

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.
Petitioner,

v.

UNIVERSITY OF WASHINGTON,
Patent Owner.

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

**PATENT OWNER’S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

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Patent Trial and Appeal Board
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EXHIBIT LIST

Exhibit No.	Description
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2002	Niedringhaus, T.P., et al., "Landscape of Next-Generation Sequencing Technologies," <i>Anal. Chem.</i> 83:4327-4341 (2011)
2003	Thompson, J.F. and Milos, P.M., "The Properties and Applications of Single-Molecule DNA Sequencing," <i>Genome Biology</i> 12:217 (2011)
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2005	Quail, M.A., et al., "A Tale of Three Next Generation Sequencing Platforms: Comparison of Ion Torrent, Pacific Biosciences and Illumina Miseq Sequencers," <i>BMC Genomics</i> 13:341 (2012)
2006	Egan, A.N., et al., "Applications of Next-Generation Sequencing In Plant Biology," <i>American Journal of Botany</i> 99(2):175-185 (2012)
2007	Kirsch, S. and Klein, C.A., "Sequence Error Storms and the Landscape of Mutations in Cancer," <i>Proc. Natl. Acad. Sci.</i> 109(36):14289-14290 (2012)
2008	Turner, S., et al., "Apparatus and Method for Performing Nucleic Acid Analysis," U.S. Patent No. 7,479,503 B2 (filed Sept. 16, 2005; issued Jan 13, 2009)
2009	Miner, B.E., et al., "Molecular barcodes detected redundancy and contamination in hairpin-bisulfite PCR," <i>Nucleic Acids Research</i> 32(17): s135 (2004)
20010	Lindahl, T. and Wood, R.D., "Quality Control by DNA Repair," <i>Science</i> , 286:1897-1905 (1999)
20011	Shibutani, S., et al., "Insertion of Specific Bases During DNA Synthesis Past the Oxidation-Damaged Base 8-oxodG," <i>Nature</i> , 349:431-434 (1991)

Exhibit No.	Description
20012	Stiller, M., et al., "Patters of Nucleotide Misincorporations During Enzymatic Amplification and Direct Large-Scale Sequencing of Ancient DNA," <i>Proc. Natl. Acad. Sci.</i> , 103(37):13578-13584 (2006)
20013	McCloskey, M.L., et al., "Encoding PCR Products with Batch-stamps and Barcodes," <i>Biochem Genet</i> 45:761-767 (2007)

I. INTRODUCTION

The Board should deny institution of *inter partes* review of claims 1-30 of U.S. Patent No. 10,760,127 (“the ’127 patent”) because the Petition falls far short of establishing a reasonable likelihood of prevailing with respect to any challenged claim.

First, Guardant Health, Inc.’s (“Guardant’s”) whole Petition is based on a misunderstanding of its primary references: Guardant assumes that the PacBio SMRT™ sequencing method disclosed in Travers (EX1021) and Travers ’075 (EX1018) utilizes a DNA amplification step after adapter ligation and prior to the sequencing step. But this assumption is contradicted by express disclosures in Travers and Travers ’075, as well as numerous other prior art references, which all unequivocally confirm that the SMRT™ sequencing method of Travers and Travers ’075 does *not* use an amplification step after adapter ligation, as required by the ’127 patent claims. Not only that, the art taught that the absence of an amplification step between adapter ligation and sequencing steps in Travers’ SMRT™ sequencing was *an advantage* of the method. This deficiency in Guardant’s Petition is fatal to all grounds of unpatentability because every claim expressly requires a separate amplification step before a separate sequencing step.

Second, Guardant’s misunderstanding of Travers and Travers ’075 naturally results in Guardant failing to establish why a skilled artisan would have had a

reason to modify Travers and Travers '075 to incorporate an amplification step after adapter ligation but prior to sequencing. This deficiency in Guardant's Petition is further underscored by the fact that the art considered Travers' lack of an adapter-DNA amplification step to be advantageous. Guardant failed to address these discrepancies in its arguments, and failed to identify a reason that would have prompted a skilled artisan reading Travers and Travers '075 to modify the SMRTTM sequencing methods to arrive at the methods claimed in the '127 patent. This is another reason Guardant's Petition should be denied.

Third, notwithstanding Guardant's misunderstanding of Travers and Travers '075, Guardant also fails to articulate why a skilled artisan reading the references would have had a reasonable expectation of successfully arriving at the claimed methods of the '127 patent. Instead, the Petition asserts conclusory statements fraught with hindsight bias.

In the absence of appropriate reasoning or evidence, Guardant has not met its burden to show any likelihood of prevailing on any challenged claim. At most, Guardant's Grounds are simply based on the argument that elements of the '127 patent claims were independently known in the art, and Guardant does not provide a valid reason that would have prompted a skilled artisan to arrive at the '127 patent's invention.

Guardant has also failed to address known objective indicia of nonobviousness of the claimed invention, a required showing in order to fully address obviousness. Guardant's Petition does *not even mention* objective indicia, and therefore cannot have fully analyzed obviousness. For this additional reason, Guardant has not met its burden.

Finally, the Board should additionally exercise its discretion to deny the Petition under 35 U.S.C. § 325(d) because (1) the same prior art was previously before the Office during prosecution or is cumulative of art considered during examination; and (2) Guardant has not demonstrated that the Examiner materially erred or that Guardant has presented additional evidence or facts that warrant reconsideration of the previously considered art. Both Travers and Travers '075—the Petition's primary references—were previously presented to the Office and considered by the Examiner. And Guardant made no attempt to explain why or how NEB Expressions (EX1014) and McCloskey (EX1023) were not cumulative of other references previously before the Office and considered by the Examiner. Guardant's Petition is a textbook example of the very type of improper, hindsight-driven arguments that *Advanced Bionics* and 35 U.S.C. §325(d) protect against.

The Petition should be denied and trial should not be instituted.

II. OVERVIEW OF THE '127 PATENT

Patent Owner University of Washington's ("UW") '127 patent relates to novel DNA-sequencing methods that employ error-correction technology, producing sequencing results that are dramatically more accurate and informative than previously known methods. This error-correction technology involves tagging sample DNA strands with short nucleic-acid identifiers to track their origin and identity through various processing steps.

One application of the patented error correction methods is DNA duplex consensus sequencing ("DCS"). Duplex sequencing tags both complementary strands of a sample of double-stranded DNA fragments in an asymmetric fashion to keep track of which strand is which (*i.e.* the "first" and "second" strands; sometimes called "top" and "bottom" strands). Tracking the DNA strand origin throughout sequencing and further processing improves sequencing accuracy by allowing one to compare strands against their complementary counterpart strand, thereby distinguishing actual mutations from sequencing errors.

III. CLAIM CONSTRUCTION

Claim terms must be given their "ordinary and customary meaning as understood by one of ordinary skill in the art" in view of the specification and prosecution history. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). UW submits that, for purposes of this institution

decision, no claim term needs specific construction beyond its plain and ordinary meaning.

The '127 patent claims recite specific steps for performing the claimed methods. In particular, independent claims 1 and 22 each requires separate steps of (a) attaching adapters to double-stranded DNA fragments; (b) amplifying the adapter-DNA fragments to produce “strand copies”; (c) sequencing the “strand copies” (i.e., sequencing the amplified adapter-DNA fragments); and then assessing sequence information via different steps comprising comparing sequence read information between the strands, grouping the sequence reads into families and collapsing the families into consensus sequences, and analyzing the sequences to identify a sequence variation. EX1001, 37:31-52, 39:56-40:25.

The 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). *Id.* Claim 1 recites the following steps (a), (b) and (c):

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;

EX1001, 37:31-52 (emphasis added). 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.*

The method of claim 22 uses similar language. Claim 22 recites the following steps (a), (b), and (c):

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;

EX1001, 39:56-40:25 (emphasis added).

Like claim 1, claim 22 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 “strand copies,” and the sequencing step (c) sequences the “strand copies” that were produced in the amplification step (b). *Id.*

The plain language of the claims is consistent with the disclosures in the specification. *Phillips*, 415 F.3d at 1313 (“the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.”) For example, the ’127 patent discloses:

[E]ach 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....*

EX1001, 15:27-34 (emphasis added); *see also, id.*, Fig. 1 (depicting PCR amplification step after adapter ligation step but prior to “massively parallel sequencing”), 3:21-27 (disclosing steps of “ligating” target DNA molecules to adapters, “amplifying” the adapter-DNA molecules, and then “sequencing the amplified ... products.”

Thus, based on the plain language of the claims, which is confirmed by the disclosures in the specification, a person of ordinary skill in the art would understand 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.

IV. OVERVIEW OF THE ASSERTED ART

The Petition's Grounds rely on the combinations of: Travers (EX1021) and Travers '075 (EX1018) (Ground 1); Travers, Travers '075, and NEB Expressions (EX1014) (Ground 2); and Travers, Travers '075, and McCloskey (EX1023) (Ground 3). None of the asserted art, whether considered alone or in any combination, teaches all the elements of the challenged claims.

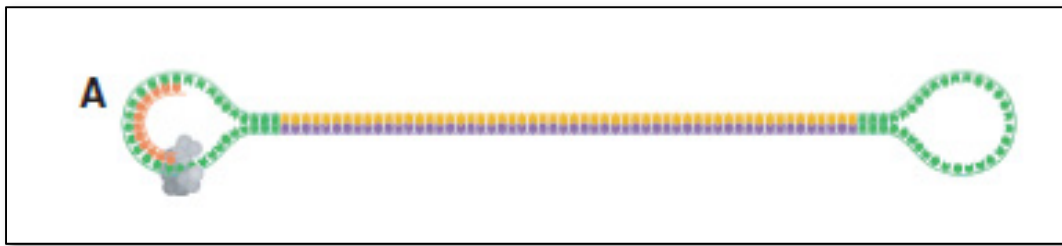
A. Travers

Guardant's Petition relies entirely on disclosures of sample preparation and sequencing methods developed by Pacific Biosciences of California, Inc.

("PacBio"): "This petition relies on a patent publication and a paper describing sample preparation and sequencing methods developed at PacBio." Pet., 6.

Guardant further admits that "the Travers paper is authored by scientists employed by PacBio (including the inventors of Travers '075) and describes applications of the sequencing methods described in Travers '075." *Id.*, 7.

The Travers paper (“Travers”) discloses a DNA sequencing template design called “SMRTbell” for use in PacBio’s “single-molecule real-time (SMRT™)” sequencing methods. EX1021, 1. Travers depicts the SMRTbell template in Figure 1 (copied below), stating that it “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.*, 3.

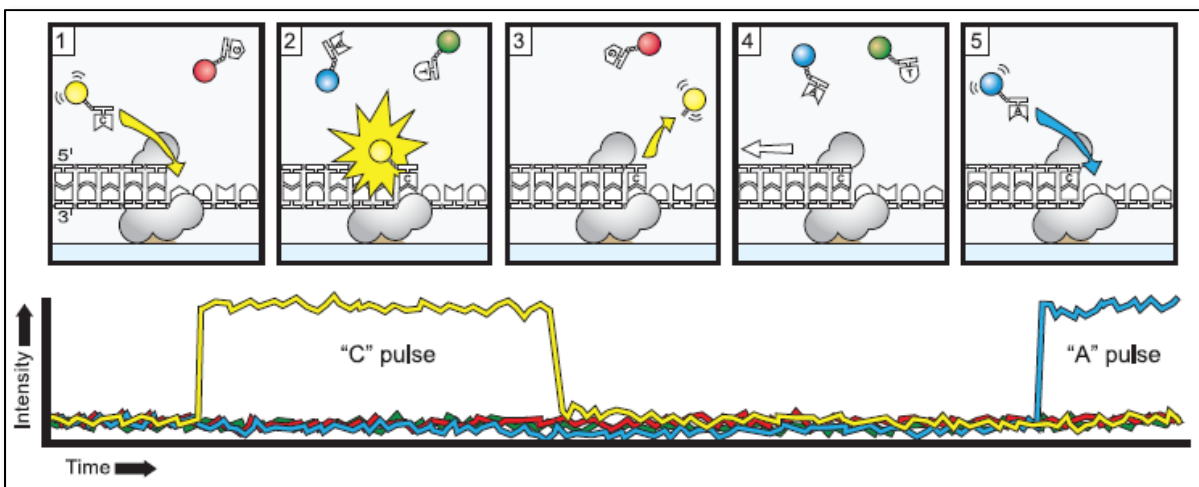


EX1021, Fig. 1. As evident in Travers’ figure above, the SMRTbell template is symmetrical between the top and bottom strands. *Id.*; *see also id.*, 3 (“In deciding on a format for SMRT™ sequencing, a number of factors were considered, including ... *uniformity of structure*....”). Travers discloses ligating the hairpin adapters to each end of the DNA molecule to generate the circular SMRTbell template, which is then ready for sequencing. *Id.*, 4, Fig. 2.

Travers explains that SMRT™ sequencing is “a method for generating sequence data that harnesses the intrinsic speed, fidelity and processivity of polymerase molecules (1).” *Id.*, 1 (citing Eid 2009, EX2001). Travers also states that “SMRT™ sequencing [is] described in [Eid 2009].” EX1021, 4. Eid 2009,

which was coauthored by Travers, is PacBio's seminal publication disclosing the SMRT™ sequencing method. EX2001, 133.

The premise behind PacBio's SMRT™ sequencing is monitoring and recording in real-time the incorporation of fluorescently labeled nucleotides by a DNA polymerase as it moves along the template molecule, with each nucleotide incorporation event emitting a different color fluorophore that is captured by a camera. EX2001, 133-134; EX1021, 4. Travers discloses that “[n]ucleotide analogs, each containing a fluorophore linked to its terminal phosphate, are incorporated into a nascent chain” and that “fluorophores are cleaved during incorporation, leaving a native product and a free fluorophore.” EX1021, 4. Travers discloses detecting the fluorescence signals of each incorporation event with a camera: “[t]he fluorescence signal for each of the analogs is observed by a CCD camera.” *Id.*, 4-5. Eid 2009 depicts the SMRT™ sequencing process in Figure 1, shown below:

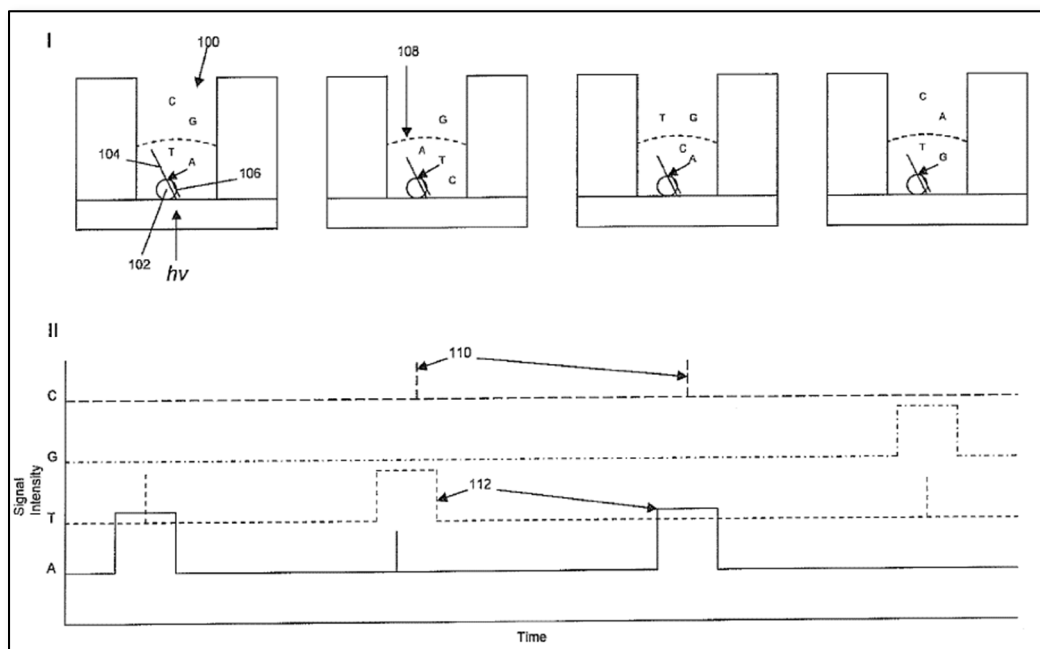


EX2001, Fig. 1; *see also*, EX1021, 4. As Eid shows in its figure, incorporation of the fluorescently labeled “C” by DNA polymerase results in a transient yellow fluorescence emission (step 2, “C” pulse), followed by incorporation of a fluorescently labeled “A” which will result in a transient blue fluorescence emission (steps 5, “A” pulse). *Id.* The color-coded emissions, each representing a different nucleotide A, T, C, or G, are captured by the camera and assembled into a nucleotide sequence in real time. EX1021, 4-5.

Thus, in Travers' SMRTTM sequencing, the strand extension of the SMRTbell template molecule (performed by a DNA polymerase enzyme) and the sequencing reaction (fluorescent flashes captured by a camera) occur simultaneously. *Id.* This is different from the claimed methods, which recite attaching adapters to DNA molecules, then amplifying the adapter-DNA molecules, and then sequencing the amplified adapter-DNA molecules. *See supra*, Section III. In Travers, however, the circular SMRTbell template molecules are subjected *directly* to sequencing, with no SMRTbell template amplification step. *See* EX1021, 4 (“[t]he circular molecules [templates] were then applied to SMRTTM sequencing....”). Indeed, Travers expressly discloses that “this protocol for template preparation requires a minimal number of steps and *does not depend on amplification.*” *Id.*, 5(emphasis added).

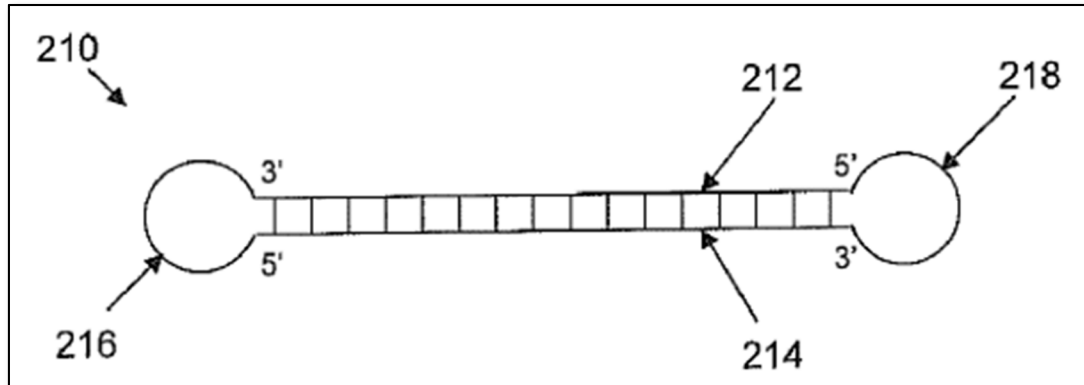
B. Travers '075

Guardant admits that Travers '075 discloses the same SMRT™ sequencing methods and SMRTbell template molecules disclosed in Travers. Pet., 6-7. Travers '075 discloses that an “exemplary sequencing process based upon such Single Molecule Real Time (SMRT™) processes is schematically illustrated in FIG. 1,” and provides a figure similar to Eid’s Figure 1 shown above:



EX1018, ¶[0043], Fig. 1. Travers '075 discloses that “[t]he reaction mixture ... 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.*, ¶[0044]. By identifying the “different spectral characteristics, one can detect, in real time, the identity of each incorporated base as it is being incorporated.” *Id.*, ¶[0045].

Figure 2 of Travers '075 (presented below) also discloses the same circular SMRTbell template format of Travers:



EX1018, Fig. 2B, ¶[0050].

Travers '075 also reiterates that the SMRT™ sequencing methods do *not* amplify the SMRTbell templates before sequencing. This is confirmed in Travers '075's working examples, none of which discloses amplifying SMRTbell template molecules before sequencing. *See id.*, ¶[0139]-[0140] (Example 1, disclosing generation of a “final template construct” and then directly performing “[t]he SMRT™ sequencing reaction” without a template amplification step); ¶[0142] (Example 2, disclosing that, after template construction, “[t]he resulting template was subjected to SMRT™ sequencing” without a template amplification step); ¶[0145] (Example 3, disclosing that, after template construction, “[t]he templates were annealed to an equivalent amount of primer, and then subjected to sequencing” without a template amplification step); ¶[0151] (Example 4, disclosing that, after template construction, “[t]he template was then sequenced

using a SMRT™ sequencing” with no template amplification step). The methods claimed in Travers '075 also lack a template amplification step after adapter ligation, consistent with the SMRT™ sequencing method. *See e.g.*, EX1018, claim 12 (“contacting the template nucleic acid segment with a primer sequence” and then “monitoring a template directed, polymerase mediated nucleic acid sequencing process to determine a sequence of nucleotides.”).

C. The art consistently confirmed that Travers' SMRT™ sequencing does not use a SMRTbell template amplification step before sequencing.

Before March 20, 2012, 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. For example, Niedringhaus 2010 reported that “[Travers’] [s]ample preparation time is decreased since *template amplification is not needed....*” EX2002, 4330 (emphasis added). Niedringhaus 2010 also disclosed that an “advantage” of Travers’ method is that there is “*no amplification of sequencing fragments.*” *Id.*, Table 2 (emphasis added); *see also*, EX2003, 5 (describing the method of Travers as “creating a circular template (called SMRTbell for single molecule real time), and then repeatedly sequencing the same molecule...” – i.e., directly sequencing the template without amplification.). Similarly, Stranneheim 2012 characterized Travers’ “sample preparation” process

as having “*no amplification*.” EX2004, 1065, Table 1. Quail 2012 reported a comparison of Illumina, PacBio, and Ion Torrent sequencing methods. EX2005, 2. Quail described the PacBio SMRT™ sequencing methods (i.e., the method of Travers) as having “an *amplification free* workflow” and further referred to the “*amplification-free* library prep of PacBio.” *Id.*, 2, 9 (emphasis added). Egan 2012 similarly reported comparing PacBio’s SMRT™ sequencing with other sequencing methods, noting that one of the “pros” of SMRT™ sequencing was that “*no template amplification* [is] needed.” EX2006, Table 1 (emphasis added).

Thus, the art consistently taught that the SMRT™ sequencing method of Travers and Travers ’075 relied upon in the Petition does not utilize any SMRTbell template amplification step after adapter attachment but before sequencing the SMRTbell templates. Moreover, the art taught that the absence of a SMRTbell template amplification step in Travers’ SMRT™ sequencing method *was an important advantage* of the workflow.

D. NEB Expressions

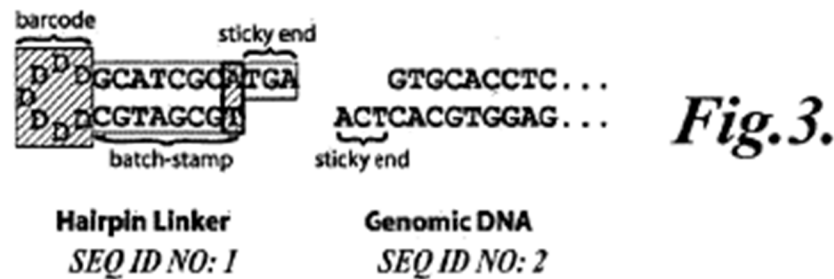
NEB Expressions is a marketing publication from New England Biolabs, purportedly published in Spring 2007. NEB Expressions discloses: “Welcome to the spring edition of NEB Expressions, in which we are pleased to introduce the 2007-08 NEB Catalog & Technical Reference.” EX1014, 1. NEB Expressions discloses a commercial product named “PreCR™ Repair Mix” for repairing

damaged DNA, comprising “a blend of recombinant proteins designed to repair damaged DNA.” *Id.* NEB Expressions discloses that the PreCR™ Repair Mix is “a cocktail of enzymes formulated to repair damaged DNA *in vitro* prior to PCR.” *Id.*, 3. According to NEB Expressions, “[t]he lesions repaired by the PreCR Repair Mix do not include all possible damages” and the repair mix cannot “effectively repair highly fragmented DNA, a common, but difficult problem.” *Id.*, 3. NEB Expressions discloses additional commercial products from NEB, such as new restriction endonucleases and various “products for RNA research.” *Id.*, 6-7. NEB Expressions does not disclose any DNA sequencing methods. *See generally*, EX1014.

E. McCloskey

McCloskey is a U.S. patent application publication purportedly published on January 25, 2007. EX1023, 1. McCloskey discloses methods of labeling DNA fragments with index barcodes. For example, McCloskey discloses that DNA fragments “are labeled with distinct sequence tags prior to PCR amplification. These sequence tags authenticate a nucleic acid sequence with information, such as the date of the experiment, and the sample identity.” EX1023, ¶[0005]. McCloskey’s index barcoding method purportedly reduces “PCR redundancy and contamination associated with PCR amplification of limited amounts of DNA template,” for example in hairpin-bisulfate PCR involving low amount of template.

EX1023, ¶¶[0092]-[0093]. McCloskey discloses using random 7-mer and 13-mer index barcodes, and directs a POSA to use 13-mer barcodes when “more independently derived sequences are required.” *Id.*, ¶¶[0100]-[0101]. McCloskey discloses ligating hairpin linkers (reproduced below) containing barcodes to genomic DNA that has been digested with specific restriction enzymes. *Id.*, ¶¶[0010], [0015], Fig. 3.



Id., Fig. 3. As McCloskey explains, “FIG. 3 shows a schematic representation of a bar-coded and batch-stamped hairpin linker (SEQ ID NO:1), designed for ligation to DraIII-cut genomic DNA of FMR1 (SEQ ID NO:2), as described in EXAMPLE 6. The letter D represents a nucleotide randomly selected from A, G, and T.” *Id.*, ¶[0015].

McCloskey’s cover page lists a co-inventor, Brooks Miner, who is also the first author on the publication, Miner *et al.*, “Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR,” *Nucleic Acids Research*, 32(17):1-4 (2004) (“Miner,” EX2009). Indeed, McCloskey’s Example 6 is a republication of the disclosures in Miner. *Compare* EX1023, ¶¶[0092]-[0106],

Figs. 3-4, *with* EX2009, 1-4, Figs. 1-2. The '127 patent cites and discusses Miner, noting that Miner discloses a “technique[] whereby DNA fragments to be sequenced are each uniquely tagged.” EX1001, 2:16-19 (citing [34]), 32:33-36 (identifying Miner as [34]).

V. GUARDANT'S GROUNDS FAIL TO ESTABLISH A REASONABLE LIKELIHOOD OF PREVAILING WITH RESPECT TO ANY CHALLENGED CLAIM.

Guardant argues that Travers combined with Travers '075 (Ground 1; Pet., 19-58) or Travers and Travers '075 combined with NEB Expressions (Ground 2; *id.*, 58-60) or Travers and Travers '075 combined with McCloskey (Ground 3; *id.*, 60-65) would have rendered obvious claims 1-30. As discussed below, the Petition fails to meet the statutory threshold for instituting IPR and should be denied. 35 U.S.C. § 314(a).

First, independent claims 1 and 22 of the '127 patent require attaching adapters to DNA molecules, amplifying the adapter-DNA molecules, and *then* sequencing the amplified adapter-DNA molecules. As shown below, the Travers publications expressly teach a simultaneous polymerase-mediated strand-extension and sequencing process known as sequencing-by-synthesis. The Travers' method, known as SMRT™ sequencing or the PacBio method, is not the same process claimed in the '127 patent. Guardant fails to account for this deficiency in the art, which is fatal to all three of the Petition's Grounds because all challenged claims

depend directly or indirectly from claims 1 and 22. This deficiency alone is sufficient grounds for the Board to deny institution.

Second, Guardant fails to articulate any reason why a POSA would have modified Travers' SMRT™ sequencing methods to arrive at the claimed method. In particular, Guardant fails to explain why a POSA would have modified Travers' SMRT™ sequencing workflow to perform a SMRTbell template amplifying step prior to sequencing. Both the Petition and Guardant's expert Dr. Quackenbush fail to address these issues entirely.

Third, Guardant fails to articulate why a POSA would have allegedly had a reasonable expectation of success in combining the asserted art and arriving at the claimed methods. Showing a reasonable expectation of success is a cornerstone of any obviousness analysis, yet the Petition provides only a single, conclusory sentence in each Ground without any explanation. Such conclusory arguments do not and cannot meet Guardant's burden under 35 U.S.C. §314(a).

Finally, Guardant has failed to address known objective indicia of nonobviousness for the '127 patent's claimed invention.

A. Guardant fails to establish that the asserted references disclose all the elements of the challenged claims.

As discussed above in Section III, the '127 patent claims require amplifying the adapter-DNA fragments prior to sequencing the amplified DNA strands ("strand copies"). Guardant's Grounds fail to establish a reasonable likelihood of

prevailing on any challenged claim at least because Guardant does not demonstrate that the Travers references disclose this key element of the challenged claims.

Institution can be denied on this basis alone.

1. Guardant fails to establish that the Travers references disclose a separate template amplification step prior to sequencing.

As discussed above in Section III, Travers discloses PacBio's SMRT™ sequencing methods and the SMRTbell template preparation system, which sequences the SMRTbell templates via nucleotide analogue strand extension. Travers discloses ligating hairpin adapters to each end of the DNA molecule to generate circular SMRTbell templates, which are then sequenced. EX1021, Fig. 2. Travers discloses that "[t]he circular molecules [SMRTbell templates] were then applied to SMRT™ sequencing, described in (1)." EX1021, 4 (citing Eid 2009, EX2001). Eid, which is PacBio's seminal SMRT™ sequencing paper, discloses that SMRT™ sequencing uses "DNA polymerase as a real-time sequencing engine—that is, direct observation of processive DNA polymerization with basepair resolution." EX2001, 133; *see also, id.*, 133-134 (disclosing "DNA sequencing based on the observation of the temporal order of fluorescently labeled nucleotide incorporations during unhindered DNA synthesis by a polymerase molecule.") This is the same methodology disclosed in Travers. Travers discloses "[o]bserving the replication of these molecules in a SMRT sequencing system."

EX1021, 1. Travers also discloses that “[n]ucleotide analogs, each containing a fluorophore linked to its terminal phosphate, are incorporated into a nascent chain” and that “fluorophores are cleaved during incorporation, leaving a native product and a free fluorophore.” *Id.*, 4. Travers discloses detecting the fluorescence signals of each incorporation event with a camera: “[t]he fluorescence signal for each of the analogs is observed by a CCD camera.” *Id.*, 4-5. Nowhere does Travers disclose amplifying the SMRTbell template molecules before performing the sequencing-by-synthesis reactions. As such, Travers’ SMRT™ sequencing does not sequence “strand copies” as claimed in the ’127 patent.

In fact, Travers expressly discloses that it does *not* use an adapter-DNA template amplification step as claimed. Travers discloses that “this protocol for template preparation requires a minimal number of steps and *does not depend on amplification*.” EX1021, 5 (emphasis added); *see also, id.*, 4 (describing that after template construction, “[t]he circular molecules were *then applied to SMRT™ sequencing...*” – i.e., the SMRTbell templates are directly sequenced with no amplification step.). Thus, Travers does not disclose amplifying the adapter-DNA template before sequencing, as required by claims 1 and 22. Guardant fails to address this deficiency.

Travers ’075 equally fails in this regard. Travers ’075 discloses the same SMRT™ sequencing method of Travers, and consistently teaches the same

sequencing-by-synthesis approach—not template amplification. For example, Travers '075 discloses that “the constructs of the invention are described *primarily, and preferably, for use directly as templates for, e.g., sequencing applications...*” EX1018, ¶[0122] (emphasis added). Travers '075 confirms this approach in its working examples. Example 1 discloses that the final template product is directly sequenced—i.e., *no template amplification step. Id.*, ¶¶[0139]-[0140]. Example 2 similarly discloses that “[t]he resulting *template was subjected to SMRTTM sequencing as described above...*”—i.e., *no template amplification step. Id.*, ¶[0142] (emphasis added). Example 3 discloses that “[t]he templates were annealed to an equivalent amount of primer, and *then subjected to sequencing*”—i.e., *no template amplification step. Id.*, ¶[0145] (emphasis added). And Example 4 discloses that “[t]he *template was then sequenced using a SMRTTM sequencing*”—i.e., *no template amplification step. Id.*, ¶[0151] (emphasis added).

Thus, Travers and Travers '075 unequivocally taught that the PacBio SMRTTM sequencing method does *not* utilize a SMRTbell template amplification step prior to sequencing. *See* Sections IV(A)-IV(B). And as discussed above in Section IV(C), the art consistently confirmed that Travers' sequencing methods do *not* include a template amplification step, and that this was an *advantage* of the method. EX2002, 4331, Table 2; EX2003, 5; EX2004, 1065, Table 1; EX2005, 2, 9; EX2006, Table 1.

Guardant's failure here is fatal to all of its grounds in the Petition, as Grounds 1-3 all assert Travers and Travers '075 as the primary references, and all challenged dependent claims depend directly or indirectly from claims 1 and 22. Thus, the Board should deny institution on this deficiency alone. *See e.g., Bungie, Inc. v. Acceleration Bay, LCC*, IPR2017-01601, Paper 11, at 13 (P.T.A.B. Jan. 9, 2018) (denying institution because the petitioner "ha[d] not shown sufficiently that the combination of [prior art] teaches or suggests all of the limitations of [an] independent claim"); 37 C.F.R. § 42.104(b)(4) (requiring petitioner to "specify where each element of the claim is found in the prior art.").

a. Guardant mischaracterizes UW's statements regarding purported disclosure of "amplification" in Travers '075.

Guardant alleges that UW "acknowledged" that Travers describes "amplification" as recited in claims 1 and 22 of the '127 patent. Pet., 24, 31-32. The underlying evidence shows that this is simply not true. Guardant provides excerpted quotations from UW's arguments made during prosecution of the application that led to U.S. Patent No. 11,198,907. For example, Guardant argues:

Patent Owner acknowledged that Travers describes "amplification of these linked original strands 'to ensure complete, and preferably redundant sequencing of the entire template.'" EX1024, 551 (citing EX1018, ¶83); *see also* EX1001, 10:63-11:18.

Pet., 24; *see also, id.*, 31-32. As Guardant noted, UW discussed Travers '075 ¶[0083]¹ in a Reply to Office Action. EX1024, 551-552. However, Guardant mischaracterizes UW's prior arguments. UW expressly disagreed with the Examiner's contention that Travers '075 discloses using amplified template products for sequencing:

The Office Action *alleges that Travers discloses this feature by teaching that “template constructs may be prepared from PCR products to provide a population of identical molecules from which to generate sequence reads”.... Applicant respectfully disagrees.*

EX1024, 551 (emphasis added). In other words, UW disagreed with the Examiner's assertion that Travers discloses using PCR products (i.e., using DNA that had undergone an amplifying step) as a template for generating sequence reads (i.e., for use in a sequencing step).

Furthermore, although UW may have used the word “amplification” when discussing Travers '075 during prosecution, this is a far cry from any so-called “admission” Guardant alleges UW made regarding Travers '075 disclosing the

¹ UW's Reply to Office Action cites Travers '075 ¶[0081]. EX1024, 551. This was a clerical error, with the intended citation to ¶[0083], evident from the quoted language. EX1024, 551; EX1018, ¶[0083].

claimed amplification step. Rather, Travers '075 ¶[0083], which UW discussed in the Reply to Office Action, discloses *sequencing-by-synthesis* using rolling circle replication – i.e., *not* an adapter-DNA molecule amplification step as claimed in the '127 patent. The relevant text from Travers '075 ¶[0083] is reproduced below:

By way of example, where a given *template is being subjected to a polymerase mediated sequencing process*, limitations on the readlength for the particular system may be factored into the selection of the overall template size, e.g., to ensure complete, and preferably redundant sequencing of the entire template.

See EX1018, ¶[0083] (emphasis added). Travers '075 clearly discloses that the “given template” is *directly subjected* to a “sequencing process” *during* rolling circle replication *without* amplifying prior to sequencing. *Id.* As discussed above in Sections IV(A)-IV(B), the Travers SMRT™ sequencing methods perform strand extension of the SMRTbell template and base calling *simultaneously* in real-time, which is different from the adapter-DNA amplification step that occurs prior to the sequencing step as claimed in the '127 patent.

Additionally, during prosecution of the '907 patent, the Examiner concluded that Travers did *not* disclose amplification of the first and second strand, stating “*Travers does not teach a method that comprises ‘amplifying each original strand of the double-stranded target nucleic acid molecule resulting in each original strand*

generating a distinct yet related set of amplified target nucleic acid products....”

EX1024, 582 (emphasis added).

Thus, the SMRT™ sequencing method of Travers and Travers '075 does not use a template amplification step after adapter attachment but prior to sequencing, as claimed in the '127 patent. Guardant's reliance on mischaracterized and out-of-context statements by UW does not cure the deficiencies of Guardant's primary references.

b. A passing reference to “amplification” in Travers '075 does not support Guardant's argument.

In alleging that Travers '075 discloses the “amplification” step as claimed, Guardant relies on a single, passing statement in Travers '075 referring to a hypothetical rolling circle replication step. Pet., 24-25, 31-32 (citing EX1018, ¶[0122]). But as shown below, this disclosure in Travers '075 fails to support Guardant's arguments. Travers '075 discloses a potential “rolling circle replication process” for template molecules, and in doing so relies on U.S. Pat. No. 7,476,503 (“the '503 patent,” EX2008):

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).*

EX1018, ¶[0122] (emphasis added).

Notably, Travers '075 begins this disclosure by expressly disclosing that the preferred embodiment in SMRTTM sequencing is to *sequence* the circular template molecules directly after adapter ligation *without a template amplification step. Id.* Travers '075 then speculates that concatemer molecules made from “rolling circle replication” may be “employed directly” as templates in a template-dependent sequencing process such as Travers 075's SMRTTM sequencing or as disclosed in the '503 patent. *Id.* However, nowhere does Travers '075 disclose *how* to modify the SMRTTM sequencing method (or the method of the '503 patent, for that matter) to utilize these concatemers in a sequencing workflow. Nor does Travers '075 disclose any applications in which this speculative modification would be useful. Given that Travers '075 discloses that the absence of a template amplification step

is an important advantage of the SMRT™ sequencing workflow, it is Guardant's burden to explain *why* a POSA would be motivated to modify the SMRT™ sequencing workflow of Travers '075 to produce concatemers prior to the template dependent sequencing process of Travers '075. As discussed below in Section V.C.1, neither Guardant nor Dr. Quackenbush provide any such explanation.

Travers '075's citation to the '503 patent does not cure this deficiency. Like Travers and Travers '075, the '503 patent does not disclose performing a template amplification after adapter ligation but before sequencing. To the contrary, the '503 patent discloses that its methods *minimize* any need for a template amplification step prior to sequencing:

This method also allows the use of target nucleic acid molecules taken *directly* from a biological sample, *minimizing the need for* cloning, subcloning, or *amplification* of the target nucleic acids *before sequencing* can take place.

EX2008, 23:51-54 (emphasis added); *see also, id.*, 33:24-27 (“In another preferred embodiment, *sequencing is performed with polymerases capable of rolling circle replication*”—i.e., the *sequencing* is performed with rolling circle replication, not template amplification prior to sequencing.).

In sum, Guardant failed to establish that Travers or Travers '075 teaches a template amplification step after adapter ligation but prior to sequencing, as

claimed. And as discussed below in Section V(C), Guardant and its expert failed to explain why a person of ordinary skill in the art would have modified the established SMRTTM sequencing methods of Travers and Travers '075 by interjecting an unnecessary template amplification step after adapter ligation. Guardant's failures are even more glaring in view of the fact that Travers, Travers '075, and the prior art all taught that the omission of a template amplification step in the Travers SMRTTM sequencing method is one of the important *advantages* of the method.

B. Neither NEB Expressions nor McCloskey cure any of the deficiencies of Travers and Travers '075.

In Ground 2, Guardant combines Travers and Travers '075 with NEB Expressions to challenge claim 11. Pet., 58-60. According to Guardant, “[t]he additional subject matter of claim 11 is disclosed by NEB Expressions.” *Id.*, 59. In Ground 3, Guardant combines Travers and Travers '075 with McCloskey to challenge claims 13-14 and 29-30. Pet., 60-65. There, Guardant relies on “the barcodes of McCloskey.” *Id.*, 63. Thus, Guardant *does not* rely on either of NEB Expressions or McCloskey for any of the elements of claims 1 or 22. *Id.* As such, Guardant's reliance on NEB Expressions or McCloskey does not cure any of the Petition's deficiencies outlined above in Section V(A). Institution on Grounds 2 and 3 should thus be denied.

C. The Board should also deny institution because Guardant fails to properly articulate why a POSA would have been motivated to modify Travers and Travers '075 and why a POSA would have had a reasonable expectation of success.

An assertion of obviousness “cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006)). As discussed below Guardant failed to articulate reasons a POSA would have modified the SMRT™ sequencing methods of Travers and Travers '075, and further failed to articulate why a POSA would have had a reasonable expectation of success in so doing.

1. Guardant fails to articulate a POSA's alleged reasons for modifying Travers and Travers '075.

As discussed above in Sections IV(A)-(C) and V(A)(1), the Travers SMRT™ sequencing method does not utilize a template amplification step after adapter ligation but prior to sequencing, as claimed in the '127 patent. Not only that, but the omission of a template amplification step after adapter ligation in SMRT™ sequencing was well known in the art as an *advantage* of the system. Travers itself discloses “this protocol for template preparation requires a minimal number of steps and *does not depend on amplification*.” EX1021, 5; *see also*, EX2002, 4331 (disclosing that Travers’ “[s]ample preparation time is decreased

since *template amplification is not needed*), Table 2; EX2003, 5; EX2004, 1065, Table 1 (disclosing that Travers requires “*no amplification*”); EX2005, 2 (disclosing that Travers uses “an *amplification free* workflow”), 9 (describing the “*amplification-free* library prep of PacBio”); EX2001, Table 1 (disclosing that one of the “pros” of SMRT™ sequencing was that “*no template amplification [is] needed.*”).

Neither the Petition nor Dr. Quackenbush even attempt to explain why a POSA would have rejected the established SMRT™ sequencing methods of Travers and Travers '075 in favor of modifying the references to interpose an amplification step after adapter attachment but before sequencing, as claimed. The Petition provides a single conclusory statement on an alleged reason to *combine* the references, arguing 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.” Pet. at 20; *see also*, EX1002, ¶63. Even if that were true, the “same PacBio methodology” disclosed in Travers and Travers '075 is the SMRT™ sequencing method, which *does not* use a template amplification step after adapter ligation but before sequencing. And neither Guardant nor its expert provides any reason whatsoever for why a skilled artisan would insert an amplification step after adapter ligation in the Travers' SMRT™

sequencing workflow. Yet *this amplification step after attaching adapters is required* before the sequencing step in every claim in the '127 patent.

“[E]ven if a reference is not found to teach away, its *statements regarding preferences are relevant* to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference.” *Polaris Indus. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018) (citing *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1051 n.15 (Fed. Cir. 2016) (en banc)). Here, Travers '075 expressly states that its *preference* is to use its circular templates directly in sequencing *without* any template amplification step. EX1018, ¶[0122] (“the constructs of the invention are described *primarily, and preferably*, for use *directly as templates* for, e.g., sequencing applications....”) (emphasis added). Thus, Travers '075's preference for omitting template amplification is directly relevant to a POSA's reason—or rather, lack of a reason—to modify the SMRT™ sequencing method by inserting a template amplification step after adapter ligation, as claimed. *Polaris*, 882 F.3d at 1069. Guardant and Dr. Quackenbush make no attempt to reconcile Travers '075's preference for the SMRT™ sequencing method with the protocol modifications that would be needed to arrive at the claimed method.

Guardant's failure to explain any rationale for modifying Travers and Travers '075 to include an unnecessary SMRTbell template amplification step in the SMRT™ sequencing method is a fatal flaw in its obviousness argument, and

the Board should deny institution. *See e.g., Johns Manville Corp. v. Knauf Insulation, Inc.*, IPR2018-00827, Paper 9, at 21 (P.T.A.B., Oct. 16, 2018) (informative); *see also, IPDataTel, LLC v. ICN Acquisition, LLC*, IPR2018-01822, Paper 19, at 19-20 (P.T.A.B., April 22, 2019) (denying institution because petitioner “fails to offer sufficient explanation as to *why or how* a person of ordinary skill in the art would have combined the teachings of [the asserted art], in order to render the claims obvious.” (emphasis in original); *Microchip Tech. Inc. v. HD Silicon Solutions LLC*, IPR2021-01421, Paper 13, at 8-9 (P.T.A.B., May 12, 2022) (denying institution due to petitioner’s failure to articulate reasons to combine or modify the references); *NetScout Systems, Inc. v. Longhorn HD LLC*, IPR2021-01258, Paper 11, at 8-9 (P.T.A.B., Feb. 10, 2022) (“[A] a party who 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.’” (quoting *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016))).

2. Guardant fails to articulate why a POSA would have had a reasonable expectation of success.

Guardant’s Petition also lacks any explanation of a reasonable expectation of success. Guardant advances a single sentence to explain an alleged reasonable expectation of success in Ground 1, stating that “a POSA would have been motivated and expected success in combining the teachings of the Travers

Publications because *each describe aspects of the PacBio workflow.*” Pet. at 20 (emphasis added); *see also*, EX1002, ¶63. Guardant then argues that the references disclose the elements of claim 1, and jumps to a conclusion that “the Travers Publications render obvious claim 1,” with no analysis or rationale for reasons to modify or reasonable expectation of success. Pet., 29; *see also, id.*, 37 (claim 22, same conclusory analysis). This falls well short of establishing *prima facie* obviousness. *See Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017) (holding it is not enough “to merely demonstrate that elements of the claimed invention were independently known in the prior art.”) In addition, Guardant also fails to articulate why a POSA would have had a reasonable expectation of successfully arriving at *any* of the challenged dependent claims in Ground 1. Pet., 37-58. “To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.” *Magnum Oil*, 829 F.3d at 1380. Guardant has not done so here, and the conclusory statements in the Petition fail to establish a reasonable likelihood of prevailing on any challenged claim.

Grounds 2 and 3 also suffer from the same deficiency. In Ground 2, Guardant provides a single conclusory sentence that a “POSA would have had a reasonable expectation of success because ... PCRTM Repair Mix is effective in

repairing deaminated cytosines and oxidized guanine.” Pet., 60. In Ground 3, Guardant again provides a single conclusory sentence that “[a] POSA would have expected success in using the random barcodes described in McCloskey because methods for making such oligonucleotides were well-known in the art.” Pet., 63. That is the entire extent of Guardant’s articulation of expectation of success in its Petition.

Guardant’s failure to articulate a POSA’s alleged reasonable expectation of success is more than sufficient reason for the Board to deny institution. Indeed, denial here would be consistent with other Board decisions involving a petitioner who failed to meet its burden of showing a reasonable expectation of success. *See e.g., Triller Inc. v. Tiktok PTE Ltd.*, IPR2022-00181, Paper 9, at 28 (P.T.A.B., May 16, 2022) (denying institution because “Petitioner provides no evidence that an ordinary artisan would have had a reasonable expectation of success....”); *Hewlett Packard v. Intellectual Ventures II LLC*, IPR2022-00115, Paper 9, at 15 (P.T.A.B., March 29, 2022) (denying institution because “Petitioner does not explain sufficiently, let alone with particularity, how or why the skilled artisan would have combined such distinct embodiments or had an expectation of success in doing so.”)

D. Guardant fails to address known objective indicia of nonobviousness.

The Petition is also facially defective for another reason. All three of Guardant's Grounds collectively challenge claims 1-30 as obvious. But Guardant fails to make a case of obviousness as a matter of law because it does not address known objective indicia of nonobviousness, namely industry praise of the invention of the '127 patent compared to Travers. This fatal defect means that Guardant's assertions have no reasonable likelihood of success.

All four *Graham* factors must be considered in an obviousness analysis. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Ignoring objective indicia in presenting an argument for unpatentability based on obviousness is, therefore, a fatal failure of proof. *Graham*, 383 U.S. at 17-18; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) (explaining that objective indicia of nonobviousness "must always when present be considered en route to a determination of obviousness"). Indeed, objective indicia of nonobviousness are "often ... the most probative and cogent evidence in the record." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (quoting *Stratoflex*, 713 F.2d at 1538).

Accordingly, objective indicia of nonobviousness must be addressed in a petition if they are developed and the petitioner is aware of them. *See Nike, Inc. v.*

Adidas AG, 812 F.3d 1326, 1335 (Fed. Cir. 2016) (“Importantly, we have repeatedly emphasized that an obviousness inquiry requires examination of all four Graham factors and that an obviousness determination can be made only after consideration of each factor.”) (citing, *inter alia*, *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012)).

The Board has “cautioned petitioners in prior proceedings that petitions may be denied if they do not address known evidence of secondary considerations.” *Stryker Corp. v. KFX Med. LLC*, IPR2019-00817, Paper 10 at 28 (P.T.A.B. Sept. 16, 2019); *see also Robert Bosch Tool Corp. v. SD3 LLC*, IPR2016-01751, Paper 15 (P.T.A.B. Mar. 22, 2017) (denying institution for failure to address objective indicia presented during an ITC proceeding); *Coalition for Affordable Drugs V LLC v. Hoffman-LaRoche, Inc.*, IPR2015-01792, Paper 14 (P.T.A.B. Mar. 11, 2016) (denying institution for failure to address objective indicia considered by Examiner during original prosecution); *Merial Ltd. v. Virbac*, IPR2014-01279, Paper 13 (P.T.A.B. Jan. 22, 2015) (denying institution for failure to address objective indicia considered by Examiner during original prosecution and noting “Merial was aware of the unexpected results showing which the Examiner found persuasive.... Merial should have addressed unexpected results in the first instance”); *Omron Oilfield & Marine, Inc. v. MD/TOTCO*, IPR2013-00265, Paper

11 (P.T.A.B. Oct. 31, 2013) (denying institution for failure to address objective indicia successfully argued in a reexamination).

Here, Guardant's failure to address the known evidence of objective indicia of nonobviousness is another significant shortcoming in the Petition. Indeed, Guardant is well aware of industry praise for the invention as recited in the challenged claims. Guardant cited, for example, Kirsch (EX2007) during prosecution of its own application that issued as U.S. Patent No. 10,889,858. Kirsch praises the '127 patent's claimed methods, speaking directly to the method's advances over 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." EX2007, 14289. Kirsch posited that Schmitt's duplex sequencing may "pave the way to explore the full power of NGS" and may ultimately "change the history of NGS." *Id.* As Kirsch further noted, the "enthusiasm [over duplex sequencing] is warranted because duplex sequencing reportedly reduces the error rate of NGS up to 10 million-fold." *Id.* This objective indicium of nonobviousness undermines Guardant's *prima facie* case and represents another procedural flaw in its Petition. Guardant's legal failure to address known objective indicia of nonobviousness thus provides a separate and independent basis to deny institution.

VI. THE BOARD SHOULD EXERCISE ITS DISCRETION UNDER § 325(d).

The Board should exercise its discretion to deny a petition when it offers substantially the same prior art or arguments that the Examiner previously considered. The Board has established a two-prong, six-factor test to determine whether to exercise discretion to deny a petition. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8-10 (P.T.A.B. Feb. 13, 2020) (discussing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017)). The Board should exercise its discretion and deny a petition that is based on art and arguments considered by the Office unless the Petition shows that the examiner made a material error. *Advanced Bionics*, Paper 6, 8-9. Under the first prong of the framework, the Board determines “whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office.” *Id.*, 8. The Board analyzes whether this prong is satisfied using *Becton* Factors (a), (b), and (d):

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;

- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art;

Id., 8-10, n.10.

If the prior art and arguments are common to both the petition and prosecution, the Board should not institute unless “the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Id.*, 8. The Petition does not meet its burden if it makes an argument upon which “reasonable minds can disagree.” *Id.*, 9. The Board analyzes whether a petition demonstrates material error using *Becton* Factors (c), (e), and (f):

- (c) the extent to which the asserted art was evaluated during examination;
- (e) whether petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Id., 8-10, n.10.

Guardant claims that “denial of institution under 35 U.S.C. § 325(d) is not appropriate here.” Pet., 65. Guardant is wrong. In fact, Guardant fails to address

any of the above factors head on. Under a proper analysis, the Board should exercise its discretion to deny institution under the *Advanced Bionics* framework, as set forth below.

A. Travers and Travers '075 were previously presented to the Office; NEB Expressions and McCloskey are cumulative of prior art evaluated during examination.

Guardant glosses over the assessment as to whether Travers and Travers '075 were previously presented to the Office and whether NEB Expressions and McCloskey are cumulative of prior art evaluated during examination. Pet at 65-67. But based on a proper evaluation of *Becton* Factors (a) and (b)² the Board should determine that the Petition presents the same or substantially the same art that was previously presented to the Office.

² The Board has held that a determination that the “Petitioner’s challenges raise substantially the same prior art previously presented to the Office, ... standing alone, warrants [the Board’s] assessment of the second” prong of the *Advanced Bionics* framework, and there was no requirement to address *Becton* Factor (d) if Factors (a) and (b) are met. *Ocado Grp. PLC v. AutoStore Tech. AS*, IPR2021-00398, Paper 10, at 20 (P.T.A.B., July 21, 2021); *see also Nespresso USA, Inc. v. K-Fee System GmbH*, IPR2021-01221, Paper 9, at 16-17 (P.T.A.B. Jan. 18, 2022).

Factors (a) and (b): There are no material differences between the asserted art and the prior art involved during examination, rendering the asserted art cumulative.

- Travers is specifically cited in the specification of the '127 patent. *See* EX1001, 10:64-66, 11:12-14 (citing and discussing Travers [49]), 33:22-25 (disclosing Travers as [49]).
- Travers was also cited in an IDS early on in examination and considered by the Examiner. EX1004, 139 (reference C69 in the IDS filed on Sept. 18, 2019), 379 (reference C69 indicated as considered by Examiner with issuance of the only rejection during prosecution on Jan. 24, 2020).
- Likewise, Travers '075 was cited in an IDS and considered by the Examiner. *Id.*, 134 (reference A24 in the IDS filed on Sept. 18, 2019), 374 (reference A24 indicated as considered by Examiner with issuance of the only rejection during prosecution on Jan. 24, 2020).

Because Travers is specifically cited in the specification and both Travers and Travers '075 were cited to the Office in an IDS, both references were “previously presented” to the Office. *Advanced Bionics*, Paper 6 at 7-8 (“Previously presented art includes ... art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent”). Thus, Guardant’s claim that “Section 325(d) should not

be applied to deny institution ... where references in a ground were listed on the IDS or even discussed in the body of the patent” is specious. Pet at 66.

As for NEB Expressions and McCloskey, Guardant fails to explain why or how either reference is not cumulative of other references previously presented to and considered by the Examiner. For example, Guardant fails to explain why or how NEB Expressions is not cumulative of other references previously presented to and considered by the Examiner, such as Stiller, Shibutani, or Lindhal, each of which are cited and discussed in the '127 patent specification and were considered by the Examiner. EX1001, 2:47-62 (citing Lindahl [43]), Shibutani [45], and Stiller [46]); *id.*, 33:1-12 (identifying references [43], [45], and [46]); EX1004, 138-139 (Lindahl [C44], Shibutani [C63], and Stiller [C66] cited in IDS filed on Sept. 18, 2019), 378-379 (references C44, C63, and C66 indicated as considered by Examiner on January 24, 2020). Lindahl, Shibutani, and Stiller disclose that deaminated cytosine and oxidized guanine were known types of DNA damage, which is cumulative of the disclosures in NEB Expressions. EX2010, 1898-1899; EX2011 431-432; EX2012, 13582.

Likewise, Guardant fails to explain why or how McCloskey is not cumulative of other references previously presented to and considered by the Examiner, such as McCloskey 2007 (EX2013) or Miner. Both McCloskey 2007 and Miner were cited and discussed in the '127 patent specification and were

considered by the Examiner. *See* EX1001, 2:15-18 (citing Miner [34] and McCloskey 2007 [35]); *see also id.*, 32:33-39 (identifying references [34] and [35]); EX1004, 138 (McCloskey 2007 [C48] and Miner [C51] cited in IDS filed on Sept. 18, 2019), 378 (references C48 and C51 indicated as considered by Examiner on January 24, 2020). McCloskey 2007 and Miner disclose randomer barcodes of varying lengths, just as in McCloskey. Indeed, McCloskey's Example 6 is merely a republication of disclosures in Miner. *Compare* EX1023, ¶¶[0092]-[0106], Figs. 3-4, *with* EX2009, 1-4, Figs. 1-2.

Moreover, there is no requirement that the asserted references be applied by the Examiner in a rejection to find that the first prong of the *Advanced Bionics* framework has been met. *Nespresso*, Paper 9 at 12 (finding references cited in an IDS and indicated as considered by the Examiner as “undeniably ... presented to the Examiner,” even though the references were not raised in a rejection).

Nevertheless, the Examiner indicated in a Notice of Allowance issued on July 15, 2020 that the closest prior art was allegedly U.S. Patent No. 9,862,995 (“Patel”), which was cited on the same IDS as McCloskey 2007, Miner, Lindahl, Shibutani, and Stiller on September 18, 2019. EX1004, 133 (reference A17), 432-433. The prosecution history of the '127 patent, therefore, indicates that the Examiner did consider Travers and Travers '075 but did not find them material to the patentability of the challenged claims. And because both Travers and Travers

'075 are the same references previously presented to the Office, and NEB Expressions and McCloskey are substantially the same as other references presented to the Office, their disclosures necessarily are cumulative with the art considered during examination.

B. Guardant fails to demonstrate that the Office erred in its previous assessment of the asserted art in a manner material to the patentability of the challenged claims.

Guardant fails to demonstrate that the Office erred in its previous assessment of Travers, Travers '075, and references substantially similar to NEB Expressions and McCloskey in a manner material to the patentability of the challenged claims by: (1) failing to take into account that the examination record indicates that the Examiner *did* assess the prior art; and (2) failing to present any evidence or facts in the Petition that warrant reconsideration of Travers and Travers '075, and consideration of NEB Expressions and McCloskey.

Factor (c): Guardant has not demonstrated that the asserted art was not evaluated during examination.

While *Becton* Factor (c) “evaluates ‘the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection,’ the focus should be on the record” of examination. *Advanced Bionics*, Paper 6 at 11. As discussed for *Becton* Factors (a) and (b), the examination record indicates that the Examiner did consider Travers, Travers '075, and references substantially similar to NEB Expressions and McCloskey, and found them lacking.

Indeed, the Examiner indicated that Travers, Travers '075, and references substantially similar to NEB Expressions and McCloskey were considered when issuing the only rejection during prosecution of the '127 patent. EX1004, 374, 378-379. The Examiner also conducted an interview with the applicants to discuss “[t]he substance of the [claimed] method.” *Id.*, 435. The Examiner pointed to Patel—not Travers, Travers '075, or references substantially similar to NEB Expressions and McCloskey—as allegedly being the closest prior art. *Id.*, 432-433. The Examiner additionally provided analysis of Patel in view of the pending claims. *Id.*

Guardant fails to meaningfully assess the Examiner's statements and activity in the examination record, claiming that “[l]imited activity during *ex parte* prosecution indicates the prior examination was cursory at best.” Pet., 66. But what is cursory is Guardant's attempt to address the examination record. Guardant's “paucity of analysis” weighs in favor of discretionary denial. *Nespresso*, Paper 9 at 26-27.

Factors (e) and (f): Guardant has not pointed out sufficiently how the Office erred in evaluating the asserted prior art and has not presented additional evidence or facts in the Petition that warrant reconsideration of the prior art or arguments.

In assessing *Becton* Factor (e), the Board “consider[s] whether Petitioner ‘point[s] out sufficiently how the examiner erred in its evaluation of the asserted prior art.’” *Nespresso*, Paper 9 at 25. In assessing *Becton* Factor (f) the Board

look[s] for some explanation of how or why ‘the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.’” *Id.*, 25. Here, the Petition does not point out sufficiently how the Examiner erred or that NEB Expressions and McCloskey present additional evidence that warrants reconsideration of Travers and Travers ’075. Pet., 65-67.

First, as discussed above for *Becton Factor* (c), Guardant’s allegation that “examination was cursory at best” is unfounded.

Second, Guardant does not assert that the Examiner overlooked any disclosure in Travers and Travers ’075; instead Guardant argues that “there was no apparent consideration of Patent Owner’s admissions regarding Travers ’075 ... before a different Examiner.” Pet. at 66. This argument fails because, as discussed above in Section V(A)(1), Guardant mischaracterized UW’s statements concerning the disclosures in Travers ’075. Moreover, UW’s statements concerning Travers ’075 were made in a Reply to Office Action on February 18, 2021, over five months *after* the ’127 patent issued. EX1024, 551, 555; EX1001, cover.

Nor has Guardant made a showing that the Examiner did not consider the disclosures of Travers and Travers ’075 and found any alleged “pertinent disclosures” of the reference relevant. Guardant’s lack of direct allegations about what the Examiner supposedly overlooked in Travers and Travers ’075 counsels that the Board should exercise its discretion under § 325(d). *Google v. Kewazinga*

Corp., IPR2021-00527, Paper 16, at 19 (P.T.A.B. Aug. 24, 2021) (“[W]hether a reference was a basis for a rejection is not dispositive, especially here where Petitioner does not identify any specific teaching that the Examiner misapprehended or overlooked.”)

In sum, Guardant's claims are without merit: Guardant has failed to demonstrate (1) that the Examiner materially erred or (2) that Guardant has presented additional evidence or facts in the Petition that warrant reconsideration of Travers and Travers '075 or consideration of NEB Expressions and McCloskey.

* * *

Under a fulsome analysis of the *Becton* Factors, it is clear that (1) the Grounds set forth in the Petition are based on the same or substantially the same art previously presented to the Office and (2) Guardant fails to direct the Board to information sufficient to establish material Examiner error or evidence in the Petition that warrant consideration of the asserted art. The Board should exercise its discretion to deny institution under § 325(d).

VII. CONCLUSION

Guardant has failed to demonstrate that it is reasonably likely to prevail with respect to any challenged claim and has not presented its grounds with sufficient particularity. Guardant has also not demonstrated that institution is warranted under § 325(d). Institution of *inter partes* review should be denied.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/R. Wilson Powers III/

Date: July 20, 2022
1100 New York Avenue, NW
Washington, DC 20005
(202) 371-2600

Ralph Wilson Powers III, Ph.D.
Registration No. 63,504
Lead Attorney for Patent Owner

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

Patent Owner certifies that this Patent Owner's Preliminary Response is 9,973 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/R. Wilson Powers III/

Date: July 20, 2022
1100 New York Avenue, NW
Washington, DC 20005
(202) 371-2600

Ralph Wilson Powers III, Ph.D.
Registration No. 63,504
Lead Attorney for Patent Owner

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

I certify that the above-captioned **PATENT OWNER'S PRELIMINARY RESPONSE** and associated **Exhibits 2001-2013** were served in their entirety on July 20, 2022, upon the following parties via email:

Michael T. Rosato
Jad A. Mills
Sonja R. Gerrard
WILSON SONSINI GOODRICH & ROSATI
701 Fifth Avenue, Suite 5100
Seattle, WA 98104
mrosato@wsgr.com
jmills@wsgr.com
sgerrard@wsgr.com

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/R. Wilson Powers III/

Dated: July 20, 2022
1100 New York Avenue, NW
Washington, DC 20005
(202) 371-2600

Ralph Wilson Powers III, Ph.D.
Registration No. 63,504
Lead Attorney for Patent Owner