Trials@uspto.gov
571-272-7822

Paper 47
Date: October 10, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.
UNIVERSITY OF WASHINGTON,
Patent Owner.

IPR2022-00817
Patent 10,760,127 B2

Before JOHN G. NEW, ZHENYU YANG, and TINA E. HULSE,
Administrative Patent Judges.

YANG, *Administrative Patent Judge*.

JUDGMENT

Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Dismissing Petitioner's Motion to Strike
37 C.F.R. § 42.5

Denying in Part and Dismissing in Part Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

I. INTRODUCTION

Guardant Health, Inc. ("Petitioner") filed a Petition (Paper 3, "Pet."), seeking an *inter partes* review of claims 1–30 of U.S. Patent No. 10,760,127 B2 (Ex. 1001, "the '127 patent"). University of Washington ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp."). We instituted trial to review the challenged claims. Paper 14 ("DI").

Thereafter, Patent Owner filed a Response to the Petition (Paper 22, "PO Resp."), Petitioner filed a Reply to Patent Owner's Response (Paper 26, "Reply"), and Patent Owner filed a Sur-reply to Petitioner's Reply (Paper 34, "Sur-reply").

Petitioner filed a Motion to Exclude (Paper 36); Patent Owner opposed (Paper 37); and Petitioner filed a reply in support of the Motion to Exclude (Paper 39). Petitioner also filed a Motion to Strike (Paper 38); and Patent Owner filed an opposition to the Motion to Strike (Paper 44).

An oral hearing for this proceeding was held on June 15, 2023, and the transcript of that hearing is of record. *See* Paper 45 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6 and issues this Final Written Decision pursuant to 35 U.S.C. § 318 and 37 C.F.R. § 42.73. For the reasons provided below, we find Petitioner has not shown, by a preponderance of the evidence, the unpatentability of any of the challenged claims.

A. Related Matters

According to the parties, the '127 patent is asserted against Petitioner in *TwinStrand Biosciences, Inc. v. Guardant Health, Inc.*, 1-21-cv-01126 (D. Del.). Pet. 11–12; Paper 6, 1.

Petitioner also filed a petition in IPR2022-00816, challenging the same claims of the '127 patent. We denied that petition. IPR2022-00816, Paper 16. Petitioner requested both panel rehearing and Precedential Opinion Panel (POP) review. IPR2022-00816, Papers 17, 18. After the POP panel declined to review, we denied Petitioner's request for panel rehearing. IPR2022-00816, Papers 21, 22.

The parties are also involved in several other *inter partes* review proceedings. *See* Papers 19, 21.

B. The '127 Patent

The '127 patent relates to methods of lowering the error rate of massively parallel DNA sequencing using duplex consensus sequencing ("DCS"). Ex. 1001, code (54), 17:8–10.

The '127 patent states massively parallel DNA sequencing "offer[ed] the unique ability to detect minor variants within heterogeneous mixtures." *Id.* at 1:32–41. It notes the rapid development of clinical applications of deep sequencing in "prenatal screening for fetal aneuploidy, early detection of cancer and monitoring its response to therapy with nucleic acid-based serum biomarkers." *Id.* at 1:42–49 (internal citations omitted). Deep sequencing, however, had limitations, including "a practical limit of detection . . . imposed by errors introduced during sample preparation and sequencing," resulting in "approximately 1% of bases [being] incorrectly identified." *Id.* at 1:60–2:7. The '127 patent states "[t]his background level of artifactual heterogeneity establishes a limit below which the presence of true rare variants is obscured." *Id.* at 2:8–10.

The '127 patent acknowledges several attempts aimed at improving the accuracy and sensitivity of sequencing. *Id.* at 2:11–32. But, according to

the '127 patent, "significant technical artifacts" still result in error rates far higher than the "true mutation frequency." *Id.* at 2:32–38.

The '127 patent states "[i]t would be desirable to develop an approach for tag-based error correction." *Id.* at 2:63–64. According to the '127 patent, its approach "reduces or eliminates artifactual mutations arising from DNA damage, PCR errors, and sequencing errors; allows rare variants in heterogeneous populations to be detected with unprecedented sensitivity; and . . . capitalizes on the redundant information stored in complexed double-stranded DNA." *Id.* at 2:64–3:2.

C. Illustrative Claims

Among the challenged claims, claims 1 and 22 are independent. They are illustrative of the claimed subject matter and, with the Certificate of Correction incorporated,[1] are reproduced below.

> 1. A method of sequencing DNA comprising:
>
> a) attaching adapters to double-stranded DNA fragments to generate a plurality of partially-complementary, asymmetrical double-stranded adapter-DNA molecules, wherein the adapters comprise barcodes selected from a plurality of distinct barcode sequences;
>
> b) amplifying original strands of at least a portion of the double-stranded adapter-DNA molecules to produce first and second strand copies;
>
> c) sequencing a plurality of first and second strand copies to obtain first and second strand sequence reads for at least a portion of the adapter-DNA molecules; and
>
> d) for at least some of the adapter-DNA molecules comprising barcodes—

[1] The Certificate of Correction was issued on March 9, 2021, before the filing of the Petition.

confirming the presence of at least one sequence read derived from each of the original first and second strands of the adapter-DNA molecules;

comparing at least one of the confirmed first and second strand sequence reads to a reference sequence; and

analyzing one or more correspondences between the at least one of the confirmed first and second strand sequence reads and the reference sequence to identify a sequence variation.

Ex. 1001, 37:31–52.

22. A method of sequencing DNA comprising:

a) attaching partially single-stranded adapters comprising barcodes selected from a plurality of distinct barcode sequences to double-stranded DNA fragments obtained from a bodily sample, wherein attachment of the adapters to double-stranded DNA fragments generates a library of tagged double-stranded adapter-DNA molecules;

b) amplifying strands from a plurality of the double-stranded adapter-DNA molecules in the library to produce strand copies;

c) sequencing a plurality of the strand copies to obtain strand sequence reads comprising one or more barcode sequences and DNA fragment-specific information; and

d) for at least some of the double-stranded adapter-DNA molecules in the library—

grouping the strand sequence reads into families based on i) the barcode sequence, and ii) DNA fragment-specific information;

collapsing a plurality of strand sequence reads within the families to provide a consensus sequence for each of the at least some of the double-stranded DNA molecules in the library;

comparing the consensus sequence to a reference sequence; and

> analyzing one or more correspondences between the consensus sequence and the reference sequence to identify a sequence variation.

Id. at 39:56–40:25.

D. Instituted Challenges to Patentability

We instituted trial to determine whether the challenged claims are unpatentable based on the following bases:

Claim(s) Challenged	35 U.S.C. §[2]	References
1–10, 12, 15–28	103	Travers '075,[3] Travers 2010[4]
11	103	Travers '075, Travers 2010, NEB Expressions[5]
13, 14, 29, 30	103	Travers '075, Travers 2010, McCloskey[6]

In support of their respective positions, Petitioner relies on the Declarations of John Quackenbush, Ph.D. (Exs. 1002, 1039) and Andres

---

[2] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the '127 patent has an effective filing date before March 16, 2013, the pre-AIA version of § 103 applies.

[3] Travers et al., US Patent Publication No. 2009/0298075 A1, published December 3, 2009 (Ex. 1018, "Travers '075").

[4] Travers et al., *A flexible and efficient template format for circular consensus sequencing and SNP detection*, 38 NUCLEIC ACIDS RESEARCH e159 (2010) (Ex. 1021, "Travers 2010").

[5] Evans et al., *DNA Damage the major cause of missing pieces from the DNA puzzle*, NEW ENGLAND BIOLABS (2007) (Ex. 1014, "NEB Expressions").

[6] McCloskey et al., US Patent Publication No. 2007/0020640 A1, published January 25, 2007 (Ex. 1023, "McCloskey").

Larrea, Ph.D. (Ex. 1033); and Patent Owner relies on the Declaration of Rahul Satija, D. Phil. (Ex. 2014).

II. ANALYSIS

A. Principles of Law

To prevail in this *inter partes* review, Petitioner "shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR*, 550 U.S. at 406.

A party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted).

In an obviousness determination, the presence or absence of a motivation to combine references, the presence or absence of a reasonable

expectation of success, as well as what a reference teaches and whether it teaches toward or away from the claimed invention, are all questions of fact. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196–97 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the "type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Here, Petitioner asserts that

> a person of ordinary skill in the art by March 20, 2012 would typically have an advanced degree, such as a Ph.D., with research experience in genomics, molecular biology, bioinformatics, or a related field, or could have less education but significant professional experience in one or more of these fields.

Pet. 11 (citing Ex. 1002 ¶¶ 46–47).

Patent Owner states that for the purposes of this proceeding, it does not dispute Petitioner's definition of the skill level. PO Resp. 5 (citing Ex. 2014 ¶¶ 28–30).

After reviewing the record, we adopt Petitioner's definition as it is consistent with the prior art's demonstration of the level of ordinary skill in the art at the time of the invention.

C. Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b). Under this standard, we construe the claim term "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (holding that the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application").

1. Adapters

Petitioner argues that we do not need to expressly construe any term in this proceeding. Pet. 13. Nonetheless, Petitioner seeks to "provide[] context for understanding the scope of the term 'partially-complementary, asymmetrical double-stranded adapter-DNA molecules.'" *Id.* Specifically, Petitioner asserts that the challenged claims "encompass adapter-DNA molecules generated by attachment of Y-shaped or U-shaped adapters comprising barcodes to each end of double-stranded DNA molecules." *Id.* at 15 (citing Ex. 1002 ¶¶ 51–52). According to Petitioner,

> standard Illumina Y-shaped adapters are partially single-stranded (the arms of the Y) and also are partially-complementary (the trunk of the Y). When the adapters are ligated to a double-stranded DNA molecule, the resulting adapter-DNA molecule is partially-complementary and asymmetric . . . The same is true when using hairpin adapters, which also are partially single-stranded and partially-complementary adapters.

Id. at 14 (citing Ex. 1002 ¶¶ 48–50). Patent Owner does not dispute these assertions. *See generally* PO Resp.

Based on the complete record, we agree with Petitioner the claims encompass Y-shaped adapters and hairpin adapters, provided that they comprise "barcodes selected from a plurality of distinct barcode sequences," which is also required by the claims.

2. Sequence of Steps

In the Decision to Institute, we agreed with Patent Owner that "(i) the claimed methods require that the amplification step occurs after adapter attachment; but before the sequencing step; and (ii) the sequencing step requires sequencing the amplified adapter-DNA products from the amplification step." DI 10 (citing Prelim. Resp. 8); *see also id.* ("[W]e find Patent Owner's argument concerning the sequential order of the steps is supported by the claim language and the disclosures in the specification." (citing Ex. 1001, 37:31–52 (claim 1), 39:56–40:25 (claim 22), 3:21–27, 15:27–34, Fig. 1)). Patent Owner reiterates its argument on this issue in its Response. PO Resp. 5–8.

Petitioner does not dispute the sequence of the recited steps. *See* Tr. 19:1–8 (Petitioner's counsel confirming "the amplification step has to be performed and completed before the sequencing step" and stating "[t]hat is the interpretation that [Petitioner] followed in mapping to the prior art").

Based on the complete record, we see no reason to change our construction of sequence of the recited steps.

3. First and Second Strand Sequence Reads

Claim 1 recites "sequencing a plurality of first and second strand copies to obtain first and second strand sequence reads for at least a portion of the adapter-DNA molecules." Ex. 1001, 37:39–41. Patent Owner asserts that the term "sequence reads," being plural, "indicates multiple and distinct sequencing reactions, each of which results in a sequence read, rather than a single sequencing reaction that produces a single sequence read containing multiple subparts (which a POSA would know are *subreads*, not sequence reads)." PO Resp. 9 (citing Ex. 2014 ¶¶ 60–65). According to Patent Owner, both the '127 patent Specification and Travers support its argument. We are not persuaded.

Patent Owner argues that, in a few instances, the '127 patent discloses "sequence reads" as corresponding to "multiple and distinct sequencing reactions." *Id.* (citing Ex. 1001, 4:12–18, 4:45–49, 9:5–9, 9:11–12). Those disclosures, however, relate to "only one method for making the invention and do[] not automatically lead to finding a clear disavowal of claim scope." *Cont'l Cirs. LLC v. Intel Corp.*, 915 F.3d 788, 797 (Fed. Cir. 2019). Patent Owner does not point to, and we cannot find, any intrinsic evidence that would limit "sequence reads" as Patent Owner contends.

Patent Owner also relies on Travers as extrinsic evidence that supports its argument. PO Resp. 9. Specifically, Patent Owner contends that Travers "refers to the sense and antisense target DNA sequences as *subreads*, which are distinct from the 'raw read sequence' or 'raw read' that comprises all of the subreads physically linked together." *Id.* (citing Ex. 1021, 2). Patent Owner, however, ignores that Travers '075 refers to the sequence of a sense or antisense strand as a "sequence read," and not a subread. *See* Ex. 1018

¶ 61. As a result, we find insufficient evidence to support Patent Owner's proposed construction of "sequence read" as requiring "multiple and distinct sequencing reactions."[7]

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). Based on the complete record, we see no need to expressly address any other claim term.

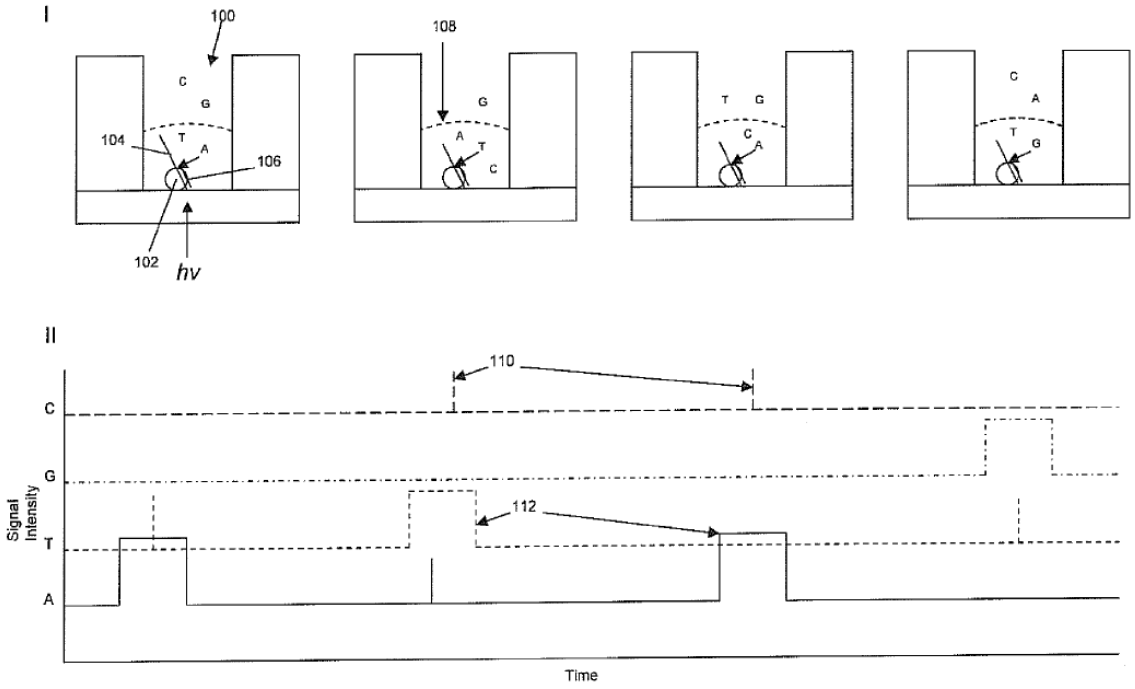
D. Relevant Disclosures of Prior Art

1. Travers '075

Travers '075 is a published U.S. patent application listing Pacific Biosciences ("PacBio") as the assignee. Ex. 1018, code (73). It relates to compositions and methods for nucleic acid sequencing, which include "template constructs that comprise double stranded portions in a partially or completely contiguous constructs, to provide for redundant sequence determination through one or both of sequencing sense and antisense strands, and iteratively sequencing the entire construct multiple times." *Id.*, Abstract.

Specifically, Travers '075 teaches Single Molecule Real Time (SMRT) sequencing, which is schematically illustrated in Figure 1A, reproduced below. *Id.* ¶ 43.

[7] Patent Owner argues that "the technical problems discussed throughout [the Patent Owner Response] apply even under Petitioner's apparent construction" of the term "first and second strand sequence reads." PO Resp. 62 n.6.



Id., Figure 1A.

Figure 1A shows the SMRT sequencing process. *Id.* ¶ 21. In Panel I, "a nucleic acid synthesis complex comprising a polymerase enzyme 102, a template sequence 104 and a primer sequence 106 complementary to a portion of the template sequence 104, is provided immobilized within a confined illumination volume (indicated by the dashed line 108), e.g., resulting from the evanescent optical field resulting from illumination of a zero mode waveguide 100." *Id.* ¶ 43.

Travers '075 teaches that "[t]he reaction mixture surrounding the complex contains the four different nucleotides (A, G, T and C) each labeled with a spectrally distinguishable fluorescent label attached through its terminal phosphate group." *Id.* ¶ 44. It explains the fluorescent label of free nucleotide provides a very short signal, whereas a nucleotide incorporated by the polymerase in a primer extension reaction provides a longer signal. *Id.* According to Travers '075, "[b]y identifying longer pulses of different

spectral characteristics, one can detect, in real time, the identity of each incorporated base as it is being incorporated." *Id.* ¶ 45.

In one embodiment, as shown in Figure 2B, Travers '075 teaches a circular template comprising a double-stranded portion linked by two single-stranded portions. *Id.* ¶ 50. Figure 2B is reproduced below.

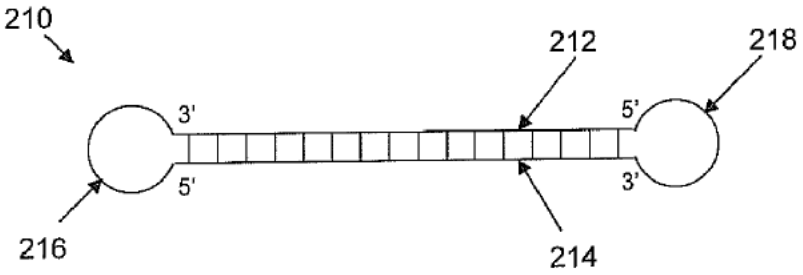


Figure 2B

Figure 2B illustrates an exemplary embodiment of a template construct used in Travers '075. *Id.* ¶ 22. "Sequence 210 includes a double stranded portion again comprised of two complementary segments 212 and 214." *Id.* ¶ 50. "[T]he 3′ end of segment 212 is joined to the 5′ end of segment 214 via oligonucleotide 216 in a first single stranded portion," and "the 5′ end of segment 212 is joined to the 3′ end of segment 214 via linking oligonucleotide 218, providing a second single stranded portion." *Id.* This construct yields "a completely contiguous or circular template sequence." *Id.*

In Figure 3B, Travers '075 teaches applying the SMRT sequencing process to the circular template of Figure 2B. Figure 3B is reproduced below.

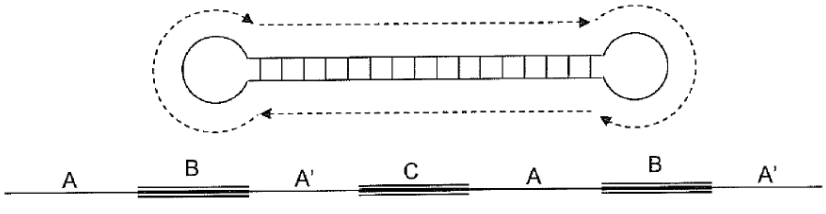


Figure 3B

Figure 3B illustrates redundant sequencing using the construct shown in Figure 2B. *Id.* ¶ 23.

> As shown, a sequencing process that is primed at one end, e.g., primed within one linking oligonucleotide sequence, e.g., linking oligonucleotide 218 of FIG. 2, proceeds along the first or sense strand 214, again providing the nucleotide sequence A of that strand. The sequence process then proceeds around the first linking oligonucleotide, e.g., linking oligonucleotide 216 from FIG. 2, to provide the nucleotide sequence B of that segment of the template. Proceeding along the antisense strand, e.g., segment 212 of FIG. 2B, provides the nucleotide sequence A', which is again, complementary to sequence A. The sequencing process then continues around the template providing the nucleotide sequence for the other linking oligonucleotide, e.g., linking oligonucleotide 218 of FIG. 2B, where the illustrated sequencing process began, providing nucleotide sequence C.

Id. ¶ 55. Travers '075 teaches carrying out the SMRT sequencing reaction on a zero mode waveguide ("ZMW") array. *Id.* ¶ 141. According to Travers '075, the surface of the ZMW well is coated with streptavidin, which allows immobilization of a biotinylated primer/template/polymerase complex via a streptavidin bridge. *Id.* ¶¶ 41, 146.

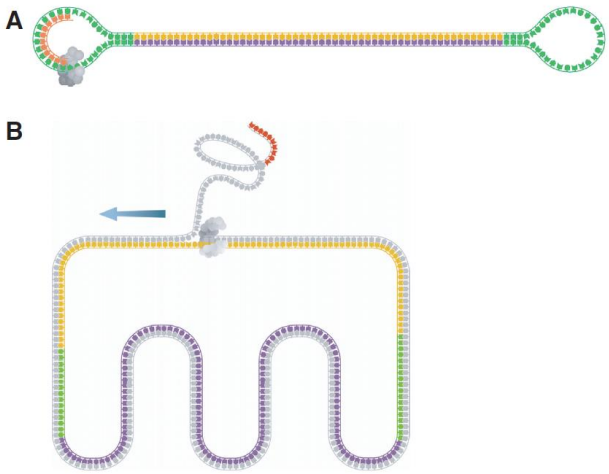
Travers '075 states that although the circular templates shown in Figure 2B are "primarily, and preferably, for use directly as templates for, e.g., sequencing applications," they "may also serve as intermediate structures in the preparation of templates that provide for sequence redundancy." *Id.* ¶ 122. Specifically, it describes using the circular template "in a rolling circle replication process to produce concatamer[8] molecules that

[8] Patent Owner use the spelling "concat*e*mer" in its papers, whereas Petitioner uses both "concat*e*mer" and "concat*a*mer." There is no dispute

include repeating copies of both the sense and antisense strands of the originating double stranded segment included within the circular nucleic acid." *Id.* (footnote added). "These replicated products," Travers '075 continues, "may then be employed directly as template molecules in a template dependent sequencing process." *Id.*

2. Travers 2010

Travers 2010 is a publication authored by PacBio employees. Ex. 1021, 1. It is undisputed that the two Travers references teach the same SMRT sequencing methods. Travers 2010 describes a SMRTbell template, designed for SMRT sequencing. *Id.*, Abstract. Figure 1, reproduced below, shows a SMRTbell template:



Id. at 3. Figure 1 is a schematic of a SMRTbell template.

As shown in Figure 1A, the SMRTbell molecule "consists of a double-stranded region (the insert) flanked by two hairpin loops. The hairpin loops present a single-stranded region to which a sequencing primer can

---

that both refer to the same thing. In this Decision, we use "concat*e*mer," except when quoting from the references or papers.

bind (orange)." *Id.* "Structurally, this format resembles a linear double-stranded molecule, and yet it is topologically circular." *Id.*, Abstract.

Travers 2010 teaches applying the circular molecule to SMRT sequencing. *Id.* at 4. Figure 1B shows that

> As a strand-displacing polymerase (gray) extends a primer from one of the hairpin loops, it uses one strand as the template strand and displaces the other. When the polymerase returns to the 5´-end of the primer, it begins strand displacement of the primer and continues to synthesize DNA (moving in the direction of the blue arrow).

Id. at 3. As a result, the sequence is derived from both sense- and anti-sense strands. *Id.*

Travers 2010 teaches immobilizing DNA polymerases and primed DNA templates onto the ZMW arrays for SMRT sequencing. *Id.* at 2. According to Travers 2010, "[p]olymerization is confined to the bottom of nanostructures known as ZMWs through a streptavidin/polymerase complex bound to a biotinylated surface." *Id.* at 4.

3. NEB Expressions

NEB Expressions teaches that deamination of cytosine and oxidation of guanine are two common types of DNA damage that may be present in typical DNA samples. Ex. 1014, 1–2. It states that the commercial product "PreCR™ Repair Mix" is "a cocktail of enzymes formulated to repair damaged DNA *in vitro* prior to PCR." *Id.* at 3. According to NEB Expressions, "PreCR™ Repair Mix" can repair deaminated cytosine and oxidized guanine. *Id.*

4. McCloskey

McCloskey teaches "the use of barcodes and batch-stamps for verifying the authenticity of PCR products and other sequence information."

Ex. 1023 ¶ 2. Specifically, it teaches labeling nucleic acid molecules with "distinct sequence tags prior to PCR amplification" to authenticate a nucleic acid sequence, which allows "identification of valid sequences, and distinguishes the valid sequences from contaminants and redundant sequences." *Id.* ¶ 5. McCloskey teaches bar-coded and batch-stamped hairpin linkers. *Id.* ¶ 15.

McCloskey further teaches "a second sequence that provides a random barcode." *Id.* ¶ 21. According to McCloskey, "[t]he length of the second sequence is sufficient to provide, with high probability, a unique identity to each target nucleic acid molecule in the sample prior to amplification," and may be "between 3 and 30 nucleotides, such as between 5 and 25 nucleotides or between 7 and 13 nucleotides." *Id.*

E. Alleged Obviousness over the Travers References

Petitioner asserts that claims 1–10, 12, and 15–28 of the '127 patent would have been obvious over the Travers references. Pet. 19–58. After reviewing the entire record developed at trial, and as explained below, we determine Petitioner has not shown, by a preponderance of the evidence, that the Travers references render the challenged claims obvious.

We focus our analysis on independent claims 1 and 22. Petitioner contends that the combination of Travers 2010 and Travers '075 teaches each limitation of claims 1 and 22. Pet. 20–37. Petitioner also contends that an ordinarily skilled artisan would have had a reason to look to both references and would have had a reasonable expectation of success in combining their teachings. *Id.* at 19–20.

Patent Owner argues that Petitioner fails to show the Travers references teach step (c) of claim 1, which recites obtaining "first and second

strand sequence reads." PO Resp. 11. Patent Owner also argues that Petitioner fails to show the Travers references teach step (d) of claim 22, which recites "grouping the strand sequence reads into families based on i) the barcode sequence, and ii) DNA fragment-specific information." *Id.* at 13 (italics omitted). Moreover, Patent Owner contends that an ordinarily skilled artisan would not have modified the teachings of the two Travers references to arrive at the claimed method. *Id.* at 18–59. Patent Owner further challenges Petitioner's showing of a reasonable expectation of success. *Id.* at 61–65.

Petitioner argues that "Patent Owner acknowledged that virtually every aspect of the claimed subject matter is disclosed by Travers." Pet. 17 (citing Ex. 1001, 33:22–25; Ex. 1024, 551). We do not need to determine whether Patent Owner had acknowledged the Travers references teach each limitation of the challenged claims *separately*, because even if that is the case, we still "must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success." *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015). And for the reason explained below, we find Petitioner has not met its burden in demonstrating that an ordinarily skilled artisan would have had a reason to combine the teachings of the two Travers references, and would have had a reasonable expectation of success in arriving at the claimed method.

1. Introduction

Especially relevant to our analysis, the Travers references teach applying SMRT sequencing methods to SMRTbell templates. *See, e.g.*, Ex. 1018 ¶¶ 50–55, Fig. 3; Ex. 1021, 3–5. In addition, Travers '075 teaches that

> the structurally circular nucleic acid segments described herein[] may be used as templates in a rolling circle replication process to produce concatamer molecules that include repeating copies of both the sense and antisense strands of the originating double stranded segment included within the circular nucleic acid. These replicated products may then be employed directly as template molecules in a template dependent sequencing process.

Id. ¶ 122.

Petitioner relies on the Travers references' teachings of rolling circle replication ("RCR") of SMRTbell templates to produce concatemer molecules as meeting step (b) of claims 1 and 22.[9] Pet. 24–25 (citing Ex. 1018 ¶ 122; Ex. 1021, Fig. 1, Fig. 4). Petitioner argues that subjecting the concatemer molecules to SMRT sequencing meets step (c) of claims 1

[9] Petitioner also quotes paragraph 83 of Travers '075 as stating template molecules are "subjected to a polymerase mediated sequencing process." Pet. 24 (quoting Ex. 1018 ¶ 83). To the extent Petitioner relies on this statement as meeting step (b) of claims 1 and 22, we disagree. As explained above, the claim language requires, and Petitioner does not dispute, that "the amplification step has to be performed and completed before the sequencing step." *Supra* Section II.C.2. The "polymerase mediated sequencing process," discussed in paragraph 83 of Travers '075, however, refers to SMRT sequencing, a sequencing-by-synthesis approach that does not require amplification. *See* Ex. 1021, 5 (stating SMRT sequencing "does not depend on amplification"); Ex. 2004, Table 1 (showing PacBio's sequencing involves "[n]o amplification").

and 22. *See* DI 19 (citing Pet. 25); Tr. 5:8–6:6 (Petitioner's counsel confirming the obviousness challenge relies on sequencing the amplified concatemer molecules on PacBio sequencing platform); *see also* Pet. 6 ("This petition relies on a patent publication and a paper describing sample preparation and sequencing methods developed at PacBio.").

We therefore focus our analysis on whether Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had a reason to use PacBio's SMRT sequencing platform to sequence the concatemer molecules, which are produced with the RCR process of SMRTbell templates, and would have had a reasonable expectation of success in doing so.

Petitioner states that "Travers '075 describes the PacBio workflow (*e.g.*, sample preparation, sequencing, and bioinformatic analysis of sequence reads)," and Travers 2010 "disclose[s] applications of the PacBio workflow described in Travers '075." Pet. 19–20; *id.* at 7 (stating Travers 2010 "describes applications of the sequencing method described in Travers '075" (citing Ex. 1021, Abstract, 7, Fig. 1)). Petitioner argues that "[a] POSA would have been motivated to look to both Travers '075 and the Travers Paper because together the references provide descriptions of the same PacBio methodology." *Id.* at 20. Pointing out that the SMRT sequencing "methodologies described in the Travers Publications became commercially available in 2010," Petitioner further argues that "a POSA would have been motivated and expected success in combining the teachings of the Travers Publications because each describe[s] aspects of the PacBio workflow." *Id.* (citing Ex. 1002 ¶¶ 51–63; Ex. 1026).

Patent Owner contends Petitioner fails to show "*why* a POSA would have been motivated to combine the PacBio SMRT sequencing applications of Travers-2010 with the unnecessary and problematic RCR embodiment mentioned in Travers-'075." PO Resp. 22–23. Patent Owner also asserts that Petitioner does not meet its burden to show reasonable expectation of success with the "scant analysis" in the form of a single, conclusory statement. *Id.* at 61.

Specifically, Patent Owner argues that using SMRT sequencing to sequence concatemers produced with the RCR process of SMRTbell templates introduces critical technical problems, which render Petitioner's proposed RCR embodiment "unworkable" because it is "incompatible with SMRT sequencing on zero mode waveguides (ZMWs)." *Id.* at 3–4, 23–55, 62–63. These technical problems, Patent Owner argues, do not exist when sequencing the circular SMRTbell molecules with PacBio's SMRT sequencing platform. *Id.* at 55. They, however, would render the concatemer molecules in Petitioner's RCR embodiment "unsequenceable in SMRT sequencing ZMWs." *Id.* at 54. Thus, Patent Owner concludes Petitioner's RCR embodiment is hindsight driven because "a POSA never would have sought out Petitioner's proposed embodiment in the first place, much less implemented it in Travers 2010's workflow with a reasonable expectation of success." *Id.* at 3.

On this record, and as explained below, we find Patent Owner's arguments more persuasive.

2. Analysis

As an initial matter, we note that, in our Decision to Institute, we did not address Patent Owner's arguments regarding motivation to combine

and/or modify and reasonable expectation of success. DI 20. That is because, we explained, based on the then-current record, we understood paragraph 122 of Travers '075 as "teach[ing] a straightforward application of SMRT sequencing to concatemer molecules." *Id.* We, however, "encourage[d] the parties to further address the relevant issues of all challenges to fully develop the record during trial." *Id.* at 22. We also cautioned the parties that "[o]ur view with regard to any conclusion reached in the [Decision to Institute] could change upon further development of the record during trial." *Id.* at 23.

And now, with a fully developed record, we have gained a better appreciation of the facts in this matter. We start our factual examination with a summary of the SMRT sequencing technology again.

PacBio's SMRT sequencing is a sequencing-by-synthesis approach. Ex. 2003, 5. Its Template Preparation and Sequencing Guide provides the SMRT sequencing workflow. Ex. 1035, 1. Relevant to our discussion, "[a] SMRTbell™ template is a double-stranded DNA template capped by hairpin loops at both ends." *Id.* at 2; *see also id.* at 22 ("[B]lunt hairpins are ligated to repaired fragment ends."). "Prior to sequencing, primer must be annealed to the SMRTbell template, and then DNA polymerase is bound to the annealed templates." *Id.* at 30. Eventually, "[p]olymerase-bound SMRTbell templates" are loaded for sequencing. *Id.* at 38.

"At the heart of PacBio's new DNA sequencing instrument is zero-mode waveguide (ZMW) technology." Ex. 1026, 675. "ZMWs are tiny nanoholes, 70 nm in diameter by 100 nm in depth, where a single molecule

of the DNA polymerase enzyme can be placed to directly observe it sequencing a strand of DNA." *Id.* Specifically,

> [w]ith PacBio's SMRT technology, the polymerase enzyme is affixed at the bottom of a ZMW well. Using a single DNA molecule as a template, the polymerase incorporates fluorescently labeled DNA bases as it reads the template. Each base has a different fluorescent dye, thereby emitting a signal out of the ZMW. A detector reads the fluorescent signal and names the base based on the color of the detected signal. Once the base is added, the fluorescent tag is cleaved by the polymerase.

Id.

At the time of the '127 patent's priority date, it was known the raw error rate of SMRT sequencing "is significantly higher than with any other [then-]current sequencing technology." Ex. 2003, 5; *see also* Ex. 2004, 9 ("SMRT sequencing has high error rates."). Creating a SMRTbell template by ligating a hairpin linker to each end of the target DNA, and then repeatedly sequencing the same molecule can overcome the high error rate. Ex. 2003, 5.

The Travers references teach directly sequencing SMRTbell template with SMRT sequencing. *See, e.g.*, Ex. 1018, Abstract, ¶ 55, Fig. 3B; Ex. 1021, Abstract, 3–4, Fig. 1, Fig. 4. Travers '075 also teaches an alternative embodiment, which amplifies the SMRTbell template with an RCR process "to produce concatemer molecules that include repeating copies of both the sense and antisense strands" of the target DNA in the SMRTbell molecule. Ex. 1018 ¶ 122.

a. Alleged Admission by Patent Owner

As explained above, in this case, we must determine whether an ordinarily skilled artisan would have had a reason to use PacBio's SMRT

sequencing platform to sequence the concatemer molecules, which are produced with the RCR process of SMRTbell templates, and would have had a reasonable expectation of success in doing so. According to Petitioner, Patent Owner has previously admitted that the invention of the '127 patent encompasses, and the Travers references teach, subjecting the RCR replicated concatemer molecules to SMRT sequencing. Pet. 17–19, 25–26, 32 (citing Ex. 1001, 10:63–11:18, 15:29–39; Ex. 1024, 551); Reply 2 (citing Ex. 1001, 10:61–11:18, claims 10, 13).

For example, Petitioner contends that during the prosecution of a related application, "Patent Owner acknowledged that virtually every aspect of the claimed subject matter is disclosed by Travers." Pet. 17. Petitioner also asserts that the challenged claims and the Specification of the '127 patent "critically rely on Travers for descriptive support," and "plainly confirm" sequencing RCR concatemers using PacBio sequencing platform. Reply 2 (citing Ex. 1001, claims 10, 13, 10:61–11:18); *see also* Paper 36, 5 (arguing "claim 1 plainly encompasses use of U-shaped adapters and rolling circle amplification, and broadly encompasses sequencing on the Pacific Biosciences sequencing platform" (citing Ex. 1001, claims 10, 13)), 6 (arguing "the specification specifically instructs use of Travers' adapters, amplification, and continuous loop sequencing as suitable for use with the disclosed methods (citing Ex. 1001, 10:63–11:15, 15:29–39)). According to Petitioner, these "admissions and concessions are fatal to the claims of the '127 patent." Reply 2. We are not persuaded by Petitioner's arguments.

First, Patent Owner did not make a "fatal" admission during prosecution. Instead, the then-applicant acknowledged that Travers '075 teaches "linking sense and antisense strands of a double-stranded nucleic

acid molecule together with a 'linking segment' (e.g., using exogenous hairpin adapters . . .), and amplification of these linked original strands 'to ensure complete, and preferably redundant sequencing of the entire template.'" Ex. 1024, 551 (citing Ex. 1018 ¶¶ 51, 83,[10] italics removed). This statement addresses Travers '075's teaching of constructing the SMRTbell template and the subsequent sequencing-by-synthesis SMRT sequencing. It is unrelated to sequencing the RCR replicated concatemer molecules.

Indeed, step (c) of claims 1 and 22 requires "sequencing *a plurality of . . . strand copies*." Ex. 1001, 37:40, 40:8 (emphasis added). Yet, the applicant emphasized Travers '075 teaches subjecting SMRTbell templates to SMRT sequencing "such that 'a *single template molecule* . . . can be sequenced in one integrated process.'" Ex. 1024, 551 (quoting Ex. 1018 ¶ 54); *see also id.* (stating the applicant "disagrees" with the examiner's allegation in an office action that Travers '075 teaches "template constructs may be prepared from PCR products to provide a population of identical molecules from which to generate sequence reads" (quoting Ex. 1024, 498)). Thus, the applicant did not admit during prosecution that the Travers references teach sequencing the RCR replicated concatemer molecules using PacBio's SMRT sequencing.

Second, Patent Owner has not made such an admission with respect to claims 10 and 13 of the '127 patent. Each of claims 10 and 13 depends from claim 1. Claim 10 specifies that the amplification may be through RCR; and claim 13 specifies that the adapters may be U-shaped (i.e., hairpin) adapters.

---

[10] The parties explain, and we agree, that the citation to paragraph 81 appears to be a typo, and the correct citation should be to paragraph 83. *See* Pet. 24 n.2; PO Resp. 65 n.7.

Ex. 1001, 39:1–4, 39:16–17. These additional limitations, however, are recited in two separate, unrelated claims. Thus, claims 10 and 13 of the '127 patent do not show that Patent Owner admitted its invention encompasses sequencing RCR replicated concatemer molecules using PacBio's SMRT sequencing.

Third, the '127 patent Specification does not support Petitioner's argument either. The '127 patent Specification cites Travers 2010 twice. In the first instance, it states "ligation and amplification with circularizing 'linkers' (i.e. hairpin linkers affixed to both ends of a fragment) has been demonstrated as a step in the Pacific Biosciences sample preparation workflow [49]." Ex. 1001, 10:63–66. Reference 49 is Travers 2010. *Id.* at 33:22–25.

Travers 2010 teaches that a SMRTbell template includes "a linear double-stranded DNA fragment." Ex. 1021, 3. "At either end, the double strand is capped with a hairpin sequence, such that there are no free 5′- or 3′-ends." *Id.*; *see also id.* at 2 (describing ligating hairpin linkers to the target DNA). The ultimate sequencing is a polymerase-mediated step. *Id.* at 3 ("When incubated in the presence of a DNA polymerase, the enzyme can bind to the primer/template complex, leading to a sequencing-productive complex."); Fig. 1B (describing SMRT sequencing as the strand-displacing polymerase "uses one strand as the template strand and displaces the other").

Thus, when discussing Travers 2010 in column 10 of the '127 patent (Ex. 1001, 10:63–66), the step of ligation with hairpin linkers refers to the construction of the SMRTbell template, whereas "amplification" refers to the sequencing-by-synthesis nature of SMRT sequencing. After all, as the Template Preparation and Sequencing Guide explains, "Pacific Biosciences'

template preparation process *does not use amplification techniques*." Ex. 1035, 5 (emphasis). Petitioner does not sufficiently explain, and we do not find, that this discussion relates to sequencing the concatemer molecules produced by RCR replication.

The '127 patent discloses "deliberate ligation of 'U-shaped' adaptors or hairpin linkers" to both ends of the target DNA to produce closed circles. Ex. 1001, 11:3–8. Citing Travers 2010 again, the '127 patent Specification states "closed circles may be pre-amplified using rolling circle amplification ***or*** serve as the substrate for continuous loop sequencing [49]." *Id.* at 11:13–15 (emphasis added).

The "closed circles" described in the '127 patent Specification refer to the SMRTbell templates in Travers 2010. Ex. 1021, Abstract (stating the SMRTbell template is "topologically circular"). Travers 2010 teaches that, in SMRT sequencing, a strand-displacing polymerase extends a primer from one of the hairpin loops in the SMRTbell templates, "us[ing] one strand as the template strand and displaces the other. When the polymerase returns to the 5′-end of the primer, it begins strand displacement of the primer and continues to synthesize DNA." *Id.* at 3; *see also* Ex. 2001, 4 (stating an "appealing feature" of SMRT sequencing is that "through the strand-displacing capability of the polymerase . . . closed circular templates can be sequenced multiple times by a DNA polymerase in a single run"). Thus, when citing Travers 2010 to discuss "closed circles may . . . serve as the substrate for continuous loop sequencing" (Ex. 1001, 11:13–15), the '127 patent refers to directly subjecting SMRTbell templates to SMRT sequencing.

Of course, the '127 patent also discloses that "closed circles may be pre-amplified using rolling circle amplification." *Id.* at 11:13–14. This is consistent with the teachings in Travers '075. *See* Ex. 1018 ¶ 122 (stating although SMRTbell molecules are "primarily, and preferably, for use directly as templates for, e.g., sequencing applications," they "may also serve as intermediate structures," through, for example, "a rolling circle replication process to produce concatemer molecules," which are later sequenced). Critically, however, the '127 patent discloses RCR as an *alternative* to SMRT sequencing, and not applying SMRT sequencing to the concatemer molecules produced by RCR. Ex. 1001, 11:13–15 (using the disjunctive "or" to link RCR and SMRT sequencing).

In addition to twice citing Travers '075, the '127 patent also mentions PacBio's sequencing platform, i.e., SMRT sequencing:

> In one embodiment, each end of the double-stranded target nucleic acid molecule is ligated to an SMI adaptor molecule. The double-stranded target nucleic acid complex is then amplified by a method known in the art (e.g., a PCR or non-PCR method known in the art), resulting in a set of uniquely labeled, amplified SMI-target nucleic acid products. These products are then sequenced using any *suitable method* known in the art including, but not limited to, the Illumina sequencing platform, ABI SOliD sequencing platform, Pacific Biosciences sequencing platform, 454 Life Sciences sequencing platform, Ion Torrent sequencing platform, Helicos sequencing platform, and nanopore sequencing technology.

Id. at 15:27–39 (emphasis added).

Petitioner contends that this passage of the '127 patent "describ[es] 'non-PCR' amplification methods and 'Pacific Biosciences sequencing platform' as within the scope of the invention." Pet. 15 (citing Ex. 1001, 15:29–39). Although the '127 patent *separately* discloses RCR

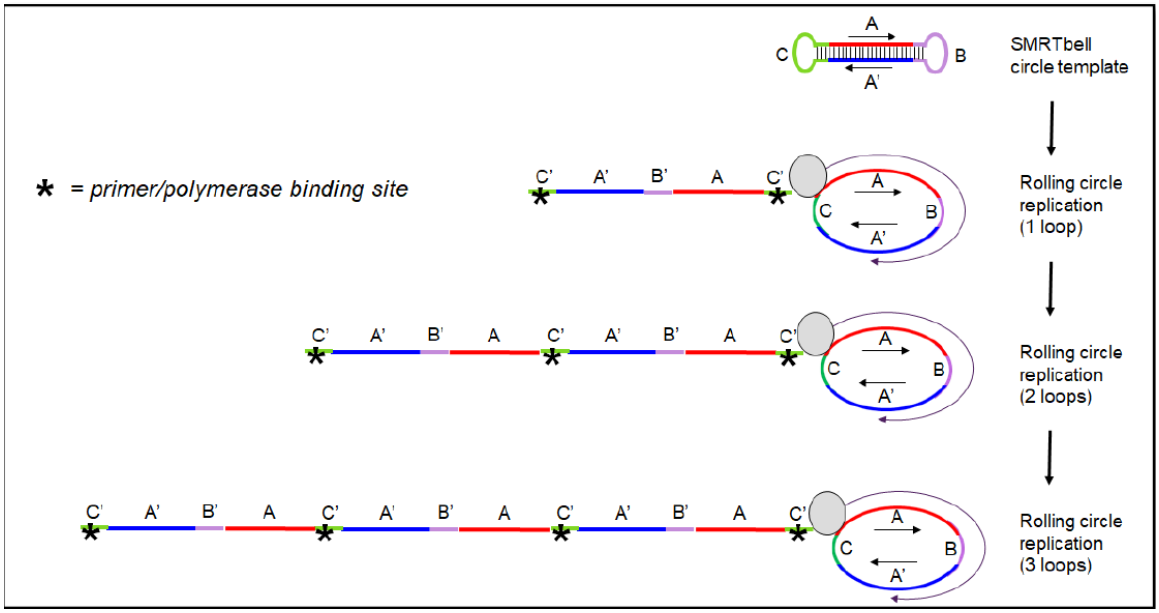
(i.e., non-PCR amplification) and PacBio's SMRT sequencing, Petitioner does not sufficiently explain, and we do not find, that the Specification of the '127 patent it relies on here describes using PacBio's sequencing platform to sequence RCR replicated concatemer products.

Instead, the '127 patent lists multiple amplification methods, and independently, multiple sequencing methods. Ex. 1001, 15:29–39. It, however, does not specify which sequencing method is "suitable" for which amplified product. *Id.* That is because, Patent Owner asserts, "[a] POSA reading the '127 patent would have known which sequencing methods were suitable for certain template preparation methods and unsuitable for others." PO Resp. 64 (citing Ex. 2014 ¶ 215). And an ordinarily skilled artisan would have known, according to Patent Owner, that RCR replicated concatemer products are "unsequenceable in SMRT sequencing ZMWs." *Id.* at 54; *see also id.* at 29 (arguing that RCR is "incompatible with SMRT sequencing"); Ex. 2014 ¶ 215 (Dr. Satija testifying that "a POSA would have understood that rolling circle replication was not suitable in the SMRT sequencing methods"). For the reasons explained below (*see infra*, Section II.E.2.b), we agree with Patent Owner and Dr. Satija. Thus, we find Patent Owner has not admitted in column 15 of the '127 patent that its invention encompasses, or the Travers references teach, sequencing RCR replicated concatemers with PacBio's SMRT sequencing.

b. Technical Issues with SMRT sequencing RCR Replicated Concatemers

Patent Owner contends that "Petitioner's hindsight-based RCR embodiment . . . would have created critical problems when used in SMRT sequencing." PO Resp. 30 (citing Ex. 2014 ¶¶ 122–127).

According to Patent Owner, one of the technical problems that would render Petitioner's proposed RCR embodiment unworkable is each RCR replicated concatemer molecule has multiple primer/polymerase binding sites. PO Resp. 31 (citing Ex. 2014 ¶¶ 128–137). Dr. Satija illustrates the products after one to three rounds of RCR replication of a SMRTbell template as follows:



Ex. 2014 ¶ 178.

The figure above shows RCR replication of a circular SMRTbell template. As shown in the figure, A and A′ represent the two complementary strands of the target DNA, and B and C represent the two hairpin linkers. The figure shows that one round of RCR replication produces a molecule with one copy of A and A′ each and two primer/polymerase binding sites, two rounds of RCR replication produces a molecule with two copies of A and A′ each and three primer/polymerase binding sites, and three rounds of RCR replication produces a molecule with three copies of A and A′ each and four primer/polymerase binding sites.

Patent Owner asserts that "the SMRT sequencing workflow requires distributing the primer/template/polymerase ternary complex at one complex per ZMW well." PO Resp. 32 (citing Ex. 2001, 3; Ex. 2002, 4; Ex. 2014 ¶ 130; Ex. 2021, 4). According to Patent Owner, "[i]f two or more polymerases generate synthesis products in a single ZMW, the multiple florescent pulses from the different polymerases would be indistinguishable and produce unusable data." *Id.* (citing Ex. 2001, 4; Ex. 2014 ¶ 133). And that, Patent Owner contends, is exactly what would happen in Petitioner's RCR embodiment, because "the linear concatemer template would contain multiple, repeating copies of the primer/polymerase binding site," which would result in unreadable sequence data. *Id.* at 33–34 (citing Ex. 2014 ¶¶ 132–137).

Petitioner does not dispute that each RCR replicated concatemer molecule has multiple primer/polymerase binding sites. *See, e.g.*, Ex. 1002 ¶ 114 (Dr. Quackenbush testifying that "[a] person of ordinary skill in the art would have understood that the concatemer molecules would have the same sequence (e.g., barcode and target molecule)"). Nonetheless, according to Petitioner, the alleged "multiple primer/polymerase binding sites" problem "is directly contradicted by the express content of the prior art, including the Travers Publications and the manufacturer's sequence guide." Reply 15 (citing Ex. 1033 ¶¶ 8, 9; Ex. 1039 ¶ 28).

Specifically, Petitioner argues that the Travers references teach "templates with more than one primer/polymerase binding sites." *Id.* (citing Ex. 1018 ¶¶ 14, 17, 67, 103, 105, 144, Fig. 7; Ex. 1021, 3; Ex. 1036, 12–13; Ex. 1037, 117:19–24). Petitioner also refers to PacBio's Template Preparation Guide for stating that "[t]he stoichiometric optimum for the

polymerase:template ratio is 2 polymerases bound to each template molecule (one to each hairpin adapter)." *Id.* at 16 (citing Ex. 1035, 34).

In addition, Petitioner asserts that "[t]emplates with multiple polymerases routinely generate useable reads. This is because typically only one polymerase becomes bound to the bottom of the ZMW." *Id.* at 17 (citing Ex. 2021, 1, 4, Fig. 6). Petitioner contends that the activity of the polymerase bound to the bottom of the ZMW is detected to provide sequencing data, whereas any additional polymerases complexed with the template "generally do not contribute signal" because they are outside the range of the excitation beam. *Id.* (citing Ex. 1033 ¶¶ 16–18; Ex. 2021, 4, Fig. 4).

We are not persuaded by Petitioner's arguments. First, the prior art references Petitioner relies on relate to sequencing SMRTbell templates; specifically, they teach two polymerase binding sites in the two hairpin adapters per SMRTbell molecule, one on each end of the target molecule. *See* Ex. 1021, Fig. 1. They do not speak to concatemers with multiple polymerase binding sites interspersed along the molecule.

Second, as explained above, a two-round RCR already generates three polymerase binding sites. *See* Ex. 2014 ¶ 178. Thus, even if we were to agree with Petitioner that the optimal stoichiometric ratio for SMRTbell templates applies to RCR produced concatemers, the polymerase to concatemer template ratio is at least three, i.e., 50% higher than the number Petitioner points to.[11] *See* Reply 16 (citing Ex. 1035, 34).

[11] The product of one round of RCR replication has only two polymerase binding sites. But, with only one copy of A and A′ each, it would not satisfy

Third, and most importantly, the prior art does not support Petitioner's arguments. The SMRT sequencing "approach is based on eavesdropping on a single DNA polymerase molecule working in a continuous, processive manner." Ex. 2021, 1 ("Within each [ZMW] chamber, a single DNA polymerase molecule is attached to the bottom surface."). Indeed, in SMRT sequencing,

> polymerase molecules are randomly distributed among the ZMWs, leading to a Poisson distribution of occupancy. At optimal loading, the distribution is 36.8% empty ZMWs, 36.8% with just one polymerase, and 26.4% with two or more. In this experiment, ~35% of the ZMWs produced traces indicative of single DNA polymerase occupancy, of which 82% produced full-length reads.

Ex. 2001, 4 (internal citation omitted).

Other prior art confirms this observation that polymerases are randomly distributed among the ZMWs such that only one third of the ZMWs contain a single polymerase. *See* Ex. 2002, 4 ("A limit to throughput was imposed by the stochastic nature of immobilizing DNA polymerases at the bottom of each ZMW. In the published study, roughly one-third of the ZMWs in the array contained a single DNA polymerase and had the capacity to generate full-length sequencing reads."); Ex. 2004, 9 ("The polymerases are randomly immobilized among the ZMWs, leading to only a third of them being occupied by a single polymerase. The rest of the ZMWs are either empty or contain two or more polymerases, which dramatically reduces the potential capacity of the ZMW array.").

---

the limitation of "sequencing a *plurality* of first and second strand copies" as required in step (c) of claim 1.

In other words, contrary to Petitioner's assertion that "typically only one polymerase becomes bound to the bottom of the ZMW" (Reply 17), in fact, a significant portion of the ZMWs (26.4%) have two or more polymerases immobilized within (Ex. 2001, 4). And these ZMWs, again, contrary to Petitioner's assertion, do not produce usable reads. *Id.* (teaching the yield could be improved by "plac[ing] a single polymerase in each ZMW").

This is because, prior art explains, "DNA polymerization is a stochastic process, where intervals between incorporation events typically vary. Thus, a population of polymerases even acting on the same template would quickly become out of phase with each other." Ex. 2021, 2. Thus, in view of the prior art, we are not persuaded that "the binding of multiple polymerases on a single template . . . was not a problem." *See* Reply 17.

Petitioner acknowledges that it is beneficial to avoid loading "multiple polymerase-template complexes in the same ZMW." *Id.* (citing Ex. 1035, 39). Citing the Larrea Declaration, Petitioner contends that loading of multiple templates "is easily mitigated." *Id.* at 18 (citing Ex. 1033 ¶ 19; Ex. 1035, 39). We are not persuaded by this argument either.

Dr. Larrea testifies that one of the two methods to "easily mitigate[]" loading multiple templates into a single ZMW is "bioinformatically trimming the read to only the high-quality region (HQR)." Ex. 1033 ¶ 19. Dr. Larrea, however, provides no support for this testimony. In fact, he does not even explain what a "high-quality region (HQR)" is. We, thus, accord little weight to this testimony. *See Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 (August 24, 2022) (precedential) (holding

"conclusory and unsupported" declaration testimony is entitled to little weight).

The other method to "easily mitigate[]" loading multiple templates into a single ZMW, according to Dr. Larrea, is "choosing an appropriate loading concentration." Ex. 1033 ¶ 19 (citing Ex. 1035, 39). PacBio's Template Preparation and Sequencing Guide indeed instructs an ordinarily skilled artisan to "[c]hoose the concentration that yields the most data output at an acceptable accuracy." Ex. 1035, 39. That advice, however, is directed to sequencing SMRTbell templates on PacBio's platform (*see generally* Ex. 1035), and does not apply to sequencing RCR produced concatemers. This is because each concatemer molecule includes multiple copies of the target sequence. *See* Ex. 1002 ¶ 114. Thus, even when only a single concatemer molecule is loaded into a ZMW at the optimal concentration, such a molecule still includes "multiple templates" and multiple polymerase binding sites.

Our understanding of this aspect of SMRT sequencing is supported by the prior art. Indeed, Travers '075 teaches preparing a template for sequencing to "prevent concatamerization" of the target DNA before ligation of the hairpin adapters. Ex. 1018 ¶ 105; *see id.* ¶ 103 (teaching "processes that reduce undesired concatamerization" of the target DNA); ¶ 106 (teaching methods to "provide protections against concatamerization" so that "concatamerization of the template fragments . . . may be avoided"). Thus, in view of the prior art, we are not persuaded that, in the context of sequencing RCR produced concatemers, loading of "multiple templates" is "easily mitigated" by "choosing an appropriate loading concentration." *See* Reply 18; Ex. 1033 ¶ 19.

In sum, we agree with Patent Owner that the multiple polymerase binding sites throughout the concatemer molecule "would have created a critical problem with SMRT sequencing's single-molecule design," which "would have dissuaded a skilled artisan from combining the RCR embodiment mentioned in Travers-'075 with Travers-2010." PO Resp. 23 (citing Ex. 2014 ¶¶ 96–100), 31 (citing Ex. 2014 ¶¶ 128–137).

And even if an ordinarily skilled artisan would have pursued sequencing RCR produced concatemers on PacBio's SMRT platform, we agree with Patent Owner that Petitioner has not met its burden to show the required reasonable expectation of success. The reasonable expectation of success requirement "refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). The challenged claims require amplification before the sequencing step. *See supra* Section II.C.2. Petitioner points to the Travers references' teachings of RCR produced concatemers as meeting this limitation. *See supra* Section II.E.1. Petitioner's analysis on reasonable expectation of success, including the allegation that Patent Owner's previous statements amount to concessions on this issue, however, is directed to sequencing SMRTbell templates, and not concatemers. *See supra* Section II.E.2.a.

In contrast, Patent Owner has provided evidence to show that an ordinarily skilled artisan would have "recognized the futility of attempting to sequence this multi-primed, multi-polymerase concatemer multi-complex in the SMRT sequencing ZMW array." PO Resp. 33 (Ex. 2014 ¶¶ 134–136). This is because, Patent Owner explains

> [t]he SMRT sequencing photodetector would be presented with numerous, concurrent nucleotide flashes occurring from the multiple, simultaneous polymerase extension reactions taking place in each ZMW. . . . These concurrent nucleotide flashes would be detected not as amplification of the signal, but rather as readings of different nucleotides all at once and therefore the order of the nucleotides (i.e., the actual sequence) would be impossible to determine.

PO Resp. 33–34 (citing Ex. 2014 ¶¶ 134–137; Ex. 1018 ¶¶ 45, 141; Ex. 1021, 4–5) (italics removed).

Petitioner does not specifically address this issue, presumably because Petitioner is of the view that "typically only one polymerase becomes bound to the bottom of the ZMW." Reply 17. But, data of the prior art show a significant portion of the ZMWs have two or more polymerases immobilized within. Ex. 2001, 4. Weighing the evidence, we are persuaded by Patent Owner's argument that, because signals coming from different polymerases "would create a jumbled mess," "a POSA would *not* have had a reasonable expectation of successfully practicing Petitioner's RCR embodiment." PO Resp. 35 (citing Ex. 2014 ¶ 136), 62 (citing Ex. 2014 ¶¶ 211–213).

Patent Owner contends that there are other technical issues that create significant problems if applying SMRT sequencing to RCR produced concatemers. For example, Patent Owner argues an RCR reaction "results in a smear of product sizes representing a vast size difference in potential templates for a sequencing reaction." *Id.* at 35–38 (citing Ex. 1021, Fig. 3; Ex. 2014 ¶¶ 139–144; Ex. 2036, 2, Fig. 3; Ex. 2037, Fig. 6). Among these differently sized products, Patent Owner continues, longer DNA molecules diffuse less efficiently than smaller DNA molecules. *Id.* at 38–40 (citing Ex. 2014 ¶¶ 145–149; Ex. 2039, Table 1, Fig. 1; Ex. 2040, 4; Ex. 2041, 3; Ex. 2056, 20).

Patent Owner explains that, in SMRT sequencing, DNA templates "are delivered to ZMWs via a random diffusion process." PO Resp. 40 (citing Ex. 2023, 5, italics removed). Thus, according to Patent Owner, two problems arise from the diffusion bias: (1) "the majority of potentially useable ZMW would be occupied by smaller DNA templates, without sufficient redundancy for resequencing" (*id.* at 38–41 (citing Ex. 2014 ¶¶ 145–164; Ex. 2023, 5; Ex. 2039, Table 1, Fig. 1; Ex. 2040, 4, Fig. 1; Ex. 2041, 3; Ex. 2056, 20; Ex. 2067, 11–12)), *see also id.* at 43 ("A POSA would have known that the smaller DNA products, however, would not provide a sufficient number of target DNA copies to be able to re-sequence the target DNA sufficiently."); and (2) "[w]hile the larger RCR concatemers *might* contain multiple copies of the target DNA, they would be outcompeted for ZMW occupancy by the smaller products" (*id.* at 44 (citing Ex. 2014 ¶¶ 165–169; Ex. 2041, 3; Ex. 2039, Fig. 1; Ex. 2040, Fig. 1)). Patent Owner cites to several references published around the critical date to support these arguments. *See id.* at 41–42 (citing Ex. 2005, 7; Ex. 2028, 1; Ex. 2042, 4; Ex. 2046, Fig. S4); *see also id.* at 41 n.3 (arguing that evidence with a post-filing date can be used to show the state of the art in general and an artisan's understanding of the prior art) (citing Ex. 2043, 3; Ex. 2044, 3).

Petitioner counters that there were "known and routine methods" to address the alleged problems related to "the presence of different sized molecules and diffusion bias favoring smaller template molecules for faster loading into ZMW." Reply 18 (citing Ex. 1033 ¶ 21; Ex. 1037, 40:2–5). According to Petitioner, an ordinarily skilled artisan would have simply followed protocols in PacBio's Template Preparation Guide as well as teachings in the Travers references and other prior art to "eliminate" the

problems resulting from diffusion bias. *Id.* at 18–20 (citing Ex. 1018 ¶¶ 145, 150; Ex. 1021, Fig. 3; Ex. 1033 ¶¶ 22–24; Ex. 1035, 3, 24, 27, 35, 38, 48; Ex. 1036, 12; Ex. 1037, 37:13–23, 43:16–45:3; 50:1–51:5; Ex. 1039 ¶ 29; Ex. 2014 ¶ 29).

In addition, Petitioner contends that "[l]oading bias is only a bias, it does not mean that larger templates are not loaded into any ZMW and sequenced." *Id.* at 20 (citing Ex. 1033 ¶¶ 25, 26; Ex. 1035, 35). Thus, Petitioner argues "Pacific Biosciences sequencing platforms would still generate useable sequence even if rolling circle amplification produced a range of concatemer sizes." *Id.* at 21 (citing Ex. 1033 ¶ 28).

On this issue, we find Patent Owner's argument more persuasive. First, it is undisputed that RCR products vary significantly in size. *See* Ex. 1021, 4, Fig. 3 (showing sizes from about 500 to 3,000 bp); *see also* Ex. 2036, 543 (stating the RCR products "generally exhibit a wide, essentially continuous distribution over length and therefore cannot be resolved by gel electrophoresis yielding a broad smear of the high molecular weight DNAs"). It is also undisputed that loading of templates into ZMWs is size dependent with small ones loading better than large ones. Ex. 1035, 35.

Second, although Petitioner points to several "known and routine methods" for size selection, those methods remove only the smaller sized polynucleotides. *See* Ex. 1018 ¶ 145 (Travers '075 stating ChromaSpin 1000 removes "any [SMRTbell] templates that contained no insert or short inserts"); Ex. 1035, 3 (PacBio's Template Preparation and Sequencing Guide teaching using the magnetic bead purification to remove the "hairpin dimers"), 24 (using AMPure PB bead purification to remove "ligation products smaller than 0.4 kb (e.g., adapter dimers)"); Ex. 1036, 12 (teaching

AMPure XP removes small fragments and "fragments greater than 100 bp were retained").

Petitioner also suggests gel electrophoresis as an "effective size selection means." Reply 19 (citing Ex. 1021, Fig. 3). As an initial matter, Figure 3 of Travers 2010 does not involve size selection; instead, as Patent Owner correctly points out, it "runs the reaction products on a gel for visualization to confirm the sequencing enzyme can operate on a SMRTBell template." Sur-reply 24–25 (Ex. 1021, 4). More importantly, PacBio's Template Preparation and Sequencing Guide explains that "[a]ny DNA damage (e.g., abasic sites, nicks, interstrand crosslinks) or contaminants (e.g., single-stranded DNA, RNA, proteins, dyes, or salts) present in the input material will impair performance of the system." Ex. 1035, 5. As a result, it specifically cautions against exposing DNA sample to "intercalating fluorescent dyes or ultraviolet radiation," which would be necessary when using gel electrophoresis for size selection. *Id.*

As Petitioner recognizes, PacBio's SMRT sequencing protocol "highly recommend[s]" selecting sequencing templates of "the same size (+/- 10%) to minimize loading bias." Reply 18–19 (citing Ex. 1035, 35); *see also* Ex. 1035, 35 (teaching addressing loading bias "is particularly important when sequencing different PCR amplicon sizes"). Yet, the methods Petitioner identifies do not limit the size variation among the RCR produced concatemers to this level, or even close to it.

Third, even if we agree with Petitioner that diffusion bias does not preclude generating useable sequence from RCR products with a wide range of sizes (*see* Reply 20), it is at least a matter that an ordinarily skilled artisan would have been cognizant of. On their own, issues resulting from diffusion

bias may not sufficiently dissuade an artisan to pursue Petitioner's RCR embodiment; together with the problem associated with multiple polymerases discussed above, however, they cast further doubt upon the reason to sequence RCR produced concatemers on PacBio's platform.

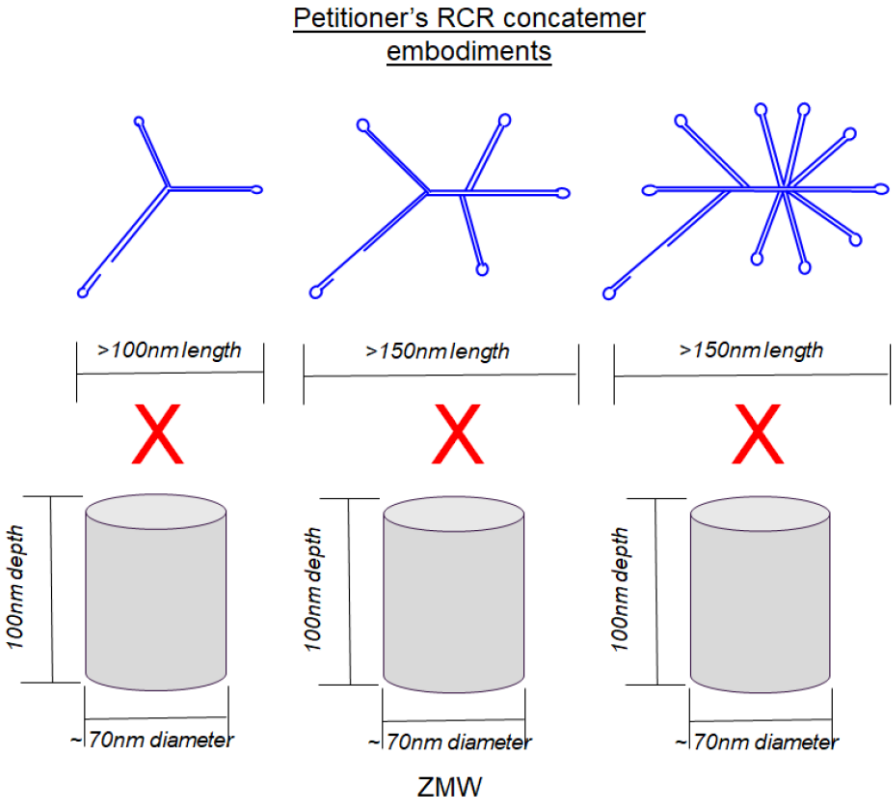
Similarly, we find the narrow diameter of ZMWs is another constraint that an ordinarily skilled artisan would have considered. It is undisputed that "a ZMW is a hole, tens of nanometers in diameter." Ex. 2021, 1; *see also* Ex. 2031, 1 ("ZMWs are tiny nanoholes, 70 nm in diameter by 100 nm in depth."). Patent Owner argues that an RCR generated concatemer molecule has "repeating complementary stretches of DNA," which "would hybridize to form complex secondary structures that would have significant difficulties even fitting into the narrow ZMW wells for SMRT sequencing." PO Resp. 48 (citing Ex. 2014 ¶ 179).

Petitioner contends this alleged problem does not exist because it is "based on a false premise" that the large concatemer molecules "assume rigid conformations that prevent them from entering ZMW." Reply 23. Instead, Petitioner emphasizes that the conformation of DNA molecules "fluctuate in solution." *Id.* (citing Ex. 1033 ¶ 34; Ex. 1037, 120:15–18; Ex. 1039 ¶ 30; Ex. 2014 ¶ 188). Moreover, Petitioner argues this alleged problem "is directly contradicted by the content of the prior art," including the Travers references and PacBio's Template Preparation and Sequencing Guide. *Id.* at 21–22 (citing Ex. 1018 ¶¶ 83, 85, 144, 150; Ex. 1021, 1, 5, Fig. 4B; Ex. 1033 ¶¶ 29–33; Ex. 1035, 6, 35; Ex. 1039 ¶ 30).

We, again, find Patent Owner's argument more persuasive. We do so even though we agree with Petitioner that the prior art references "expressly describe sequencing far larger templates and 'no evidence of an intrinsic

limit in the size of template.'" *Id.* at 22 (quoting Ex. 1021, 1). That is because the prior art references are specifically directed to SMRTbell templates, and do not discuss RCR produced concatemers with repeating complementary stretches of DNA. *See* Ex. 1018 ¶¶ 144, 150, Fig. 16; Ex. 1021, 1.

For concatemers, Dr. Satija "performed in-silico DNA structure modeling with the same template sequences disclosed in Travers 2010," and showed that "repeating concatemer copies of DNA will form complex secondary and tertiary structures." Ex. 2014 ¶¶ 180–189. One of the schematics provided by Dr. Satija is reproduced below.



The figure above is a cropped schematic "depict[ing] the large concatemers shown to scale with the size of the ZMWs." *Id.* ¶ 188. For this schematic, Dr. Satija "used the structures formed from the concatemer after

3 full loops." *Id.* Dr. Satija testifies that "the concatemers would have difficulties physically fitting within the narrow wells of Travers '075 and Travers 2010." *Id.* We find Dr. Satija's testimony credible, because he explained in detail the underlying facts, methodology, and data before opining on the issue. *See id.* ¶¶ 180–184.

In its Reply, Petitioner does not address the secondary structures formed by the self-hybridization of the repeating complementary stretches of DNA. And, contrary to Petitioner's assertion, Patent Owner and Dr. Satija do not argue that the concatemers "assume rigid conformations." *See* Reply 23. Indeed, Dr. Satija testifies that

> a POSA would understand that the precise three-dimensional structure of the folded concatemer molecule would also *fluctuate in solution*. Therefore, any individual dimension could span at least two arms of the starshaped structure. A POSA would therefore not have expected these concatemer molecules to readily fit in the ZMW wells even when considering the tertiary structures of these molecules.

Ex. 2014 ¶ 188 (emphasis added).

Travers 2010 teaches that when "deciding on a format for SMRT™ sequencing, a number of factors were considered," including, among others, "uniformity of structure and compatibility with ZMW geometry." Ex. 1021, 3. Thus, we find the combination of the ZMWs' narrow diameter and the concatemers' complex structures further undermines Petitioner's position that an ordinarily skilled artisan would have had a reason to sequence the RCR produced concatemer molecules on PacBio's SMRT sequencing platform.

Petitioner faults Patent Owner for arguing RCR embodiment is inferior than sequencing SMRTbell templates. *See* Tr. 17:4–7 (Petitioner's counsel arguing that there "seems to be a suggestion that superiority should

be established when there are multiple embodiments of this requirement that, you know, one has to be demonstrated as superior to the other").

To the extent Patent Owner's argument may be construed this way, we reject that argument. But even though the rationale to combine or modify prior art teaching need not be "the *best* option," it still must be "a *suitable* option." *PAR Pharm.*, 773 F.3d at 1198. Here, Patent Owner has produced sufficient evidence to show that, because of a multitude of technical issues, PacBio's SMRT sequencing platform is not a suitable method to sequence RCR produced concatemers. In other words, Petitioner has not persuaded us that an ordinarily skilled artisan would have had a reason to carry out its RCR embodiment with a reasonable expectation of success.

3. Summary

In sum, Petitioner has not met its burden to show that an ordinarily skilled artisan would have had a reason to sequence RCR replicated concatemers on PacBio's sequencing platform with a reasonable expectation of success. Thus, Petitioner has not shown the Travers references render the claims 1–10, 12, and 15–28 obvious.[12]

F. Other Grounds

Claim 11 depends from claim 1. Petitioner asserts that claim 11 would have been obvious over the combination of Travers '075, Travers 2010, and NEB Expressions. Pet. 58–60.

[12] The parties dispute whether there are objective indicia to support a conclusion of nonobviousness. PO Resp. 68–74; Reply 23–27; Sur-reply 27–29. We do not address this issue because we determine Petitioner has not met its burden in showing the reason to combine/modify the Travers references or the reasonable expectation of success.

Each of claims 13 and 14 depends from claim 1, and each of claims 29 and 30 depends from claim 22. Petitioner contends that claims 13, 14, 29, and 30 would have been obvious over the combination of Travers '075, Travers 2010, and McCloskey. *Id.* at 60–65.

For these challenges, Petitioner relies on the same combined teachings in the Travers references as those asserted in its challenge of claims 1 and 22. *Id.* at 58–65. For the same reasons as explained above, we conclude Petitioner has not met its burden in demonstrating the obviousness of claim 11, 13, 14, 29, and 30. *See supra* Section II.E; *see also In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.").

III. PETITIONER'S MOTION TO STRIKE

Petitioner filed a Motion to Strike Exhibits 2072 and 2073, and "the portions of the Sur-reply that rely on the improper new evidence within these exhibits." Paper 38 ("MTS"), 1. For the reasons explained below, we dismiss Petitioner's MTS.

Patent Owner filed Exhibits 2072 and 2073 as deposition transcripts of Drs. Larrea and Quackenbush, respectively. Sur-reply ix. Petitioner points out Exhibits 2072 and 2073 "each include multiple additional documents:" Exhibit 2072 includes "Exhibits" 1–9, and Exhibit 2073 includes "Exhibits" 1–4. MTS 1.

Petitioner contends that Patent Owner runs afoul of our rules. *Id.* at 1–2 (citing 37 C.F.R. §§ 42.6, 42.23(b), 42.63). Specifically, Petitioner argues that Exhibits 2072 and 2073 are improper because combined documents are not permitted under 37 C.F.R. § 42.6(a)(3). *Id.* In addition, Petitioner asserts that "Exhibits 2072 and 2073 are also improper because

they include 'new evidence other than deposition transcripts of the cross-examination of any reply witness.'" *Id.* at 2 (quoting 37 C.F.R. § 42.23(b)).

Patent Owner relies on a previous Board decision in which a panel stated that "if exhibits are introduced during a deposition for the purposes of testing the witness' testimony, a party should be able to submit those exhibits with the transcript, so the Board has the full context available in order to evaluate the testimony." Paper 44, 1 (quoting *Ascend Performance Materials Operations LLC, v. Samsung SDI Co.*, IPR2020-00349, Paper 53, 12 (PTAB July 15, 2021)). Patent Owner argues that "each deposition exhibit was introduced to impeach and test the witness' direct testimony, and was relevant to their cross-examination." *Id.* Patent Owner provides a table explaining the purported relevance of "Exhibits" 1–9 within Exhibit 2072 and "Exhibits" 1–4 within Exhibit 2073. *Id.* at 1–2.

As an initial matter, we note that the cases Patent Owner relies on are not persuasive. For example, the patent owner in IPR2020-00349 filed the deposition exhibits separately, and did not combine them with the deposition transcript. IPR2020-00349, Paper 53, 12–13 (agreeing to consider "Exhibits 2047, 2048, and 2051" for the purposes of evaluating the deponent's testimony). And, although a Board panel in CBM2014-00056 allowed certain combined documents, the offending party there did not, as Patent Owner here does, file those documents at the Sur-reply stage. CBM2014-00056, Paper 37, 11–12 (excusing petitioner's "improper use of sub-exhibits within" a reply declaration).

We also are not persuaded by Patent Owner's argument that the deposition exhibits were for impeachment purposes. Petitioner argues that

these exhibits "were introduced in deposition without substantive questioning." MTS 2; *see also* Paper 39, 4 ("PO introduced documents without eliciting any testimony from the deponent to impeach, and without otherwise laying appropriate foundation."). We agree. During the deposition, Patent Owner's counsel merely read, without substantive questioning, excerpts of the exhibits into the record. *See, e.g.*, Ex. 2072, 51:23–53:15 (counsel only asking "Did I read that correctly" each time after reading three passages of Exhibit 8).

That said, because in rendering this Decision, we do not rely on Exhibits 2072 or 2073, including the "Exhibits" attached thereto, we dismiss the MTS as moot.

IV. PETITIONER'S MOTION TO EXCLUDE

Petitioner filed a Motion to Exclude Exhibit 2014, "Exhibits" 1–9 within Exhibit 2072, and "Exhibits" 1–4 within Exhibit 2073. Paper 36 ("MTE"), 1. Petitioner, as the party moving to exclude evidence, bears the burden of proving that it is entitled to the relief requested, namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a); *see also* Consolidated Trial Practice Guide[13] ("CTPG") 8, 37 (explaining that a motion to exclude is based on inadmissibility). For the reasons explained below, we dismiss in part and deny in part Petitioner's MTE.

A. Exhibit 2014

Petitioner moves to exclude the Satija Declaration (Ex. 2014) "because Dr. Satija's proffered opinions are frivolous and are not 'the

[13] Available at https://www.uspto.gov/TrialPracticeGuideConsolidated.

product of reliable principles' and methods 'reliably applied' to the facts of this case." MTE 1. According to Petitioner, "[t]he bulk of Dr. Satija's declaration is spent arguing that the Travers embodiment employing amplification prior to sequencing, while admittedly disclosed, is inoperable and thus a POSA would have been dissuaded from doing it, allegedly undermining motivation to combine." *Id.* at 2. Petitioner alleges that Dr. Satija's testimony is "legally erroneous at least because the challenged claims are admittedly directed to amplification followed by PacBio sequencing, as disclosed in the Travers references." *Id.* at 5. We are not persuaded.

As an initial matter, as explained above (*see supra* Section II.E.2.a), although Dr. Satija and Patent Owner admitted that the Travers references teach "amplification prior to sequencing" in general, that admission does not extend to RCR amplification to generate concatemer molecules followed by sequencing on PacBio's platform. Thus, Dr. Satija's testimony is not, as Petitioner incorrectly argues, "legally erroneous" or "frivolous."

More importantly, in disagreeing with the analyses in the Satija Declaration, Petitioner challenges the sufficiency, and not the admissibility, of the evidence. A motion to exclude is not a proper vehicle for this purpose; instead, such arguments "should appear only in the merits documents." *See* CTPG 79. Thus, we deny the MTE with regard to the Satija Declaration.

B. "Exhibits" in Exhibits 2072 and 2073

Petitioner moves to exclude "Exhibits" 1–9 within Exhibit 2072 and "Exhibits" 1–4 within Exhibit 2073. MTE 1.

In rendering this Decision, we do not rely on "Exhibits" 1–9 within Exhibit 2072 and "Exhibits" 1–4 within Exhibit 2073. Thus, we dismiss the MTE in this regard.

V. CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has not met its burden to show an ordinarily skilled artisan would have had a reason to combine the teachings of the two Travers references, and would have had a reasonable expectation of success in arriving at the claimed method. Because Petitioner relies on this combination in all its challenges, Petitioner has not shown, by a preponderance of the evidence, that claims 1–30 would have been obvious over the asserted prior art.

In summary:

Claim(s)	35 U.S.C. §	References	Claims Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–10, 12, 15–28	103	Travers '075, Travers 2010		1–10, 12, 15–28
11	103	Travers '075, Travers 2010, NEB Expressions		11
13, 14, 29, 30	103	Travers '075, Travers 2010, McCloskey		13, 14, 29, 30
Overall Outcome				1–30

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has not proven, by a preponderance of the evidence, that claims 1–30 of the '127 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is *denied-in-part* and *dismissed-in-part*;

FURTHER ORDERED that Petitioner's Motion to Strike is *dismissed as moot*;

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

FOR PETITIONER:

Michael T. Rosato
Jad A Mills
Sonja R. Gerrard
WILSON SONSINI GOODRICH & ROSATI
mrosato@wsgr.com
jmills@wsgr.com
sgerrard@wsgr.com

FOR PATENT OWNER:

Ralph Wilson Powers III, Ph.D.
David H. Holman, Ph.D.
Kristina C. Kelly
Christopher M. Gallo
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
tpowers-PTAB@sternekessler.com
dholman-PTAB@sternekessler.com
kckelly-PTAB@sternekessler.com
cgallo-PTAB@sternekessler.com