct Sequencing Of Small Genomes On The Pacific Biosciences RS Without Library Preparation,” <i>BioTechniques</i> , 53(6): 365-72 (2012)
2043	Patent Owner’s Pre-Institution Sur-Reply, <i>TwinStrand Biosciences, Inc. v. Guardant Health, Inc</i> , Case No. IPR2022-00746 (P.T.A.B.), Paper No. 13, filed Aug. 15, 2022
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2045	Deposition Transcript of John Quackenbush, Ph.D., <i>Guardant Health, Inc. v. University of Washington</i> , Case No. IPR2022-00817 (P.T.A.B), Dec. 19, 2022
2046	Loomis, E. W., et al., “Sequencing The Unsequenceable: Expanded CGG-Repeat Alleles Of The Fragile X Gene,” <i>Genome Research</i> , 23:121-28 (2014)
2047	Drmanac, R., et al., “Human Genome Sequencing Using Unchained Base Reads on Self-Assembling DNA Nanoarrays,” <i>Science</i> , 327: 78-81 (2010)
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2049	U.S. Provisional Application No. 61/072,160 to Patel et al., filed Mar. 28, 2008
2050	Schmitt, M. W., et al., “Detection Of Ultra-Rare Mutations By Next-Generation Sequencing,” <i>Proceedings of The National Academy of Sciences</i> , 109(36):14508-13 (2012)
2051	Kelvey, J., “Liquid Biopsies Generate Ample Insights from Sparse Clues,” Genetic Engineering & Biotechnology News (2020)
2052	LeMieux, J., “Sequencing’s Stars Urge Exploration of New Dimensions” Genetic Engineering & Biotechnology News, 40(4) (2020)
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2055	“Quality Scores for Next-Generation Sequencing,” Illumina (2011)
2056	“12A: Nomenclature,” Encyclopedia of Separation Science, Academic Press, 4712-53 (2000) (excerpt)
2057	Larkin, J., et al., “Length-Independent DNA Packing into Nanopore Zero-Mode Waveguides for Low-Input DNA Sequencing,” <i>Nature Nanotechnology</i> , 12(12) 1169-75 (2017)
2058	Kalendar, R., et al., “Java Web Tools For PCR, In Silico PCR, And Oligonucleotide Assembly And Analysis,” <i>Genomics</i> , 98:137-44 (2011)

Exhibit No.	Description
2059	Kalendar, R., et al., “Java Web Tools For PCR, In Silico PCR, And Oligonucleotide Assembly And Analysis,” <i>Genes, Genomes and Genomics</i> , 3(1):1-14 (2009)
2060	Vincze, T., et al., “NEBcutter: A Program To Cleave DNA With Restriction Enzymes,” <i>Nucleic Acids Research</i> , 31(13):3688-91 (2003)
2061	Reuter, J. S., “RNAstructure: Software For RNA Secondary Structure Prediction And Analysis,” <i>BMC BioInformatics</i> , 11(129):1-9 (2010)
2062	Kennedy, S. R., et al., “Detecting ultralow-frequency Mutations by Duplex Sequencing,” <i>Nature Protocols</i> , 9(11):2586-2606 (2014)
2063	Ng, D. W. and Wong, C. K. B, “Self-Recognition Of DNA From Life Processes To DNA Computation,” <i>Biophysical Reviews and Letters</i> , 2(2):123-37 (2007)
2064	<i>Curriculum Vitae</i> of Rahul Satija, D.Phil
2065	“TwinStrand’s Duplex Sequencing Goes Deep,” GenEdge, Genetic Engineering & Biotechnology News (2020)
2066	Semsarian, C., et al., “Molecular Medicine in the 21 st Century,” <i>Internal Medicine Journal</i> , 31:53-59 (2001)
2067	Forthofer, R. N., et al., “Biostatistics: A Guide to Design, Analysis, and Discovery,” Chapter 5: Probability Distributions, <i>Elsevier Academic Press</i> , 103-133 (2007) (excerpt)
2068	Esteban, J. A., et al., “Fidelity of Φ 29 DNA Polymerase,” <i>The Journal of Biological Chemistry</i> , 268(4):2719-26 (1993)

Exhibit No.	Description
2069	DNA Secondary Structures for 6x Product
2070	DNA Secondary Structures for 10x Product
2071	DNA Secondary Structures for 20x Product
2072	Deposition Transcript of Andres Larrea, Ph.D., May 9, 2023
2073	Deposition Transcript of John Quackenbush, Ph.D., May 15, 2023

I. INTRODUCTION

Petitioner’s obviousness theory relies on combining two prior art references (Travers-2010 and Travers-075) to manufacture a linear, rolling circle replication (RCR) DNA concatemer to be sequenced using PacBio’s SMRT sequencing (“Petitioner’s RCR embodiment”). But neither the Petition nor Reply bother to articulate an actual reason to combine the references. Nor does Petitioner provide *any reason* to deviate from the established SMRTbell template design in Travers-2010 by using an RCR embodiment conjectured, but not enabled, in Travers-075.

Petitioner repeatedly argues that the ’127 patent specification supposedly “admits” that Petitioner’s RCR embodiment is within the scope of the challenged claims. But the ’127 patent never says that linear RCR products can be used with PacBio’s sequencing—ever—let alone with the methods as claimed. Petitioner’s allegations of supposed “admissions” in the patent are fallacious.

Petitioner’s proposed RCR embodiment is fraught with several critical problems—all overlooked in the Petition—which indicate a skilled artisan would not have been able to make the embodiment. Petitioner’s Reply (which includes several improper new arguments), along with testimony from its two reply declarants, fails to resolve these critical problems. Petitioner has thus failed to meet its burden, and the Board should reject the Petition.

II. PETITIONER MISCHARACTERIZES THE '127 PATENT'S DISCLOSURE AND FABRICATES ALLEGED "ADMISSIONS."

The POR identified fatal flaws in the Petition. Petitioner's Reply fabricates so-called "admissions" in the '127 patent, arguing that "the '127 patent critically relies on Travers to claim the very subject matter PO now frivolously argues is not enabled." Reply, 1-3, 5-6, 9, 12, 24. This is nonsense. Neither the specification (nor Patent Owner or its expert) make any such admissions. And the specification never suggests Petitioner's RCR embodiment is enabled.

Petitioner misinterprets disclosures in the specification, alleging that the patent "admits" to using Petitioner's RCR embodiment. *Id.*, 3-4, 6-7, 12 (citing EX1001, 10:63-11:18). But these disclosures do *not* discuss using PacBio sequencing in the claimed methods *at all*. Columns 10-11 of the specification discuss "Product I" (a template molecule comprising a Y-shaped adapter on one end and a hairpin adapter on the other):



EX1001, 9:55-65.

Product I is unrelated to PacBio sequencing because it contains "flow cell

binding sites” (denoted as “FC1” and “FC2,” *see id.*, 8:12-31), which PacBio does not use. Petitioner’s declarant Dr. Larrea admitted on cross-exam that Travers “does not use a flow cell” and SMRTbell templates do not have, and PacBio does not use, flow-cell binding sites. EX2072, 35:18-37:1. Accordingly, Product I’s flow-cell binding sites definitively show it is designed for sequencing on a *flow-cell* (e.g., *Illumina*) and is *incompatible* with PacBio sequencing.

The specification discloses that “*Product I* contains a self-complementary hairpin sequence that can *impair polymerase extension* during amplification.” EX1001, 10:55-57.¹ The patent explains, however, that molecules with a hairpin linker like Product I can indeed still be amplified using polymerases such as those disclosed in reference [50] (Kaur) and [49] (Travers-2010).² *Id.*, 10:55-66. This in no way is a concession that Petitioner’s RCR embodiment is encompassed within the claimed methods. After all, Product I was designed for sequencing on a flow-cell (e.g., *Illumina*), *not* PacBio. EX2072, 35:18-36:21. After explaining that Product I is amplifiable, the specification discloses, “the published linker sequences from either of [Kaur or Travers-2010] would be adequate for use *in the assay*”—i.e., *assay with Product I*, which is *not* compatible with or designed for

¹ Emphasis is added unless otherwise noted.

² Travers-2010 does not disclose template amplification after ligation prior to SMRT sequencing. EX2014, ¶¶101-112.

PacBio sequencing. EX1001, 10:66-11:2³. The specification simply points to a sequence in a hairpin adapter design that would be suitable in the specific assay for Product I. Additionally, the other products schematized throughout the specification incorporate or contemplate flow-cell binding sites, making them inappropriate and unusable in PacBio sequencing. *See Id.*, 8:1-15:5. The specification comes nowhere close to Petitioner’s imagined admissions.

Even when mentioning DNA flanked by U-shaped adapters, the specification explicitly states that the U-shaped adapters are for “protect[ion] from digestion” by exonucleases during clean-up, and that the circles can later be “open[ed] once again” for “subsequent steps”—i.e., *not* for use in PacBio’s SMRT sequencing. *Id.*, 11:8-18.

Petitioner also misconstrues the patent’s statement that “closed circles may be pre-amplified using rolling circle amplification or serve as the substrate for continuous loop sequencing.” Reply, 4-5. First, Petitioner ignores the disjunctive “or” in the quoted sentence (“or serve as the substrate”). Indeed, continuous loop sequencing is incompatible with a linear concatemer molecule generated from rolling circle amplification. Petitioner also ignores the fact that using “closed circles” as the substrate “for continuous loop sequencing” is an explicit reference

³ Moreover, the hairpin in Product I does not provide any asymmetry—the asymmetry comes from the Y-shaped adapter on the opposite end of the molecule.

to PacBio's SMRT sequencing as an alternative for closed-circle constructs *but not within the scope of the challenged claims*, which require a template amplification step after ligation but before sequencing. Paper 14, 18.

Second, the specification's reference to "pre-amplif[ying]" the closed circles with "rolling circle amplification" says *nothing* about using an RCR product *in PacBio's SMRT* sequencing. Rather, a POSA would have understood that these "pre-amplified" products would need to be *re-fragmented* (as the patent indicates) and then *PCR-amplified to add flow-cell binding sites*. EX1001, 11:12-17, 3:61-64, FIG. 1; EX2014, ¶¶214-216. Thus, the specification never discloses making Petitioner's RCR concatemer and sequencing it in PacBio's system.

Petitioner also wrongly alleges that Dr. Satija "confirm[ed] claims encompass but are not limited to Travers' amplification embodiment." Reply, 3 (citing EX1037, 94:24-95:15). To the contrary, Dr. Satija testified that Petitioner's RCR embodiment fails to satisfy all of the claim elements and thus is clearly *not* "encompassed" by them. EX2014, ¶¶75-95. Moreover, the specification expressly teaches using a "suitable" sequencing method, and Dr. Satija explained at length why a POSA would have viewed Petitioner's embodiment as inoperable and "*unsuitable*" for the claimed methods. EX2014, ¶¶113-197, 215; EX1001, 15:33-39.

Accordingly, Petitioner's alleged admissions are based on a self-serving

misreading of the specification and mischaracterization of Dr. Satija's testimony.

III. PETITIONER'S ART FAILS TO DISCLOSE ALL OF THE CLAIM ELEMENTS.

A. Petitioner's combination fails to disclose "first and second strand sequence reads."

A POSA reading the plain language of the claims in view of the specification would have understood that the "first and second strand sequence reads" of claim 1 result from *at least two distinct sequencing reactions*, each of which produces a separate sequence read for each strand. *See* EX2014, ¶¶60-65, 75-80; POR, 8-13. The POSA would have understood that this distinction of strand sequence reads in the '127 patent is distinct from the single sequencing reaction that generates a long continuous read containing multiple *subreads*, as in Travers-2010 and Travers-075. *Id.*; EX1021, 2, 5; EX1018, FIG. 3B. The Petition never accounted for this fundamental difference between the claimed methods and those of Travers-2010 and Travers-075. *Id.*

Petitioner now wrongly argues that the challenged claims do not "require" a distinct sequencing reaction for each strand. Reply, 6-7. Dr. Satija explained in detail how a POSA would have interpreted "first and second strand sequence reads" in the claims and how this construction is essential to understanding the claimed method. EX2014, ¶¶60-65, 75-80; POR, 8-13. The plain language of the claim enumerates two sequence reads (first and second strand) and the intrinsic

evidence and common sense of a POSA confirms that this language denotes distinct strand sequence reads from distinct reactions. EX1001, 4:12-18, 4:45-49, 9:5-9, 9:11-12; POR, 9; EX2014, ¶62.

Petitioner alleges that the POR arguments are “limited” to embodiments utilizing Y-shaped adapters, PCR, and Illumina sequencing. Reply, 7. That argument ignores pertinent disclosures in the specification, such as the Abstract (describing “*independently tagging and sequencing each of the two strands of a DNA duplex*”) and Figure 4 (depicting a separate “sequence read” generated from each of the “top strand” and “bottom strand”). EX1001, Abstract, 4:38-62. Petitioner also ignores the specification’s discussion of the U-shaped adapter embodiment, “Product I,” discussed above.



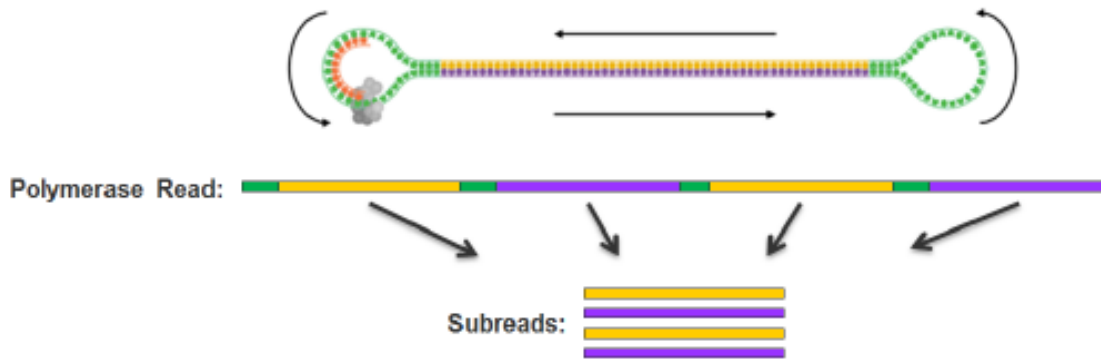
EX1001, 8:54-65, 9:51-65.

For Product I, the specification describes the “sequence seen in *Read 1*” as having “the sequence corresponding to the complementary DNA duplex strand seen in *Read 2*” —i.e., separate *sequence reads* (Read 1 and Read 2) for the *top and bottom strands*. EX1001, 6:20-30. The specification further discloses that

mutations in Product I sequence reads are scored only when present in “*each strand ... i.e., at the same position in both Read 1 and Read 2.*” *Id.*; *see also id.*, 9:1-14. These are *separate* sequence reads, generated by *separate* reactions, even in embodiments using U-shaped adapters.

In contrast, a POSA would have known that a “sequence read” in SMRT sequencing is a string of repeating *subreads*, all of which came from a single, contiguous sequencing reaction, and thus fails to meet this claim limitation. *See* POR, 8-12 (claim 1) and 13-15 (claim 22); EX1021, 2 (distinguishing subreads from reads); EX1018, FIG. 3B (depicting a single sequence read comprising repeating subreads). Dr. Larrea admitted on cross-examination that each “read” in PacBio sequencing “come[s] from *an individual polymerase*” and encompasses “multiple passes around a template.” EX2072, 38:16-23, 39:3-9. This testimony confirms that PacBio sequencing generates a single contiguous output of sequence data from one sequencing reaction.

PacBio’s Glossary document makes a clear distinction between a sequencing read (“polymerase read”—the single contiguous read) and subreads, explaining that each “polymerase read” is “partitioned” into subreads:



EX2072, 39:20-42:25, 95, 97. Dr. Larrea admitted that PacBio’s “*subreads*” were a convenient way of describing *portions of the read*.” EX2072, 42:21-25.

Notably, the “polymerase read” in PacBio’s figure above is nearly identical to Travers-075’s “sequence readout” in Figure 3B (again depicting a single contiguous read):

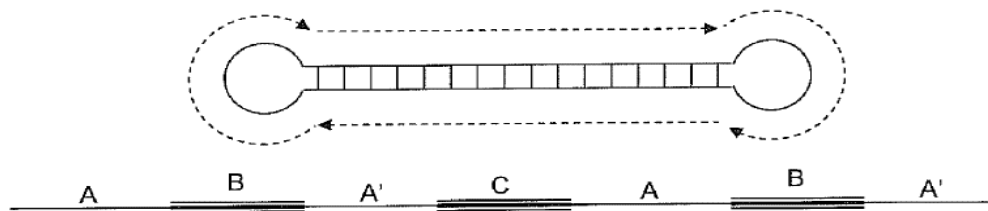


Figure 3B

EX1018, FIG. 3B, ¶55. Thus, a “sequence read” as taught in Travers-2010 and Travers-075 cannot meet the claim limitation of “first and second strand sequence reads.” EX2014, ¶¶60-65, 75-80; POR, 8-13.

Petitioner implies that Dr. Satija’s definition of “sequence read” is any “contiguous set of DNA nucleotides” that correspond to the output of a DNA sequencing reaction. Reply, 7-8; EX1039, ¶11 (citing EX2014, ¶60). Petitioner

conveniently ignores the very next sentence in Dr. Satija’s declaration, where he unequivocally states: “a POSA would understand ‘first and second strand sequence reads’ to mean a distinct sequence read of the first strand and a separate, distinct sequence read of the second strand.” EX2014, ¶60.

Accordingly, Petitioner failed to show that its art combination discloses all the elements of the claims. EX2014, ¶¶60-65, 75-80; POR, 8-13.

B. Petitioner’s combination fails to disclose claim 22’s grouping strand sequence reads into families.

Claim 22 requires “*grouping the strand sequence reads into families* based on i) the *barcode sequence*, **and** ii) *DNA fragment-specific information...*” EX1001, 40:12-16; POR, 13-15; EX2014, ¶¶81-87. As discussed above, a “sequence read” of Travers-2010 and Travers-075 does not meet the “obtaining first and second strand sequence reads” limitation of claim 1.⁴ For similar reasons, Travers-2010 and Travers-075 do not disclose “grouping the strand sequence reads into families” based on barcode sequence and DNA fragment specific information, as required in claims 22-30. Because the subreads are already physically linked

⁴ Petitioner wrongly alleges that Patent Owner “does not dispute” that Travers 2010 or Travers-075 discloses “strand sequence reads” as required in claims 22-30. Reply, 6. Patent Owner disputed this in the context of claim 22’s “grouping” step. POR, 13-15; EX2014, ¶¶81-87.

there is no need to group them, and no family-grouping step is performed. POR, 13-15; EX1021, FIG. 4; EX1018, FIG. 3B; EX2014, ¶¶60-65, 75-87.

Petitioner ignores the specification's description of a grouped "family" of strand sequence reads, and its Reply arguments address only *sample grouping*, not family grouping, as claimed, which is a fundamentally different process.

Petitioner's expert Dr. Quackenbush previously testified that a patent with the same specification as the '127 patent uses a "molecular barcoding approach" that involves "identification and *grouping of sequence reads derived from PCR duplication*" and that "[t]hese *groups of sequence reads* are typically referred to as '*families*.'" EX2073, 93:11-95:19, 311 (¶33). This testimony is consistent with the '127 specification: "[*e*]ach *family pair* reflects *one* double-stranded DNA fragment." EX1001, 4:17-18; 3:61-64 (disclosing generating "*families of PCR duplicates*"); 16:40-41 (disclosing "group[ing] into *families of paired target nucleic acid strands*"); Figure 1. The methods in the Travers documents, however, conduct no family grouping step because all of the PacBio subreads are already physically linked together as products of the same sequencing reaction.

Further, Travers certainly does not use its *index* (sample) barcodes in any family grouping step. In fact, Travers-075 discloses that its subread alignment can be performed "even without knowledge of the sequence of the connecting oligonucleotide." EX1018, ¶98; EX2014, ¶¶81-87.

Travers-075's index barcodes serve a completely different purpose than the '127 patent's molecular barcodes of claim 22 (referred to as "SMIs" throughout the specification). EX1037, 89:16-20 (testifying that "the use of *indexed barcoded* samples is *very different* from the claim step of *grouping the strands of sequence reads into families* based on the barcode and DNA fragment-specific information."); *id.*, 53:19-54:6, 86:18-20; EX2014, ¶¶83-84. Petitioner cannot dispute this distinction, as it has adamantly argued before the European Patent Office that a POSA would *not* have considered using index barcodes (tracking sample source—i.e., Travers-075) as molecular barcodes (grouping molecules originating from the same template—i.e., the challenged claims). EX2019, 18; EX2014, ¶85; POR, 14-15.

Travers-075's alignment of subreads proceeds exactly the same way with or without an indexing barcode because Travers-075's subreads are physically linked and aligned irrespective of any barcode. As such, neither Travers document discloses claim 22's family-grouping step.

C. Petitioner's combination fails to disclose claim 19's using the asymmetric nature of the adapter-DNA fragments.

Claim 19 recites using the asymmetric nature of the adapter-DNA molecules to differentiate first and second strand sequence reads. EX1001, 3:64-4:3; 37:32-39, 39:41-46; EX2020, 482. The Travers combination fails to disclose this limitation because the references only suggest using adapter sequences as a

“registration” sequence to mark where the sense sequence ends and the antisense sequence begins. POR, 15-18; EX2014, ¶¶88-95; EX1018, ¶¶54, 76; EX1021, FIG.

4. Nothing in the Petition’s two sentences addressing claim 19 explains how or why a POSA reading the Travers documents would have used any *asymmetry* of adapter-DNA molecules to differentiate between first and second strand sequence reads, as claimed. Pet., 52-53.

Petitioner’s Reply attempts to sidestep this issue by arguing that Travers-2010’s adapter-DNA molecules are asymmetric because Travers allegedly may attach different adapters on each end. Reply, 12. But this does not relieve Petitioner of its burden to show that the art actually teaches a method of *using* the asymmetric nature of the adapter-DNA molecules to differentiate first and second strand sequence reads, as claimed. The Petition never showed that.

Moreover, Petitioner fails to address how any adapter-DNA *asymmetry would be maintained* and used to differentiate strands in Petitioner’s linear RCR concatemers. Petitioner argues there “is no distinction” between Travers’ use of adapters as “landmarks” and the claimed use of asymmetry. Reply, 13. But there is a crucial distinction. Because claim 19 relies on the asymmetry to differentiate first and second strand reads, that asymmetry must be *maintained* in the amplified product *and used* to differentiate first and second strand reads. Petitioner’s proposed embodiment loses any such asymmetry when the molecule is replicated

because it becomes linear and single-stranded. Therefore, asymmetry cannot be the basis for distinguishing reads. Instead, Travers uses its adapter sequence as landmarks, irrespective of any asymmetry. EX2014, ¶¶88-95.

IV. THE PETITION RELIES ON COMBINING TRAVERS-2010 AND TRAVERS-075, YET FAILS TO EXPLAIN WHY A POSA WOULD COMBINE THEM.

A. Petitioner was required to articulate a reason to combine the art, yet failed to do so.

Petitioner unquestionably relies on *combining* Travers-2010 and Travers-075 to allegedly meet all the claim limitations. Pet., 6 (“This petition relies on a patent publication *and* a paper...”); Pet., 19 (“the *combination* of [Travers-075] *and* [Travers-2010]...”); EX1002, ¶120 (relying exclusively on Travers-2010 for claim element 22.6), ¶181 (same for claims 24-25). The Petition makes no attempt to articulate why a POSA would have combined these references in the way Petitioner combines them.

The Petition’s sole rationale for combining Travers-075 with Travers-2010 is merely that the references describe “the same PacBio methodology” and “aspects of the PacBio workflow.” Pet., 20. Legal precedent requires rejecting Petitioner’s superficial explanation of a “reason” to combine the asserted art. *Trivascular Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016) (“the Board ‘must still be careful not to allow hindsight reconstruction of references ... without any explanation as to *how* or *why* the references would be combined to produce the

claimed invention.”). Requiring that a petitioner articulate a reason to combine the art makes sense. It would be unjust if petitioners could rely on disclosures from multiple references, yet provide only superficial reasons to combine them. Thus, the Board should follow precedent and reject Petitioner’s combination.

Nor can Petitioner recast its obviousness combination as a single-reference obviousness theory. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1330-31 (Fed. Cir. 2019). Petitioner must be held to the obviousness combination proposed in its Petition, and as shown in the POR and this Sur-Reply, that combination fails on multiple levels.

B. Petitioner identifies no advantages of its RCR embodiment over Travers-2010’s SMRTbell sequencing.

The Institution Decision suggested that Travers-075 may not require “modification,” but the Board did not have the full trial record and did not know the litany of disadvantages and problems with Petitioner’s RCR embodiment. Paper 14, 20; POR, 29-55; EX2014, ¶¶193-197. When considering obviousness, however, “the benefits, both lost and gained, should be weighed against one another.” *Henny Penny*, 938 F.3d at 1332.

Here, *Petitioner has never identified a single advantage* of its RCR embodiment or any reason to depart from the SMRTbell method in Travers-2010. Meanwhile, Patent Owner provided ample evidence demonstrating fundamental problems with Petitioner’s approach. EX2014, ¶¶113-197.

First, the RCR polymerase “would certainly *introduce errors* in the amplification process” and a POSA would have no reason to introduce “an unnecessary amplification step into the amplification-free SMRT sequencing workflow ... [which] would only *make SMRT sequencing worse....*” EX2014, ¶¶110-111; EX2017, 2; EX2068, 6. This issue is uncontested. Neither Petitioner nor its declarants respond to this issue at all.

Moreover, Petitioner failed to proffer even a scintilla of evidence that anyone—*ever*—has implemented its proposed RCR embodiment in the 13 years between the Travers publications and today. *See Raytheon Tech. v. General Electric Co.*, 993 F.3d 1374, 1381 (Fed. Cir. 2021) (“the evidence of record must still establish that a skilled artisan could have made the claimed invention.”). Here, the evidence shows that Petitioner’s embodiment is not enabled, nor was there any reason to attempt to implement it in the first place. POR, 59-61; EX2014, ¶¶206-210.

V. PETITIONER’S EMBODIMENT IS NOT ENABLED, NOR WOULD A POSA HAVE HAD A REASONABLE EXPECTATION OF SUCCESS IN MAKING IT ANYWAY.

Dr. Larrea admitted that SMRT sequencing was a “nascent” and “cutting-edge” technology at the relevant timeframe. EX2072, 28:7-15. “Nascent technology, however, must be enabled with a ‘*specific and useful teaching.*’” *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004). The scant

disclosures in Travers-075 provide no “specific and useful teaching” to enable Petitioner’s RCR embodiment. The balance of the evidence shows it would not work.

A. Petitioner’s Reply advances improper new argument.

The Reply concedes that a POSA attempting Petitioner’s RCR embodiment would need to engage in a variety of tedious and extraneous exercises, such as various DNA size-selection processes, DNA diffusion rate-control protocols, and attempts to re-circularize the RCR concatemer, *all with no upside* compared to the normal SMRTbell workflow. Reply, 18-21. Even if a POSA had this backwards ambition, nowhere does the Petition mention these new methods, much less explain why, in the face of such inefficiency, a POSA would have implemented Petitioner’s embodiment. Nor does the Reply. The Board should reject Petitioner’s belated theories. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369–70 (Fed. Cir. 2016); 37 C.F.R. §42.23(b).

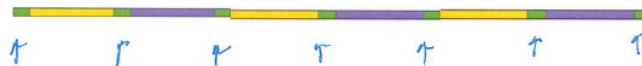
Even on the merits, Petitioner’s newfound extraneous steps still fail to resolve Problems 1-4, and still fail to justify any reason for engaging in such tedium to arrive, at most, at a less-efficient and less-accurate method than SMRTbell sequencing.

B. POSAs knew that having numerous polymerases in a single ZMW was not conducive to base calling (Problem 1).

A POSA would not have expected Petitioner’s RCR embodiment to produce

useable sequencing data due to the presence of multiple polymerases firing simultaneously in the ZMW (Problem 1). EX2014, ¶¶128-137; POR, 31-35. EX2014, ¶¶133-135. The Petition failed to account for this issue entirely, and the Reply offers no credible response.

Petitioner argues that “*typically* only one polymerase becomes bound to the bottom of the ZMW” and that additional polymerases, if present, “*generally* do not contribute signal...” Reply, 17 (citing EX2021). But EX2021 does not address Problem 1 because EX2021 only discloses using *SMRTbell templates*, which bind—at most—two polymerase molecules (one on each hairpin). EX2021, 10-11. In contrast, Petitioner’s RCR embodiment generates a smear of concatemer template sizes ranging from hundreds to over 3,000 bases long (*see* EX1021, FIG. 3). Dr. Larrea admitted at deposition that these putative templates would have contained *numerous* polymerase binding sites. Dr. Larrea annotated (in blue) RCR-generated concatemer figures with a range of 7, 11, or even 21 different polymerase binding sites. EX2072, 29:13-32:18, 91-94; EX2014, ¶¶128-137. Dr. Larrea’s annotated figures are produced below⁵:



⁵ These concatemers correspond to RCR products produced in Travers-2010, Figure 3.

EX2072, 92 (depicting seven polymerase binding sites produced from 3 loops around a SMRTbell).

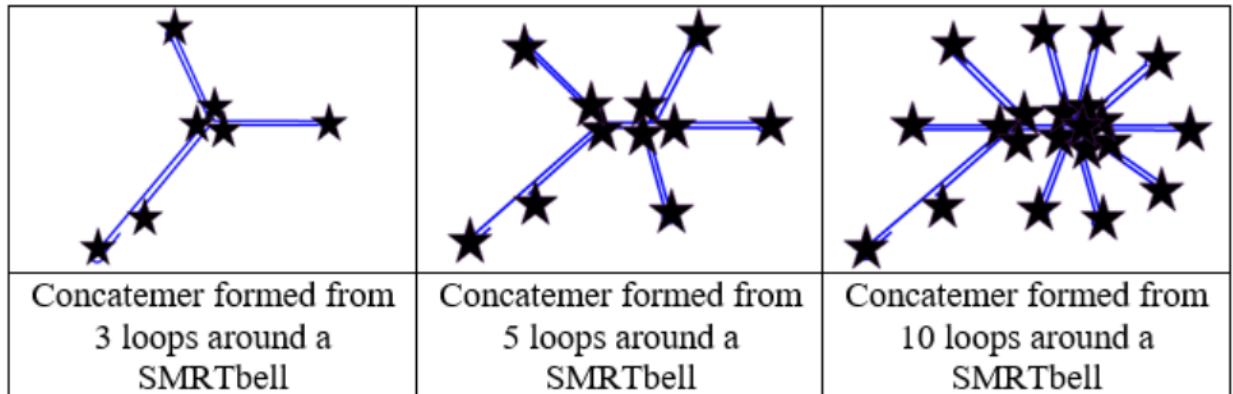


Id., 93 (depicting 11 polymerase binding sites produced from 5 loops around a SMRTbell).



Id., 94 (depicting 21 polymerase binding sites produced from 10 loops around a SMRTbell).

Petitioner also does not dispute that these RCR concatemers would form secondary structures as Dr. Satija demonstrated. EX1033, ¶¶29-34; EX1039, ¶30; EX2014, ¶188. Thus, placing Dr. Larrea's annotated polymerase binding sites (denoted with stars below) onto Dr. Satija's secondary structure figures further demonstrates why a POSA would have expected multiple polymerases to bind to the floor of the ZMW and render Petitioner's embodiment useless:



EX2014, ¶¶185-189 (annotated). Moreover, the polymerases in SMRT sequencing bind to the ZMW floor via biotin-streptavidin interaction, which Dr. Larrea admitted is a very “strong interaction.” EX2072, 37:2-9; EX1021, 2; EX2026, 2. Thus, when any of the multiple polymerases bound to a concatemer template comes in contact with the ZMW floor, it would be bound and held there. *Id.*

Petitioner implies that PacBio’s SMRT sequencing welcomes multiple polymerases per ZMW, and only “cautions” against “multiple templates” in the ZMW. Reply, 17-18 (citing EX1035, 39). Record evidence says otherwise. Petitioner’s reply exhibit “cautions” against “multiple *polymerase*-template complexes in the same ZMW” (i.e., *multiple polymerases* and multiple templates), because an “overloaded SMRT Cell” will impact “raw accuracy and read length.” EX1035, 39. EX1035 shows that with increased ZMW occupancy (“overloading”), there is a corresponding and dramatic *decrease in sequence accuracy*:

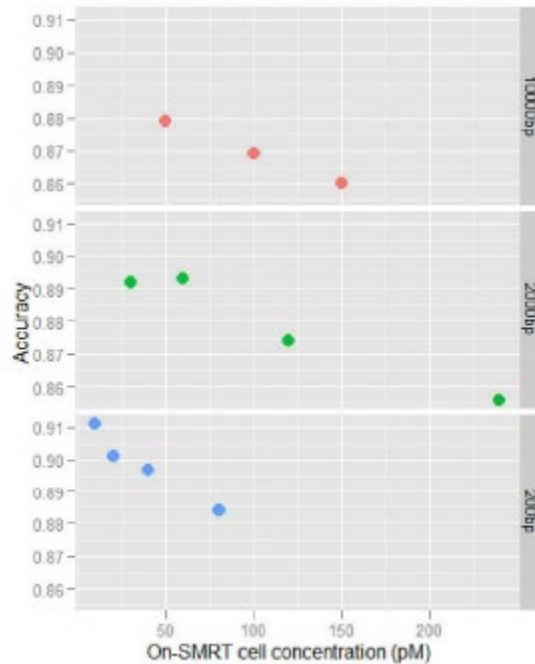


Figure 13 Effects of loading to accuracy with increasing On-SMRT Cell Concentration. Overloading affects raw accuracy and read length.

EX1035, 40, FIG. 13.

This is consistent with the understanding in the art, which consistently taught *avoiding* multiple polymerase molecules per ZMW. EX2030, 5 (seeking to “minimize contributions from *multiply occupied ZMWs*.”); EX2001, 4 (seeking “optimal loading” of ZMWs with “just one polymerase” per ZMW.); EX2026, Table S3. Additionally, PacBio’s Glossary describes three categories of “productivity” from ZMWs (P=0, P=1, and P=2), noting that multi-polymerase-occupied ZMWs are “*not conducive to base calling*.” EX2072, 97; *id.*, 41:12-18 (Larrea testifying that “no useable data was generated from that ZMW”). Indeed, having multiple templates—each with one or more polymerase—per ZMW is analogous to Petitioner’s RCR concatemer in a ZMW (multiple template copies

with multiple polymerases). *Id.*

This principle of SMRT sequencing is reflected in US2009/0024331 (“Tomaney”), which Travers-075 cites and incorporates by reference “in its entirety for all purposes.” EX1018, ¶¶135, 141; EX2072, 56:20-59:3, 132-195. Tomaney teaches *excluding* data from specific ZMWs when “*multiple[] polymerases* are sequencing in [the] ZMW” because those ZMWs will “*not provide useful data.*” EX2072, 58:9-59:3, 189 (¶¶178, 181); *see also, id.*, 174 (¶74), 182-183 (¶141). Dr. Larrea admitted he did not even consider Tomaney. EX2072, 57:8-13.

There is no dispute that the goal of loading polymerase/primer/SMRTbell complexes onto ZMWs was to obtain a Poisson distribution to “maximize” the number of “single polymerase-bound templates” per ZMW. EX2072, 33:18-34:8; EX2001, 4; EX2030, 4; EX2014, ¶156. A POSA would have readily appreciated that having numerous polymerases bound to each concatemer template (as in Petitioner’s embodiment) would obliterate the normal Poisson distribution for single polymerase occupancy. EX2001, 4; EX2030, 4; EX2014, ¶¶128-137.

Petitioner’s only proffered “evidence” for anyone purportedly desiring multi-polymerase ZMW occupancy is a single sentence taken out of context from EX1035, which states, “[t]he stoichiometric optimum for the polymerase:template ratio is 2 polymerases bound to each template molecule (one to each hairpin

adapter).” Reply, 16 (quoting EX1035, 34). This sentence merely reflects the optimum stoichiometric *ratio* for achieving Poisson distribution *with normal SMRTbell templates*—not large concatemers with *numerous* bound polymerase enzymes. Dr. Larrea states that this stoichiometric ratio can “maximize[]” the “*potential* for obtaining a sequence read for that template.” EX1033, ¶10. This stoichiometry becomes vastly more complicated (and unworkable) in Petitioner’s RCR embodiment, in which the concatemer template has *many* (and varied numbers of) polymerase binding sites. EX2014, ¶¶128-137; EX2072, 91-94. Even in reply, Petitioner never addresses how a POSA could determine the appropriate dilution of primer/polymerase in its RCR embodiment to arrive at a workable solution given the multiple (and varied number of) polymerase binding sites in its smear of concatemers.

Finally, Petitioner offers no rebuttal for the fact that a POSA would be unable to control *where* within the RCR concatemer the polymerases will initiate the sequencing reaction. POR, 55; EX2014, ¶¶164, 202. Dr. Larrea agreed on cross-examination that polymerase binding to the concatemers “would be stochastic” and that “there would be no way to control which of the binding sites bound polymerase over any other site.” EX2072, 32:10-18. Thus, in Petitioner’s embodiment, there would be no way to control read length or how many subreads would be sequenced. *Id.*

C. Petitioner’s new arguments do not resolve Problems 2 and 3.

In Reply, Petitioner argues that a POSA could have engaged in a variety of diffusion rate-control and template size-selection protocols to sift through the milieu of RCR concatemer sizes. Reply, 18-20. Petitioner’s newfound arguments are based on evidence specific to *SMRTbell templates*—not Petitioner’s smear of RCR concatemers. Even putting this technical oversight aside, Petitioner’s evidence still does not support its argument. For example, Travers-075 discloses using “ChromaSpin 1000” to remove only the smaller fragments. EX1018, ¶145. Dr. Larrea confirmed this at deposition, agreeing that ChromaSpin 1000 columns remove DNA molecules “<300 bp” and *retain* all DNA molecules “>1,350 bp.” EX2072, 50:18-51:9; *id.*, 108. EX1035’s discloses using “magnetic bead purification” to remove “hairpin dimers” and “AMPure PB beads” to remove “*ligation products smaller than 0.4 kb* (e.g., adapter dimers).” EX1035, 3, 24; EX2072, 45:9-15. Likewise, EX1036 discloses using “AMPure XP” beads to *retain* “fragments *greater than 100 bp*.” EX1036, 12; EX2072, 48:1-8. Thus, in each case, Petitioner’s proposed “size selection” techniques would retain a massive smear of RCR products and do nothing to resolve Problems 2 and 3.

Relying on Figure 3 of Travers-2010, Petitioner’s Reply also proposes “gel electrophoresis” as a size-selection technique. Reply, 19. But Travers-2010’s gel electrophoresis does not involve *size selection* at all. EX1021, 4. Travers simply

runs the reaction products on a gel for visualization to confirm the sequencing enzyme can operate on a SMRTBell template. *Id.* And as Dr. Larrea acknowledged at deposition, gel electrophoresis exposes the DNA to intercalating dyes and ultraviolet radiation. EX2072, 52:8-53:15; *id.*, 127. EX1035, however, expressly cautions *against* using DNA samples that have been “exposed to intercalating fluorescent dyes or ultraviolet radiation” in the PacBio workflow. EX1035, 5.

Petitioner also now argues that a POSA could *re-circularize* the linear RCR concatemer templates “to increase redundancy.” Reply, 20-21 (citing EX1020). This is improper new argument. 37 C.F.R. 42.23(b). Nowhere does the Petition propose re-circularization as part of its RCR embodiment. Petitioner’s Reply relies on EX1020 (the ’503 patent) for re-circularization, but the Petition only cites EX1020 for disclosures of consensus sequencing—nothing to do with amplification or re-circularization. Pet., 3, 40, 43, 47. Regardless, Petitioner still fails to explain why a POSA would have been motivated to engage in such an unnecessary and tedious library preparation process over the normal SMRT sequencing workflow, just to arrive back at circular templates *the POSA already had*. EX2014, ¶¶96-197.

D. Petitioner does not dispute that the RCR concatemers would permit multiple polymerase molecules to bind to the ZMW floor.

In discussing the template size issues of Problem 4, Petitioner again relies only on evidence pertaining to *SMRTbell templates*, and fails to grapple with the

secondary structures of the Petition's RCR concatemers. While *linear* SMRTbells of various sizes might be able to enter a tiny ZMW, such evidence says nothing about concatemer molecules forming complex structures. Petitioner relies on Travers-2010 and Travers-075, which only discuss the ability of *SMRTbell templates*, not RCR concatemers, to enter the ZMW. Reply, 22; EX1021, 1; EX2072, 28:16-21, 54:1-56:19; EX1018, ¶¶83, 85, 144, 150. Petitioner's EX1035 also only concerns SMRTbells. Reply, 23; EX1035, 35 ("*SMRTbell templates*"); 6 ("*SMRTbell library*"). Thus, in *each* case, Petitioner's evidence of "large templates" only pertains to long, linear *SMRTbells*, not large concatemers with complex secondary structures and numerous bound polymerase molecules. EX2014, ¶¶170-197.

Petitioner does not dispute that the RCR concatemers would indeed form these secondary structures. EX1033, ¶¶29-34; EX1039, ¶30. Nor does Petitioner dispute that the RCR concatemers would have numerous polymerase binding sites. EX2072, 30:4-32:18; *id.*, 91-94. And both parties agree that the structures fluctuate in solution. EX2014, ¶188; EX1037, 120:15-18; Reply, 23. Thus, Petitioner's argument that these structures are flexible *might* lessen their steric hindrance with regard to Problem 4, but it would have only exacerbated Problem 1. Such flexible, fluctuating structures would increase the likelihood that multiple biotinylated-polymerases would bind the bottom of the streptavidin-coated ZMW and produce

interfering signal. EX2072, 37:2-9; EX2014, ¶¶170-197.

VI. PETITIONERS INCONSISTENT CLAIM CONSTRUCTION POSITIONS SHOW ITS ARGUMENTS ARE NOT CREDIBLE

Petitioner failed to inform the Board that it argued certain terms of the '127 patent were indefinite during *Markman* proceedings in district court. POR, 10. EX2073, 13:1-20:11, 274-278. Those positions were rejected. POR, 10; EX2018, 15-20, 23-25. Additionally, Dr. Quackenbush and Guardant have recently argued in district court that claim 1's comparing, analyzing, and confirming steps are "indefinite" because they are allegedly step plus function elements. EX2073, 102:15-105:9, 369 (¶298). As such, Dr. Quackenbush's testimony should receive little weight because he failed to construe claims consistently and Guardant has not been forthright with the Board. 37 C.F.R. §42.104(b)(3).

VII. OBJECTIVE INDICIA WEIGH TOWARDS PATENTABILITY.

Petitioner does not dispute Patent Owner's evidence of industry praise, long-felt need, and unexpected results. POR, 68-74; EX2014, ¶¶225-244; Reply, 23-27. In fact, Petitioner failed to address the industry praise in GEN Edge (EX2065) entirely, and left Patent Owner's evidence of unexpected results unrebutted. Reply 23-27; EX1039, ¶¶32-39. Petitioner only disputes whether there is a nexus between Patent Owner's evidence and the challenged claims. Reply, 23.

Petitioner argues that Patent Owner's evidence is exclusively tied to "DCS of the Schmitt reference," which Petitioner alleges is an "unclaimed feature[]," and

further that the challenged claims are “so broad as to encompass the prior art.”

Reply, 23-25. This argument fails on multiple levels. First, Patent Owner’s objective indicia are not exclusively linked to “DCS of the Schmitt reference.” For example, the industry praise in GEN Edge—which Petitioner *completely failed to address in its Reply*—describes Patent Owner’s invention as “independently track[ing] both strands of individual DNA molecules and compar[ing] the results.” EX2065, 2. This is praise for *duplex sequencing*, but is not limited to SSCS:DCS methods. Petitioner ignores this.

Second, Petitioner’s argument that the claims “encompass the Travers Publications” is factually incorrect. *See supra*, Section III.A-III.C; POR, 11-18. Petitioner’s reliance on the Board’s institution decision in IPR2022-00816 is also misplaced, as that decision only addresses claim 1, *not* claims 2-9, 16, 18, or 19 that were discussed in the POR. IPR2022-00816, DI, 13; POR, 68-74. Petitioner’s reliance on Vogelstein (EX1022) also fails because Petitioner has not established that Vogelstein is prior art. Reply, 27; EX1039, ¶¶38-39. The Vogelstein PCT application was filed and published after the ’127 patent’s earliest priority date of March 20, 2012, and Petitioner has not shown that Vogelstein is entitled to benefit of either of its provisional applications.

Petitioner also applies an incorrect legal standard, requiring that objective indicia be exclusively tied to novel features of the claims, rather than the *invention*

as a whole. The Federal Circuit rejected this very argument in *WBIP, LLC v.*

Kohler Co., 829 F.3d 1317 (Fed. Cir. 2016). “While objective evidence of nonobviousness lacks a nexus if it exclusively relates to a feature that was ‘known in the prior art,’ the obviousness inquiry centers on whether ‘the claimed invention as a whole’ would have been obvious.” *Id.*, 1330; *see also, Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) (holding that objective indicia applies to the invention as a whole, rather than “prior art features” in isolation or unclaimed features).

Patent Owner’s evidence of industry praise, long-felt need, and unexpectedly superior results are for the claimed *invention as a whole* and are relevant objective indicia for at least claims 2-9, 16, 18, and 19. *WBIP*, 829 F.3d at 1330-1331. Patent Owner’s objective indicia have a nexus with the challenged claims, and Petitioner has failed to show otherwise. POR, 68-74; EX2014, ¶¶225-244.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Patent Owner's Sur-Reply complies with the type-volume limitation of 5,600 words, comprising 5,582 words, excluding the parts exempted by 37 C.F.R. § 42.24(c).
2. This Patent Owner's Sur-Reply complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Respectfully submitted,

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PATENT OWNER'S SUR-REPLY** and **EXHIBITS 2072-2073** were served in their entireties on May 24, 2023 upon the following parties via electronic mail:

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