

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.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

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 Patent Owner Preliminary Response. Paper 10 (“Prelim. Resp.”).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a).

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Accordingly, we institute an *inter partes* review of all challenged claims based on all grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

A. Related Matters

According to the parties, the ’127 patent is asserted against Petitioner in *TwinStrand Biosciences, Inc. et al. 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. In a concurrently issued decision, we deny that petition.

Patent Owner further identifies IPR2022-00449 and IPR2022-00450 as related proceedings. Paper 6, 1. In those two cases, Petitioner challenged the claims of Patent No. 10,689,699, which is in the same family as the ’127 patent challenged here. We denied those petitions. IPR2022-00449,

Paper 13; IPR2022-00450, Paper 13. Petitioner has requested review of each of those decisions by the Precedential Opinion Panel. *See* IPR2022-00449, Paper 19; IPR2022-00450, Paper 19. Those requests are currently pending.

B. The '127 Patent and Related Background

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, according to the '127 patent, 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—

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

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

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. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

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

Petitioner relies on the declaration of John Quackenbush, Ph.D., as support for its Petition. Ex. 1002.

II. ANALYSIS

A. Discretionary Denial

Patent Owner contends that we should exercise our discretion under 35 U.S.C. § 325(d) to deny the Petition. Prelim. Resp. 39–48. We are not persuaded.

Under § 325(d), in determining whether to institute an *inter partes* review, “the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” Our § 325(d) analysis employs a

² Travers et al., US Patent Publication No. 2009/0298075 A1, published December 3, 2009 (Ex. 1018, “Travers '075”).

³ 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”).

⁴ Evans et al., *DNA Damage the major cause of missing pieces from the DNA puzzle*, NEW ENGLAND BIOLABS (2007) (Ex. 1014, “NEB Expressions”).

⁵ McCloskey et al., US Patent Publication No. 2007/0020640 A1, published January 25, 2007 (Ex. 1023, “McCloskey”).

two-prong framework: (1) whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of those arguments.

Advanced Bionics, LLC v. MED-EL Electromedizinische Geräte GmbH, IPR2019-01469, Paper 6 (“*Advanced Bionics*”), 8 (PTAB Feb. 13, 2020) (precedential).

It is undisputed that “Travers is specifically cited in the specification [of the ’127 patent] and both Travers and Travers ’075 were cited to the Office in an IDS.” Prelim. Resp. 42. Thus, we agree with Patent Owner that these references were previously presented to the Office, even though the examiner never relied on, or even discussed, them in any manner.

Because we find the first prong of the *Advanced Bionics* analysis is satisfied,⁶ we must determine whether Petitioner has shown a material error by the examiner in her consideration of Travers and Travers ’075 (collectively, “the Travers references”). We find Petitioner has met its burden on this issue.

In the Reasons for Allowance, the examiner characterized the claimed method as “provid[ing] the ability to label each strand of a target with asymmetric adaptors that enable strand specific labeling.” Ex. 1004, 432.

⁶ Patent Owner also contends that, although NEB Expressions and McCloskey were not previously presented to the Office, they are cumulative of prior art evaluated during examination. Prelim. Resp. 43–44. We do not need to resolve this issue because each challenge asserted in the Petition relies on Travers and Travers ’075, and as explained below, we find Petitioner has shown that the examiner misapprehended or overlooked the teachings of Travers.

According to the examiner, “a careful search of the prior art does not find any references which teach adapters of the format as claimed.” *Id.*

Petitioner argues the examiner erred in this statement because “adapters that enable strand specific labeling were known in the art, widely used, and even commercially available as of the earliest claimed filing date of the ’127 patent.” Pet. 66–67. Petitioner points out that the ’127 patent acknowledges so. *Id.* at 67 (citing Ex. 1001, 10:63–11:2). We agree with Petitioner.

Indeed, citing Travers, the ’127 patent discloses that “ligation and amplification with circularizing ‘linker’ (i.e. hairpin linkers affixed to both ends of a fragment) has been demonstrated as a step in the Pacific Biosciences sample preparation workflow.” Ex. 1001, 10:63–66. According to the ’127 patent, “the published linker sequences” of Travers “would be adequate for use” in its method. *Id.* at 11:1–2.

On this record, Petitioner has shown the examiner misapprehended or overlooked the teachings of Travers. *See* Pet. 10–11 (citing Ex. 1004, 432–33) (arguing the examiner’s failure to identify and apply “known and well-documented” art teaching “adapters comprising barcodes” constitutes material error). Thus, we decline to exercise our discretion to deny institution under § 325(d).

B. 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) (2020). Under that standard, 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.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

The parties agree that, for purposes of this Decision, no claim term needs specific construction beyond its plain and ordinary meaning. Pet. 13; Prelim. Resp. 4–5. Each party, however, seeks to clarify the scope of the challenged claims. We address them below.

1. Adapters

Petitioner argues the 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.” Pet. 15 (citing Ex. 1002 ¶¶ 51–52). According to Petitioner,

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. (citing Ex. 1002 ¶¶ 48–50). Patent Owner does not dispute these assertions.

Based on the current 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

Patent Owner contends that “[t]he plain language of independent claims 1 and 22 makes clear that the amplifying step (b) occurs *after*

attaching adapters in step (a) and *before* the sequencing step (c).” Prelim.

Resp. 5. According to Patent Owner,

Claim 1 recites that the adapter attachment step (a) generates “adapter-DNA molecules,” the amplification step (b) amplifies the “adapter-DNA molecules” from step (a) to produce “first and second strand copies,” and the sequencing step (c) sequences the “first and second strand copies” that were produced in the amplification step (b).

Id. at 6; *see also id.* at 7 (the same analysis and conclusion on claim 22).

In general, unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one. *Loral Fairchild Corp. v. Sony Corp.*, 181 F.3d 1313, 1322 (Fed. Cir. 1999) (stating that “not every process claim is limited to the performance of its steps in the order written”). Such a result can ensue, however, when the method steps implicitly require that they be performed in the order written. *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1342–43 (Fed. Cir. 2001). Based on the current record, we find Patent Owner’s argument concerning the sequential order of the steps is supported by the claim language and the disclosures in the specification. *See, e.g.*, Ex. 1001, 37:31–52 (claim 1), 39:56–40:25 (claim 22), 3:21–27, 15:27–34, Fig. 1. Therefore, we agree 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.” Prelim. Resp. 8.

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). On this record and for purposes of this Decision, we see no need to address any other claim term.

C. Alleged Obviousness over the Travers References

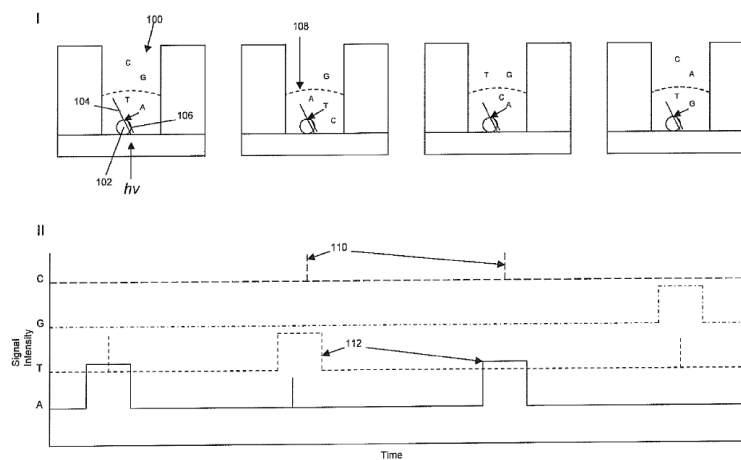
Petitioner asserts that claims 1–10, 12, 15–28 of the '127 patent would have been obvious over the Travers references. Pet. 19–58. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

1. Prior Art Disclosures

a. Travers '075

Travers '075 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.” Ex. 1018, Abstract.

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



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).” *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.

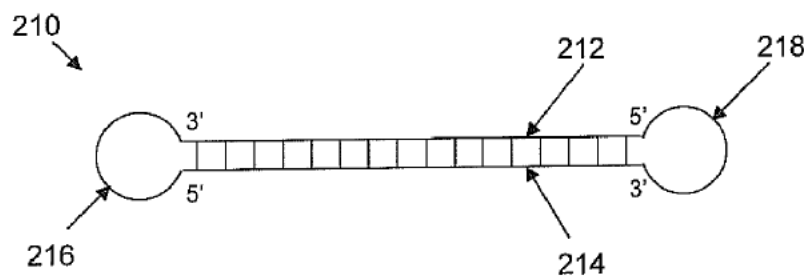


Figure 2B

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.

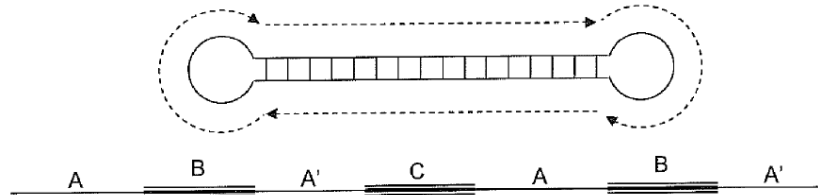


Figure 3B

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.

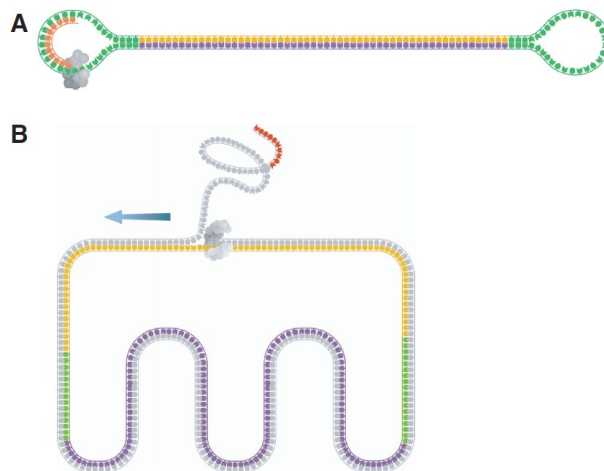
Id. ¶ 55.

Travers ’075 states that although the constructs of its invention, such as the circular template 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 molecules that include repeating copies of both the sense and antisense strands of the originating double stranded segment included within the circular nucleic acid.” *Id.* “These replicated products,” Travers ’075 continues, “may then be employed directly as template molecules in a template dependent sequencing process.” *Id.*

b. Travers

Travers describes a template design for single-molecule sequencing referred to as a SMRTbell template.⁷ Ex. 1021, 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 structure “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 bind (orange).” *Id.*

⁷ The parties agree that the two Travers references disclose the same SMRT sequencing methods and SMRTbell templates. *See* Pet. 20; Prelim. Resp. 12.

“Structurally, this format resembles a linear double-stranded molecule, and yet it is topologically circular.” *Id.*, Abstract.

Travers 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.*

2. Analysis

We focus our analysis on claim 1. Petitioner contends that the combination of Travers and Travers '075 teaches each limitation of claim 1. Pet. 20–29. Petitioner accounts each limitation in detail. *Id.* 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 challenges that Petitioner fails to show the Travers references teaches a separate template amplification step prior to sequencing. Prelim. Resp. 18, 20–29. Patent Owner also argues that Petitioner fails to explain why an ordinarily skilled artisan would have modified the SMRT sequencing method taught in the Travers references to arrive at the claimed method and why there is a reasonable expectation of success when doing so. *Id.* at 19, 30–35.

Based on the current record, and as explained below, we find Petitioner's argument more persuasive.

a. Claim Limitations

As summarized above in Section II.C.1, the Travers references teach applying SMRT sequencing methods to SMRTbell templates. *See* Ex. 1018 ¶¶ 50, 54, 55; Ex. 1021, 4. We find Petitioner has shown sufficiently that the Travers references teach step (a) of claim 1.⁸ Petitioner argues, and Patent Owner does not dispute, that the Travers references teach attaching hairpin adapters to double-stranded DNA fragments using ligation to generate partially-complementary, asymmetrical double-stranded adapter-DNA molecules. *See* Pet. 21–22 (citing Ex. 1002 ¶¶ 67–70; Ex. 1018 ¶¶ 51, 92, 105; Ex. 1021, 1, Figure 1). It is also undisputed that Travers '075 teaches that the adapters comprise barcodes selected from a plurality of distinct barcode sequences. *See id.* at 22–24 (citing Ex. 1002 ¶¶ 71–76; Ex. 1018 ¶¶ 16, 100–102, 144, claim 34).

The parties, however, disagree on whether the Travers references teach amplification of the adapter-DNA molecules before sequencing. Petitioner argues yes (Pet. 24–25); Patent Owner counters no (Prelim. Resp. 20–30).

As explained above, we agree with Patent Owner that in claim 1, the amplifying step (b) occurs after the adapter-attaching step (a) and before the sequencing step (c). *See supra* Section II.B.2. Patent Owner argues the Travers references “teach a simultaneous polymerase-mediated strand-extension and sequencing process known as sequencing-by-synthesis.”

⁸ At this stage of the proceeding, we do not need to decide whether the preamble of claim 1 is limiting because Petitioner shows sufficiently, for purposes of institution, that the Travers references teach the preamble. *See* Pet. 20–21.

Prelim. Resp. 18. According to Patent Owner, “[n]owhere does Travers disclose amplifying the SMRTbell template molecules before performing the sequencing-by-synthesis reactions.” *Id.* at 21 (citing Ex. 1021, 1, 4–5). Pointing to the working examples of Travers ’075, “none of which discloses amplifying SMRTbell template molecules before sequencing,” Patent Owner contends that Travers ’075 confirms that “SMRT™ sequencing methods do *not* amplify the SMRTbell templates before sequencing,” *Id.* at 13–14 (citing Ex. 1018 ¶¶ 139–140, 142, 145, 151), 22. Patent Owner further presents several prior-art references to support its argument that, before the critical date, “the art consistently reiterated that the SMRT™ sequencing methods of Travers do not use any SMRTbell template amplification step after adapter ligation but before or during sequencing of the SMRTbell template molecules.” *Id.* at 14–15 (citing Exs. 2002, 2003, 2004, 2005, 2006).

We do not disagree with Patent Owner that the evidence it refers to shows that the Travers references teach an embodiment that does not require amplification before sequencing. That, however, does not paint the whole picture. Rather, Travers ’075 explicitly teaches

Although the constructs of the invention are described primarily, and preferably, for use directly as templates for, e.g., sequencing applications, it will be appreciated that these structures may also serve as intermediate structures in the preparation of templates that provide for sequence redundancy in line with that provided by such constructs. For example, 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, as described elsewhere herein (See also U.S. Pat. No.

7,476,503, which is incorporated herein by reference in its entirety for all purposes). Likewise, duplication processes may be employed to produce multiple copies of a prepared circular construct using methods previously described (See, e.g., U.S. Patent Application No. 61/072,160, previously incorporated herein by reference in its entirety for all purposes).

Ex. 1018 ¶ 122.

Petitioner relies on this teaching to argue that the Travers references teach the amplification step recited in step (b) of claim 1. Pet. 24–25 (citing Ex. 1019 ¶ 122).

Patent Owner emphasizes that paragraph 122 of Travers '075 begins by disclosing sequencing without amplification as the preferred embodiment. Prelim. Resp. 27. Patent Owner dismisses the rest of the paragraph as a “passing reference to ‘amplification,’” which amounts to nothing but a “speculative modification.” *Id.* at 26–27. Patent Owner contends that Petitioner fails to explain why an ordinarily skilled artisan would have been motivated to modify the SMRT sequencing methods, or how to do so. *Id.* at 27–28, 30–33. Based on the current record, we find Petitioner’s argument more persuasive.

For an obviousness analysis, a reference is prior art for all that it teaches. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989). The fact that an embodiment is preferred “is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.” *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

Based on the current record, we agree with Patent Owner that the Travers references describe SMRT sequencing, which does not require amplification before sequencing, as the primary and preferred embodiment.

See Ex. 1018 ¶ 122. But, even though the Travers references focus on SMRT sequencing, that does not negate the additional teachings of other embodiments. Indeed, Travers '075 explicitly teaches producing “concatamer molecules that include repeating copies of both the sense and antisense strands” of constructs, such as the SMRTbell templates, by “a rolling circle replication process.” *Id.* We find Petitioner has shown sufficiently that this teaching meets the amplification limitation recited in step (b) of claim 1. *See* Pet. 24–25.

Petitioner further relies on Travers '075's teaching of using the replicated concatamer molecules as templates in a template dependent sequencing process. *Id.* at 25 (citing Ex. 1018 ¶ 122). We find Petitioner has shown sufficiently that the Travers references teach step (c) of claim 1, which requires sequencing after amplification.

Patent Owner contends that Petitioner fails to show how to modify the preferred SMRT sequencing methods in the Travers references. Prelim. Resp. 27. Based on the current record, we do not see a need for modification. Travers '075's paragraph 122 is merely directed to an alternative use of the circular molecules (comprised of the DNA fragment of interest linked by the hairpin linkers), such as SMRTbell templates. *See* Ex. 1018 ¶ 122 (discussing “the constructs of the invention” and “the structurally circular nucleic acid segments”). As we understand it, these molecules may be subject to SMRT sequencing directly, or they may be amplified to produce concatemer molecules, which are then subject to SMRT sequencing. *Id.* Petitioner relies on the latter in this case, and we find that showing sufficient for institution purpose.

Because we understand Travers '075's paragraph 122 as explicitly teaching steps (b) and (c) without requiring modification, we do not need to address Patent Owner's argument regarding motivation to combine and/or modify. *See* Prelim. Resp. 30–33. For the same reason, we do not need to address Patent Owner's argument regarding reasonable expectation of success, because paragraph 122 appears to teach a straightforward application of SMRT sequencing to concatemer molecules. *See* Ex. 1021, 1 (teaching there is “no evidence of an intrinsic limit in the size of template that can be created”).

Petitioner argues that the Travers references teach step (d) of claim 1. Pet. 26–28. Patent Owner does not address these arguments. Based on the current record, we find Petitioner has made a sufficient showing regarding step (d) of claim 1.

In sum, based on the current record, Petitioner has shown, for institution purposes, that the Travers references teach each limitation of claim 1.

b. Alleged Evidence of Objective Indicia

Patent Owner asserts that Petitioner fails to address known objective indicia of nonobviousness. Prelim. Resp. 19, 36–38. According to Patent Owner, Petitioner “is well aware of industry praise for the invention as recited in the challenged claims.” *Id.* at 38. Specifically, Patent Owner points to Kirsch,⁹ which Petitioner allegedly cited during prosecution of its own patent application. *Id.* According to Patent Owner, “Kirsch praises the '127 patent's claimed methods, speaking directly to the method's advances over

⁹ Kirsch et al., Sequence Error Storms and the Landscape of Mutations in Cancer, 109 Proc. Natl. Acad. Sci. 14289–90 (2012) (Ex. 2007, “Kirsch”).

the prior art: ‘Based on the data presented in the article by Schmitt et al., the Gordian knot in sequencing accuracy has apparently been cut by the duplex sequencing approach.’” *Id.* (quoting Ex. 2007, 14289). We are not persuaded.

Objective evidence of nonobviousness is relevant only if there is a nexus between this evidence and the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). The patentee bears the burden of showing that a nexus exists. *Id.* Here, Kirsch does not discuss the ’127 patent; instead, it mentions an article “by Schmitt et al.” Ex. 2007, 14289. Patent Owner does not present the article “by Schmitt et al.” or discuss how that article relates to the ’127 patent. Thus, based on the current record, it is unclear whether Kirsch qualifies as relevant evidence of objective indicia. As a result, we decline Patent Owner’s invitation to deny the Petition on the basis that Petitioner has not addressed Kirsch. Prelim. Resp. 38.

3. Summary

In sum, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing that claim 1 would have been obvious over the Travers references.

Petitioner’s contentions on claim 22, the only other independent claim, are similar to those on claim 1. *See* Pet. 29–37. Petitioner also presents its obvious analysis regarding dependent claims 2–10, 12, 15–21, and 23–28. *Id.* at 37–58. Patent Owner does not make separate arguments to address these claims. Based on the current record, we determine Petitioner has made a sufficient showing regarding these claims too. Thus, we institute an *inter partes* review as to all challenges raised in the Petition. *See* Patent

Trial and Appeal Board Consolidated Trial Practice Guide 64 (Nov. 2019)¹⁰ (“The Board will not institute on fewer than all claims or all challenges in a petition.”); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”).

D. Other Grounds

Petitioner asserts that claim 11 would have been obvious over the combination of Travers ’075, Travers Paper, and NEB Expressions. Pet. 58–60. Petitioner also contends that claims 13, 14, 29, and 30 would have been obvious over the combination of Travers ’075, Travers Paper, and McCloskey. Pet. 60–65. As discussed above, we institute trial because Petitioner has met its burden in its challenge based on the Travers publications. Thus, we do not address these grounds. We, however, encourage the parties to further address the relevant issues of all challenges to fully develop the record during trial.

III. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. We, thus, institute an *inter partes* review of all challenged claims on all asserted grounds.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of

¹⁰ Available at <https://www.uspto.gov/sites/default/files/documents/tpgnovpdf>.

any challenged claim. Our view with regard to any conclusion reached in the foregoing could change upon further development of the record during trial.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board's Rules.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on all challenged claims of the '127 patent based on all the asserted grounds set forth in the Petition; and

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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