

IPR2022-00817

Guardant Health, Inc.

v.

University of Washington



University of Washington Oral Hearing
Demonstratives

June 15, 2023

Demonstrative Exhibit—not evidence

EX2074
Guardant Health, Inc. v. Univ. of Washington
IPR2022-00817

The '127 Patent's groundbreaking sequencing technology

U.S. Patent 10,760,127



EX1001, Fig. 1; Inst. Dec., 3

EX1001, 21:46-49; POR, 68

EX1001, 3:64-65; POR, 68

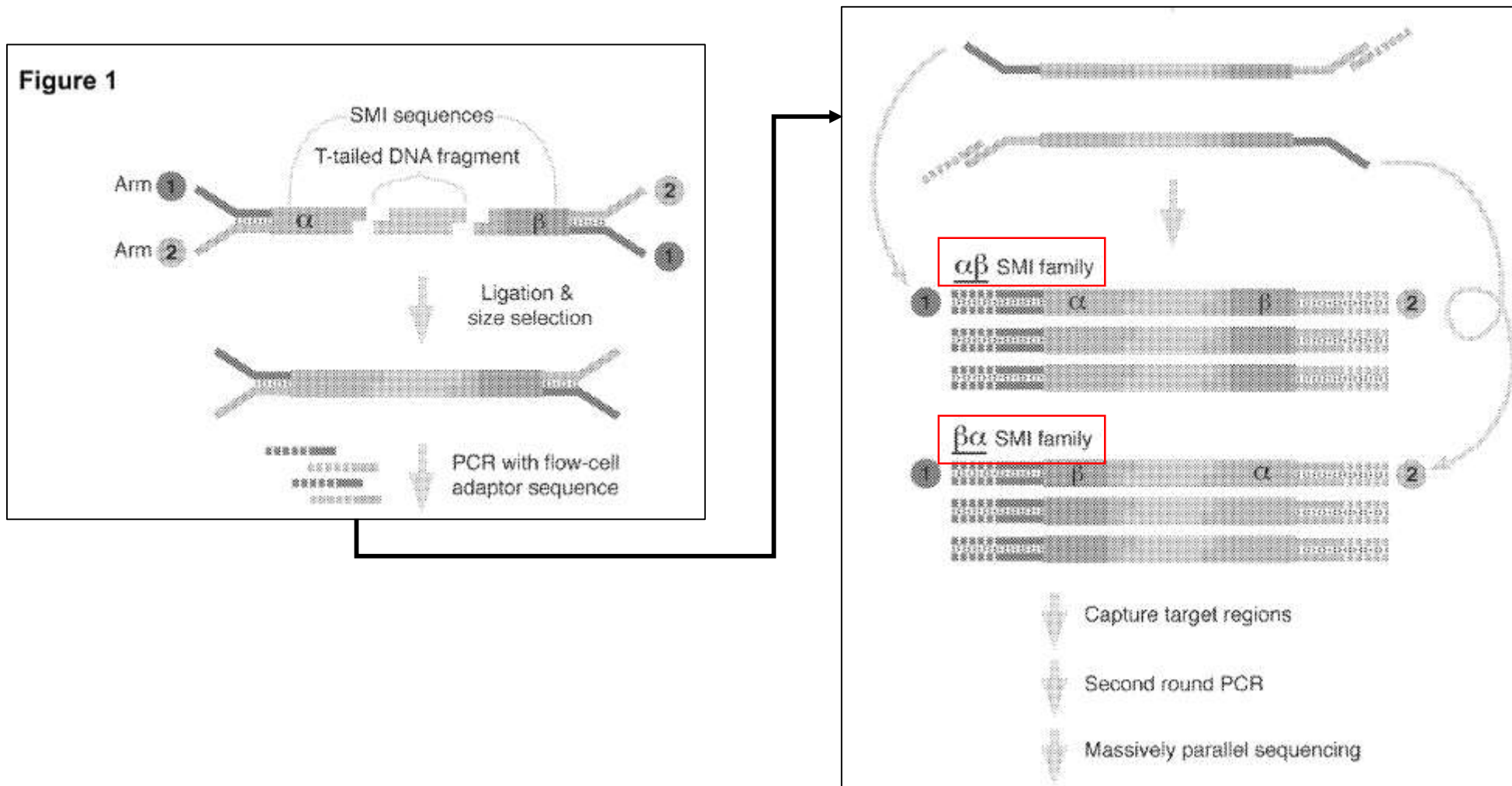
“Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing.”

those of the other half of the same molecule. Duplex Consensus Sequencing (DCS), significantly lowers the error rate of sequencing. In some embodiments, the DCS method

vidually tagged strands are then PCR amplified. Every duplicate that arises from a single strand of DNA will have the same SMI, and thus each strand in a DNA duplex pair generates a distinct, yet related population of PCR duplicates after amplification owing to the complementary nature of the SMIs on the two strands of the duplex. Comparing the

duplicates. By virtue of the asymmetric nature of adapted fragments, two types of PCR products are produced from each capture event. Those derived from one strand will have

Overview of Duplex Consensus Sequencing



Guardant's RCR Embodiment

Demonstrative Exhibit—not evidence

Guardant's Rolling Circle Replication Embodiment

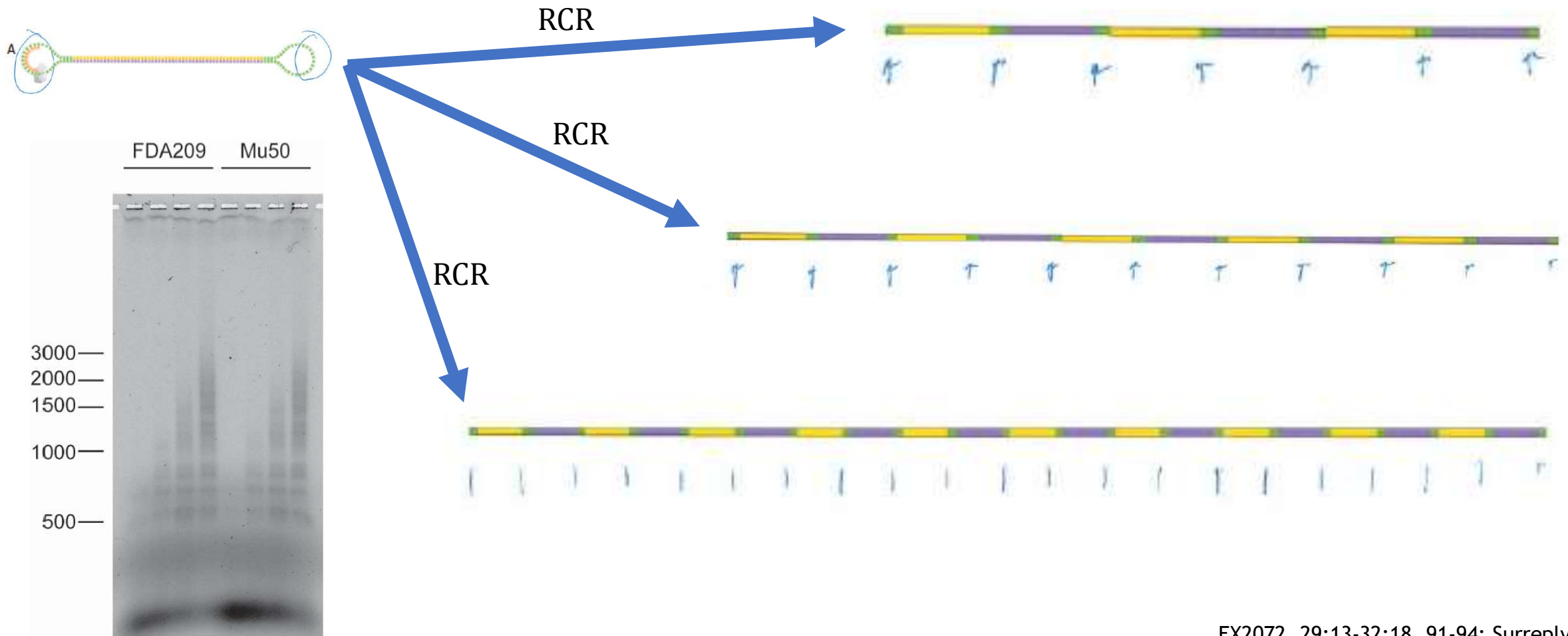
Petition

mediated sequencing process.” EX1018, ¶83. Travers further describes amplification of template molecules prior to redundant sequencing. For example, Travers explains that “rolling circle replication” of SMRTbell templates produces concatemer molecules comprising “repeating copies of both the sense and antisense strands of the originating double stranded segment.” EX1018, ¶122; *see also* EX1021, Figure 1, Figure 4. Travers further explains that these “replicated products may then be employed directly as template molecules in a template dependent sequencing process.” EX1018, ¶122. Accordingly, the Travers

Pet., 24-25; POR, 3

Guardant's RCR embodiment fundamentally changes the template from a circular SMRTbell to large, linear concatemer molecules

SMRTbell template



EX1021, Fig. 3

Demonstrative Exhibit—not evidence

EX2072, 29:13-32:18, 91-94; Surreply, 18-19;
EX2014, ¶¶98, 122, 178; POR, 29, 47; EX1021, Fig. 3

Dr. Larrea admitted that SMRT sequencing was a “nascent” technology

Dr. Larrea Deposition Transcript (EX2072)

Q. Sure. This passage says that these technologies were recently developed.

So my question was: SMRT sequencing was nascent, cutting-edge technology in 2010. Correct?

MR. MILLS: Same objections.

A. In 2010 PacBio was cutting-edge technology.

Q. So you agree that it was cutting-edge technology as of 2010?

A. Yes.



Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1254 (Fed. Cir. 2004)

“Nascent technology, however, must be enabled with a ‘specific and useful teaching.’”

**A POSA would have had no reason to
combine Travers 2010 and Travers '075 to
arrive at the '127 patent claims**

Guardant relies on both Travers 2010 and Travers '075 to allegedly meet all the claim limitations

Petition

This petition relies on a patent publication and a paper describing sample preparation and sequencing methods developed at PacBio. These publications are collectively referred to as “The Travers Publications” and are described below.

Pet., 6; Surreply, 14; POR, 25-26

Petition

A. [Ground 1] Claims 1-10, 12, 15-28 are unpatentable as obvious under 35 U.S.C. §103 over the Travers Publications

As explained herein, the combination of Travers '075 and the Travers Paper disclose or teach every element of claims 1-10, 12, 15-28. Travers '075 describes

Guardant relies on a combination of Travers 2010 and Travers '075

Both Travers '075 and Travers 2010	Only Travers '075	Only Travers 2010
Claims 1 preamble, 1.1, 1.3-1.7, 2, 5-8, 10-11, 19, 22, 29-30	Claims 1.2, 3, 12-18, 20-21, 23, and 26-28	Claims 9 and 24-25

Guardant fails to provide sufficient rationale for combining Travers 2010 and Travers '075

Petition

described in Travers '075. 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. Moreover, 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. *See also*

Pet., 20; Surreply, 14; POR 23-29



Trivascular Inc. v. Samuels, 812 F.3d 1056, 1066 (Fed. Cir. 2016)

“the Board ‘must still be careful not to allow hindsight reconstruction of references ... without any explanation as to *how* or *why* the references would be combined to produce the claimed invention”

'127 Patent claims require amplifying after attaching adapters and before sequencing

Claim 1:

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

Claim 22:

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

Board Agreed with Univ. of Washington Regarding Sequence of Steps Claimed

IPR2022-00817 Institution Decision



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. Institution Decision (Paper 14), 9-10

Guardant does not dispute that the ’127 patent claims recite an amplification step that is followed by sequencing

Pet., 3-4

Demonstrative Exhibit—not evidence

A POSA would have understood that a major advantage of the PacBio SMRT sequencing workflow was it did not use amplification after ligation

Travers 2010 (EX1021):

aration. Furthermore, this protocol for template preparation requires a minimal number of steps and does not depend on amplification.

EX1021, 5; POR, 24, 26



Polaris Indus. v. Arctic Cat, Inc., 882 F.3d 1056, 1069 (Fed. Cir. 2018)
“[A reference’s] statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference.”

POR, 26

Prior art taught the advantages of no amplification in the SMRT sequencing workflow

Niedringhaus

Advantages

Long average read lengths; decreased sequencing time compared to first-gen platforms; no amplification of sequencing fragments; longest individual reads approach 3,000 bases

EX2002, 4330, Table 2; POR, 24

Schadt

to result in a matter of minutes as opposed to days (14). In addition, SMRT sequencing does not require routine PCR amplification needed by most SGS systems, thereby avoiding systematic amplification bias. Because the processivity of the

EX2023, 7; POR, 24

Liu

The key difference between NGS and single-molecular sequencing technology is that, in NGS, DNA molecules have to be amplified before sequencing, while the latter enables us to sequence a single DNA molecule; thus, avoid the time, error and cost associated with sample preparation and amplification. Single Molecule Real Time (SMRT™)

EX2024, 4; POR, 24-25

next generation sequencing. The sample needed for running SMRT™ DNA sequencing is ~1 ng of DNA, which suggests that no PCR amplification is needed. This also lowers the risk of having systematic amplification bias.

EX2024, 3; POR, 25

Demonstrative Exhibit—not evidence

Guardant never explains why POSA would have sought to toss aside the established and advantageous SMRT sequencing workflow in Travers-2010

Nowhere in the Petition or in Dr. Quackenbush's declaration does Guardant explain why a POSA would have opted to modify the advantageous SMRT sequencing workflow in Travers 2010 with Travers '075's RCR step.

POR, 25

Dr. Satija (UW)

amplification process. EX2017, 2; EX2068, 6. As such, a POSA would have known that introducing an unnecessary amplification step into the amplification-free SMRT sequencing workflow, as Dr. Quackenbush proposes, would only make SMRT sequencing worse by generating more sequence errors into the already error-ridden SMRT sequencing workflow. Indeed, SMRT sequencing was already

EX2014, ¶111; POR, 26-27



Personal Web Techs., LLC v. Apple, Inc., 848 F.3d 987, 994 (Fed. Cir. 2017)

“a clear, evidence-supported *account of the contemplated workings of the combination* is a prerequisite to adequately explaining and supporting a conclusion that a relevant skilled artisan would have been motivated to make the combination and reasonably expect success in doing so.”

Demonstrative Exhibit—not evidence

POR, 25, 57

POSA would have understood that introducing an unnecessary amplification step into the SMRT sequencing workflow would introduce errors

Johne 2009 (EX2017)

The 3'-to-5' DNA exonuclease activity of the phi29 polymerase enables the enzyme to perform proofreading, which makes it suitable for genetic studies. Its error rates have been calculated to be between 10^{-5} and 10^{-6} in biochemical assays [26], or 9.5×10^{-6} by direct sequencing of 500 000 bp after phi29 polymerase-mediated amplification [27].

EX2017, 2; EX2014, ¶111; POR, 26; Surreply, 16

Egan 2012 (EX2006)

Pacific BioScience PacBio
HRS ¶

Highest error
rates, requires
multiple rounds
of sequencing
to reduce

EX2006, 5; POR, 27; EX2014, ¶111

Esteban 1993 (EX2068)

11). With Mg^{2+} , the error frequency (the inverse of the insertion discrimination factor; see (4)) of $\phi 29$ DNA polymerase ranged from 2.2×10^{-5} (T:dCMP misinsertion) to 4×10^{-6} (T:dTMP misinsertion); the T:dGMP misinsertion showed an intermediate frequency (5×10^{-6}). Using Mn^{2+} as the

EX2068, 6; EX2014, ¶111; POR, 26; Surreply, 16

Guardant does not contest that RCR would introduce errors

Dr. Satija (UW)

111. For starters, a POSA would not have wanted to include an additional amplification step into the SMRT sequencing workflow because of the known error rates associated with DNA polymerases. For example, the polymerases used

EX2014, ¶111; POR, 26; Surreply, 16

PO Surreply

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

Surreply, 16

Demonstrative Exhibit—not evidence

Guardant's RCR embodiment creates critical problems

Problem 1: RCR linear concatemers would bind multiple polymerases per concatemer molecule, rendering the sequencing data completely unreadable.

Problem 2: the smaller-sized RCR replication products would not possess sufficient copies of the target DNA required for SMRT sequencing, rendering them unsuitable for SMRT sequencing applications.

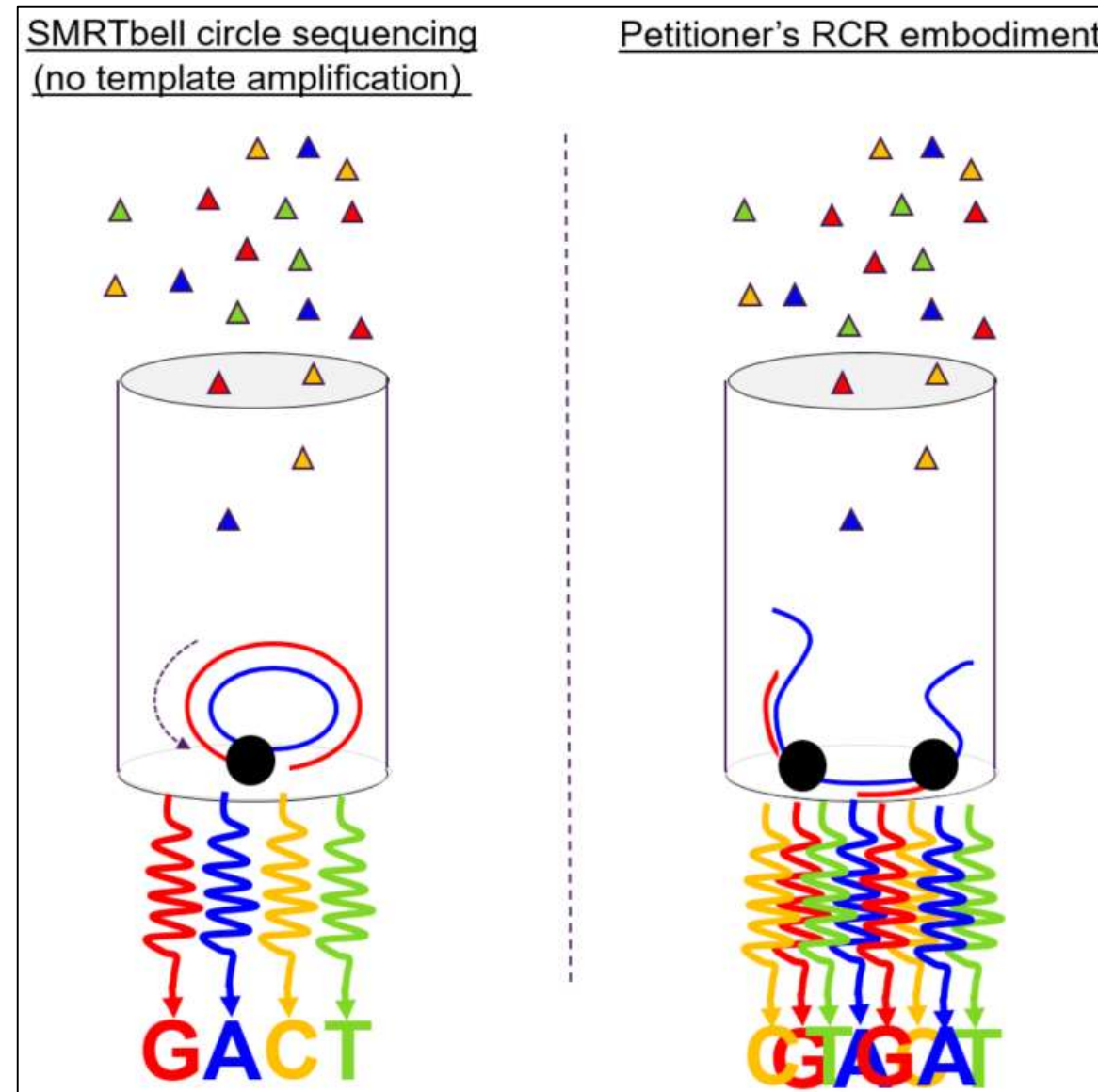
Problem 3: due to their slower diffusion, the large linear concatemers would not efficiently compete for occupancy in the ZMW wells for SMRT sequencing.

Problem 4: the large linear concatemers would form complex secondary structures and be unable to fit into the tiny ZMW wells for SMRT sequencing.

Problem 1: multiple polymerase binding would render data unreadable

Demonstrative Exhibit—not evidence

Problem 1: If two or more polymerases bind to the floor of a ZMW, the data would be unusable



Demonstrative Exhibit—not evidence

EX2014, ¶134-135; POR, 33-35

Problem 1: SMRT sequencing requires that the ternary complex be distributed at one complex per ZMW well

Eid 2009 (EX2001)

Experimental geometry. A single molecule of DNA template-bound Φ 29 DNA polymerase is immobilized at the bottom of a ZMW, which is illuminated from below by laser light. The ZMW nanostructure provides excitation

EX2001, 3; EX2014, ¶130; POR, 32

Niedringhaus 2010 (EX2002)

Once the ZMW array fabrication and detection scheme was established, the major technical hurdles for this technology came in the form of immobilizing a single functioning DNA polymerase at the bottom of each ZMW, which can process fluorescently labeled nucleotide substrates. This was accomplished in two

EX2002, 4; EX2014, ¶130; POR, 32

PacBio Backgrounder (EX2021)

The ZMW provides a window for watching DNA polymerase as it performs sequencing by synthesis. Within each chamber, a single DNA polymerase molecule is attached to the bottom surface such that it permanently resides within the detection volume. Phospholinked nucleotides, each type labeled with a different colored

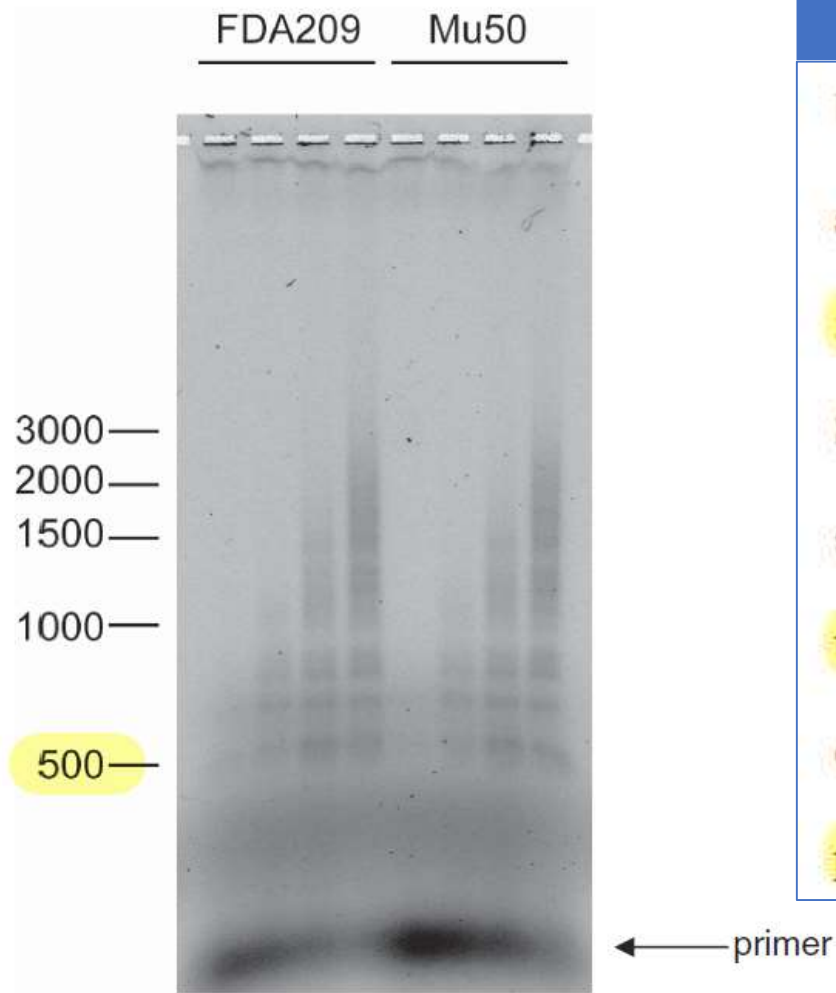
EX2021, 4; EX2014, ¶130; POR, 32

In this way, each ZMW provides a window that enables the real-time observation of a single molecule of DNA polymerase as it synthesizes DNA, with the ability to detect a single incorporation event against the background of fluorescently labeled nucleotides at biologically relevant concentrations.

EX2021, 1; EX2014, ¶130; POR, 32

Problem 1: Guardant's RCR embodiment would have repeating copies of primer/polymerase binding sites

Travers 2010 (EX1021)



EX1021, Fig. 3; EX2014, ¶133; POR, 33

Dr. Satija (UW)

binding sites. For example, as discussed above, Travers 2010 discloses generating a range of rolling circle replication product sizes, the smallest of which is about 500 nucleotides long. EX1021, Fig. 3. However, Travers 2010 teaches that the SMRTbell circle template has a length of 336 nucleotides, which means that the smallest product at 500 nucleotides represents about 1.5 times around the circle template. EX1021, 4. With 1.5 revolutions around the SMRTbell circle template, or about 3 target copies, there would be at least two copies of the primer/polymerase binding site. EX1021, 4. Thus, a POSA would expect that the

Problem 1: Dr. Larrea admitted that linear concatemer templates would have numerous polymerase binding sites

SMRTbell template



Dr. Larrea identified **two polymerase binding sites** on a normal SMRTbell.

3 loops around SMRTbell template



Dr. Larrea admitted that there were **seven polymerase binding sites** produced from 3 loops around a SMRTbell.

5 loops around SMRTbell template



Dr. Larrea admitted that there were **11 polymerase binding sites** produced from 5 loops around a SMRTbell.

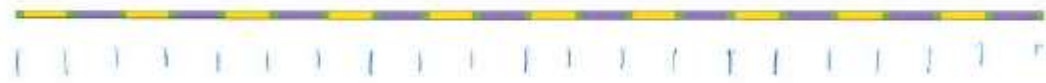
10 loops around SMRTbell template



Dr. Larrea admitted that there were **21 polymerase binding sites** produced from 10 loops around a SMRTbell.

Problem 1: Dr. Larrea admitted that linear concatemer templates would have numerous polymerase binding sites

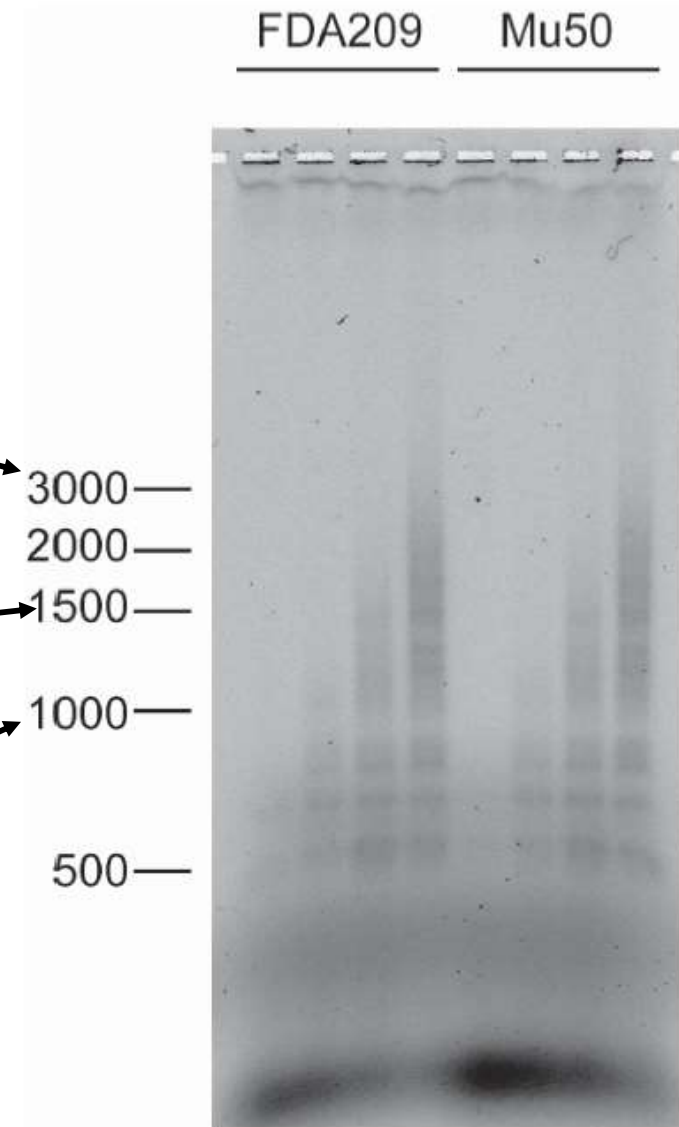
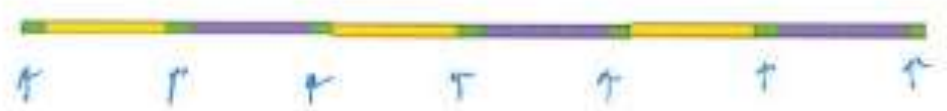
10 loops around SMRTbell template



5 loops around SMRTbell template



3 loops around SMRTbell template



Demonstrative Exhibit—not evidence

EX1021, 3, Fig. 3; POR, 31-33; Surreply, 18-19;
EX2014, ¶128-137; EX2072, 29:13-32:18, 91-94

Problem 1: Dr. Larrea admitted that polymerase binding is unpredictable

Dr. Larrea Deposition Transcript (EX2072)

Q. So if you look at Exhibits 3, 4, and 5, polymerase binding on each of these structures would be stochastic. Correct?

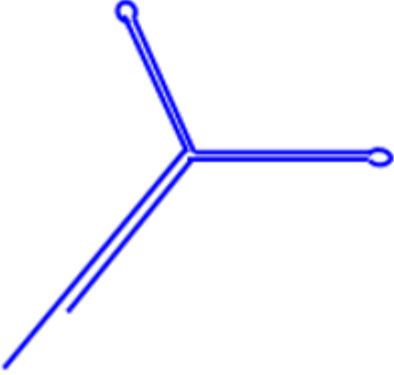
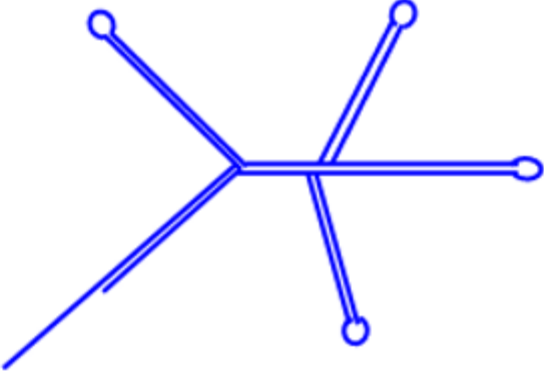
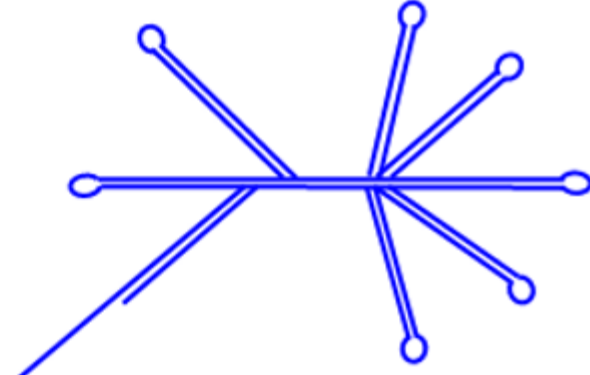
A. Yes.

Q. And there would be no way to control which of the binding sites bound polymerase over any other site. Correct?

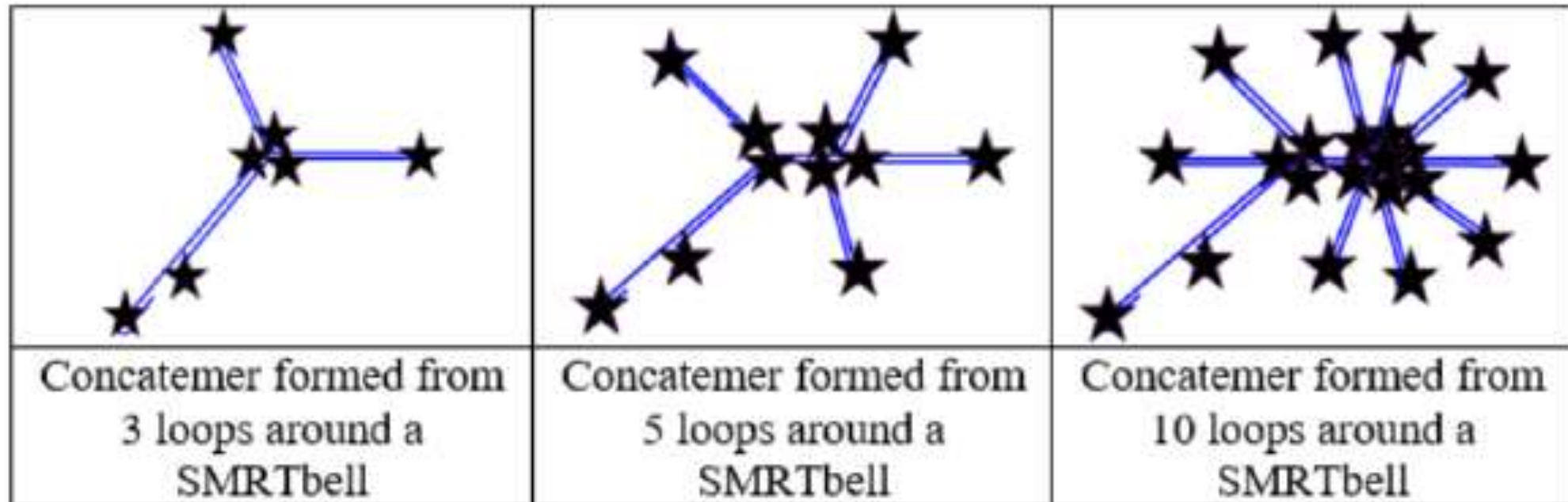
MR. MILLS: Objection to form. Scope.

A. Based on this cartoon, that is correct.

It is **undisputed** that Guardant's RCR concatemers form complex secondary structures

		
Concatemer formed from 3 loops around a SMRTbell	Concatemer formed from 5 loops around a SMRTbell	Concatemer formed from 10 loops around a SMRTbell

Problem 1: Guardant does not dispute that RCR concatemers would form secondary structures that multiple polymerases can bind to



★ = polymerase binding sites

Problem 1: Dr. Larrea admitted that the biotin-streptavidin interaction between polymerases and the ZMW floor is very “strong”

Dr. Larrea Deposition Transcript (EX2072)

Q. Do you agree that the interaction between streptavidin and biotin is one of the strongest noncovalent interactions in nature?

A. The strong interaction between biotin and streptavidin is often used for a variety of reasons. Whether it's the strongest, I can't speak to.

Q. Do you agree that it's very strong?

A. It's a strong interaction.

Problem 1: The art taught to avoid multiple polymerase molecules per ZMW

Eid 2009 (EX2001)

occupancy (34). At optimal loading, the distribution is 36.8% empty ZMWs, 36.8% with just one polymerase, and 26.4% with two or more.

EX2001, 4; Surreply, 21

Korlach 2008 (EX2030)

interval). The polymerase concentration was reduced 3-fold to yield lower total occupancies (average of $\approx 25\%$) to minimize contributions from multiply occupied ZMWs (SI Table 2 and SI Fig. 10). The histogram of DNA lengths synthesized in ZMWs

EX2030, 5; Surreply, 21

Problem 1: Dr. Larrea admitted that no useable data was generated from a ZMW with multiple polymerases

PacBio Glossary of Terms

- **productivity:** A measure of the reads from a ZMW. $P=1$ means that there is a polymerase read from that ZMW. $P=0$ means that a ZMW did not produce a read and is presumed to be lacking a polymerase. $P=2$ means “other” and the signal collected from the ZMW was not conducive to efficient base calling, possibly due to multiple template-polymerase complexes bound in the ZMW, high background signal, and so on.

EX2072, 96; Surreply, 21

Dr. Larrea Deposition Transcript (EX2072)

Q. (By Mr. Powers) And one of the reasons something could be a P2 is because there were multiple template-polymerase complexes bound in the ZMW. Right?

MR. MILLS: Objection to scope.

A. One of the reasons that it could be P2 would be that it just meant that no usable data was generated from that ZMW.

Demonstrative Exhibit—not evidence

EX2072, 41:12-18; Surreply, 21

Problem 1: Tomaney teaches excluding data from ZMWs when multiple polymerases are sequencing in the ZMW

US2009/0024331 (“Tomaney”) is incorporated by reference in Travers ’075

sequence data (See, e.g., Published U.S. Patent Application No. 2009-0024331, the full disclosure of which is incorporated herein by reference in its entirety for all purposes).

Surreply, 22; EX1018, ¶135, 141

Tomaney

originated. This information is used in specific embodiments to determine if multiples polymerase are sequencing in a ZMW, in which case data from that specific ZMW may be excluded from further data analysis. The location of a fluo-

Surreply, 22; EX2072, 189(¶178)

excluded from further analysis. Because large numbers of reaction locations are being prepared and monitored, it is expected that in some systems some percentage of reaction locations will not provide useful data. This may occur if no reaction enzyme becomes located in a particular ZMW, if more than one reaction enzyme is located in a ZMW or if a reaction enzyme is otherwise producing problematic data.

Surreply, 22; EX2072, 58:9-59:3, 189(¶181)

Dr. Larrea did not consider Tomaney

Dr. Larrea Deposition Transcript (EX2072)

Q. Did you review U.S. Patent Application 20090024331 before rendering your opinions in this case?

A. I did not. I focused my analysis on the four alleged problems that Dr. Satija raises in his declaration.

EX2072, 57:8-13; Surreply, 22

Dr. Larrea admitted that the goal of loading SMRTbell complexes onto ZMWs was to maximize the number of single polymerase-bound templates

Dr. Larrea Deposition Transcript (EX2072)

Q. Do you agree that the CMW loading as described in Travers 2010 and Travers 075 follow a Poisson distribution?

A. I agree that that was the goal of the loading.

Q. And the goal of a Poisson loading in the PacBio system is to obtain as many zero-mode waveguides as possible loaded with a single SMRTbell template. Correct?

A. It was the method used to maximize single loading --

Q. When you say --

A. -- of SMWs.

Q. I'm sorry. When you say "single loading," you mean a single polymerase-bound template in a zero-mode waveguide. Right?

A. In a zero-mode waveguide. That's correct.

Guardant wrongly argues that the stoichiometric optimum for the polymerase:template ratio is 2 polymerases bound to each template

The stoichiometric optimum for the polymerase:template ratio is 2 polymerases bound to each template molecule (one to each hairpin adapter).

EX1035, 34; Reply, 16

This sentence only reflects the optimum stoichiometric ratio for achieving Poisson distribution with normal SMRTbell templates, not large concatemers.

Dr. Larrea (Guardant)

number of templates that lack a bound polymerase. When every priming site of a template is complexed with a primer and polymerase, the potential for obtaining a sequence read for that template is maximized.

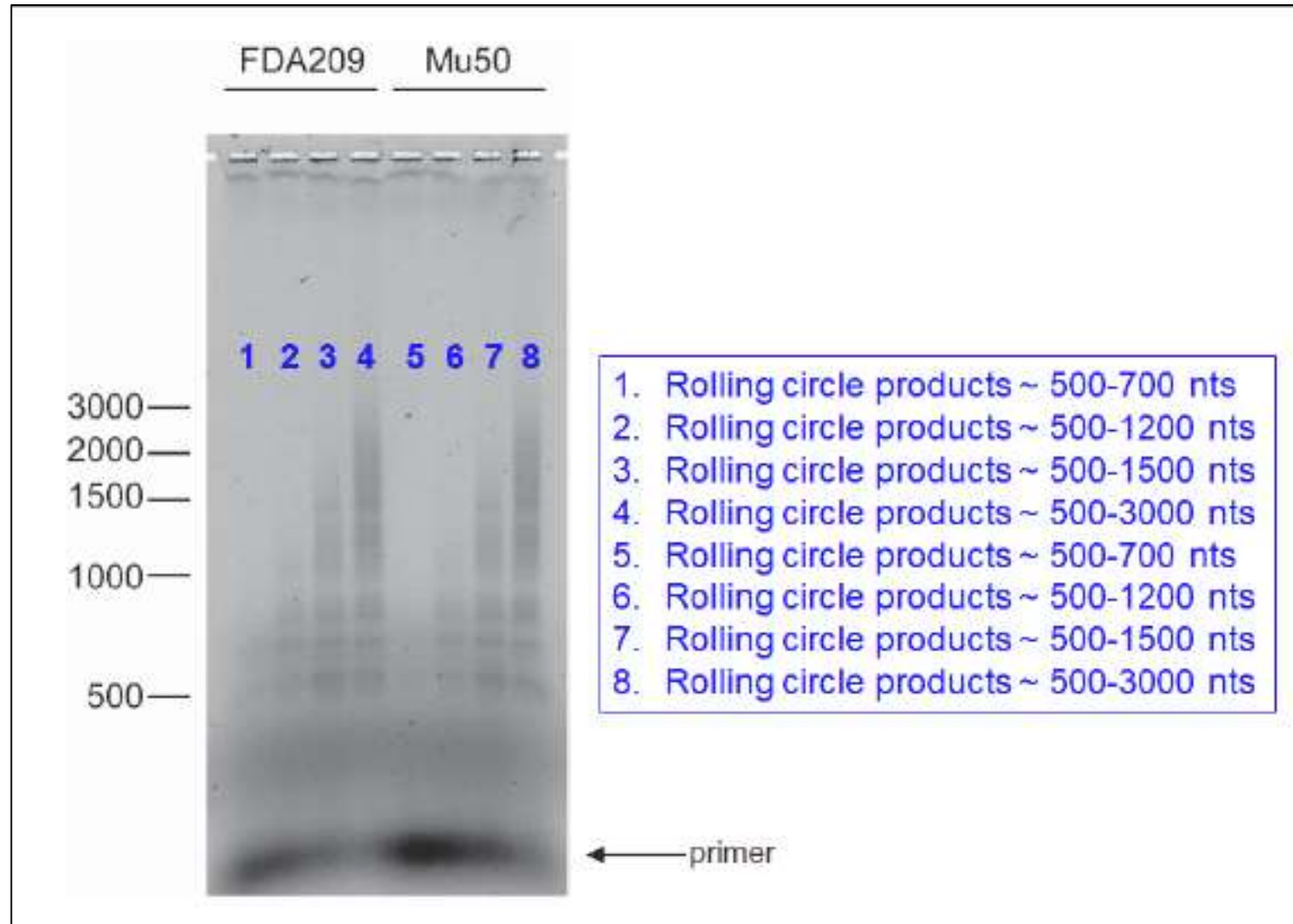
Demonstrative Exhibit—not evidence

EX1033, ¶10; Surreply, 22-23

Problem 2: smaller-sized RCR products would not possess sufficient copies required for SMRT sequencing

A POSA would have known that rolling circle replication produces a smear of reaction products with a wide range of sizes

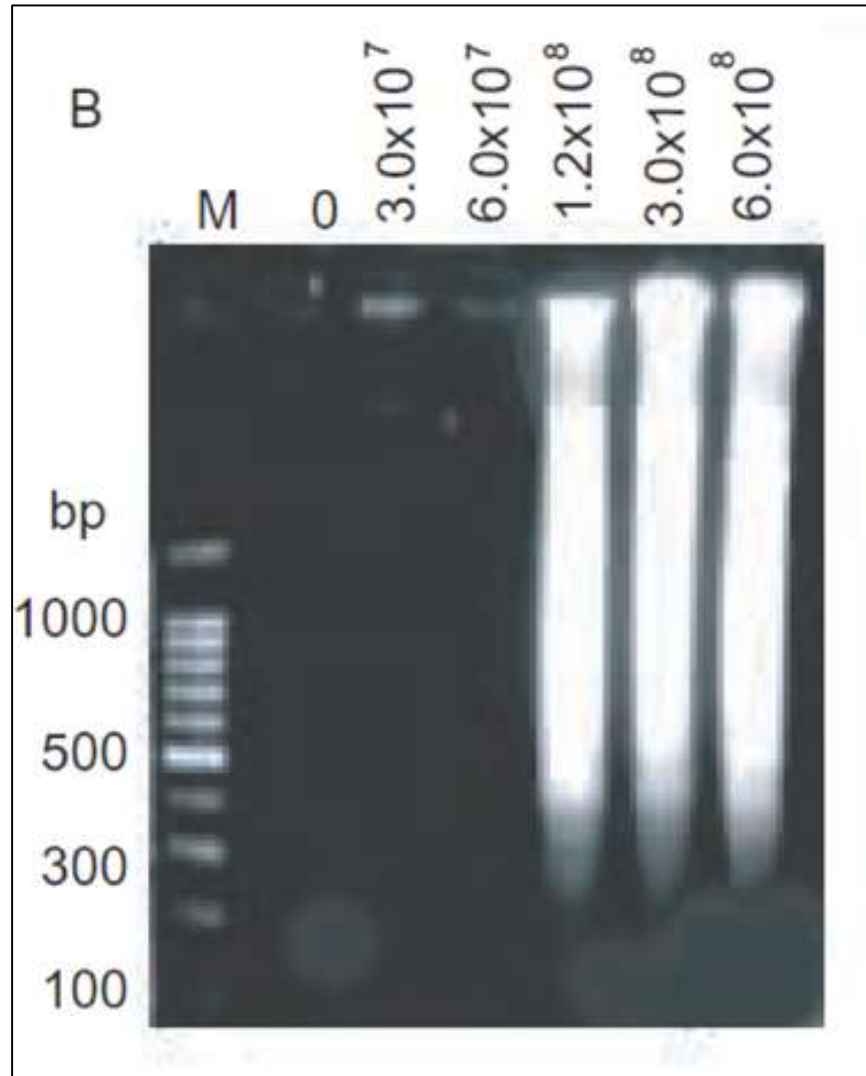
Travers 2010 (EX1021)



Demonstrative Exhibit—not evidence

EX1021, Fig. 3 (annotated); EX2014, ¶141;
POR, 35-36; Surreply, 24

The art taught that rolling circle replication produces a smear of products



Demidov 2002 (EX2036)

employs a pair of primers. The single-primed, or linear RCA (FIGURE 1A–C) results in the monotonous rolling out of long, repeated sequences of DNA with a gradual accumulation of RCA products. These products generally exhibit a wide, essentially continuous distribution over length and therefore cannot be resolved by gel electrophoresis yielding a broad smear of the high molecular weight DNAs (FIGURE 3B). As

EX2036, 2; EX2014, ¶142; POR, 37

EX2036, Fig. 3B; EX2014, ¶142; POR, 37

Demonstrative Exhibit—not evidence

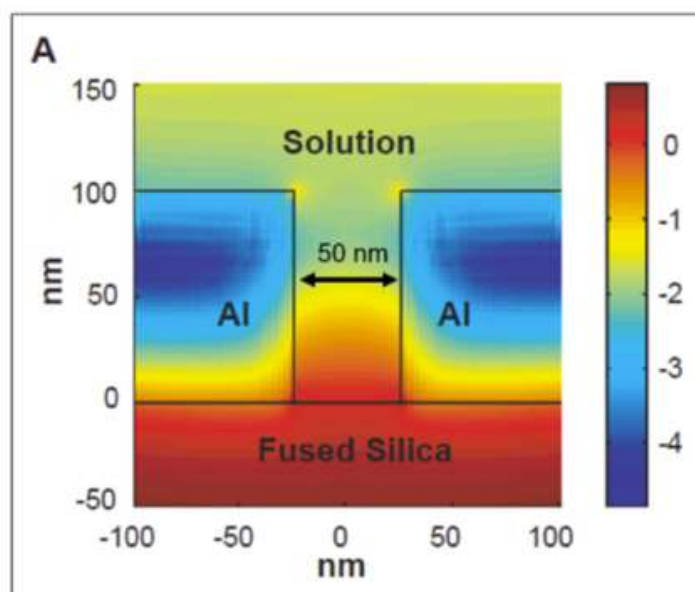
A POSA would have known that ZMWs are small with a diameter between 50-100 nm

Schadt (EX2023)

A ZMW is a hole, tens of nanometers in diameter, fabricated in a 100 nm metal film deposited on a glass substrate.

EX2023, 5; EX2014, ¶153; POR, 35, 45

Levene (EX2029)



Korlach (EX2030)

sively on the ZMW floor. Increased DNA polymerase loading was observed with larger ZMW diameters (Fig. 4B, black squares). The fraction of single DNA polymerase molecular occupancies was derived from these data by using Poisson statistics (Fig. 4B, gray circles). Single active polymerase loading to $\approx 30\%$ yield was achieved over a wide range of ZMW diameters (70–100 nm).

EX2030, 4; EX2014, ¶153; POR, 35, 45-46; Surreply, 22

Fig. 2. (A) Three-dimensional finite-element time-domain simulation of the intensity distribution (log scale) for a zero-mode waveguide 50 nm in diameter and 100 nm long. (B) $S(z)$ curves for different waveguide diameter, d . (C) V_{eff} and the corresponding concentration for which there is, on average, one molecule ($\langle N \rangle = 1$).

Problem 2: POSA would understand that there is a loading bias in favor of small templates

Zhang 2012 (EX2028)

However, there is a loading bias against large DNA fragments in the PacBio sequencing process. The PacBio technique uses single

(SMRT) cell. Smaller PCR products will load into the PacBio wells with a greater efficiency than larger PCR products. When PCR products ranging from 500 bp to 5 kb are pooled and sequenced together using PacBio, the smaller products have a substantially higher coverage than the larger products resulting in poor quality or incomplete sequences for the larger PCR products.

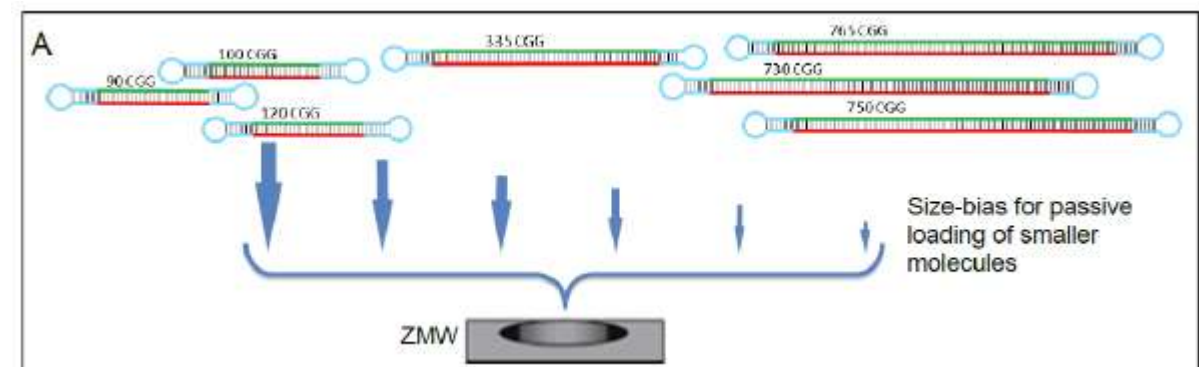
EX2028, 61; EX2014, ¶159; POR, 41-42

Coupland (EX2042)

the difference in plasmid length. There is a loading inefficiency of larger molecules because of their lower diffusion coefficient, as well as the disparity between the molecule's hydrodynamic radius and the very small zero-mode waveguide (ZMW). Future upgrades to the

EX2042, 4; EX2014, ¶161; POR, 42

Loomis (EX2046)



EX2046, Fig. S4 (excerpt); EX2014, ¶162; POR, 42

Demonstrative Exhibit—not evidence

Problem 3: large linear concatemers would not efficiently compete for occupancy in the ZMW wells

Problem 3: Larger concatemer products would be outcompeted by smaller products for diffusion into ZMWs

Dr. Satija (UW)

166. However, larger molecules would not fare any better. Larger concatemers generated from rolling circle replication would instead be outcompeted for occupancy of the ZMW wells by the smaller products due to DNA diffusion bias. EX2041, 3; EX2039, Fig. 1; EX2040, Fig. 1.

DNA diffusion bias. EX2041, 3; EX2039, Fig. 1; EX2040, Fig. 1. Dr.

Quackenbush has also not accounted for the well-known diffusion issues affecting large concatemer products that are associated with the SMRT™ sequencing applications of Travers 2010. A POSA would have also known that the large concatemer molecules produced from rolling circle replication would not readily diffuse into the narrow ZMW wells and would be inefficient templates for SMRT™ sequencing.

Guardant's Reply size-selection protocols do not solve the problem

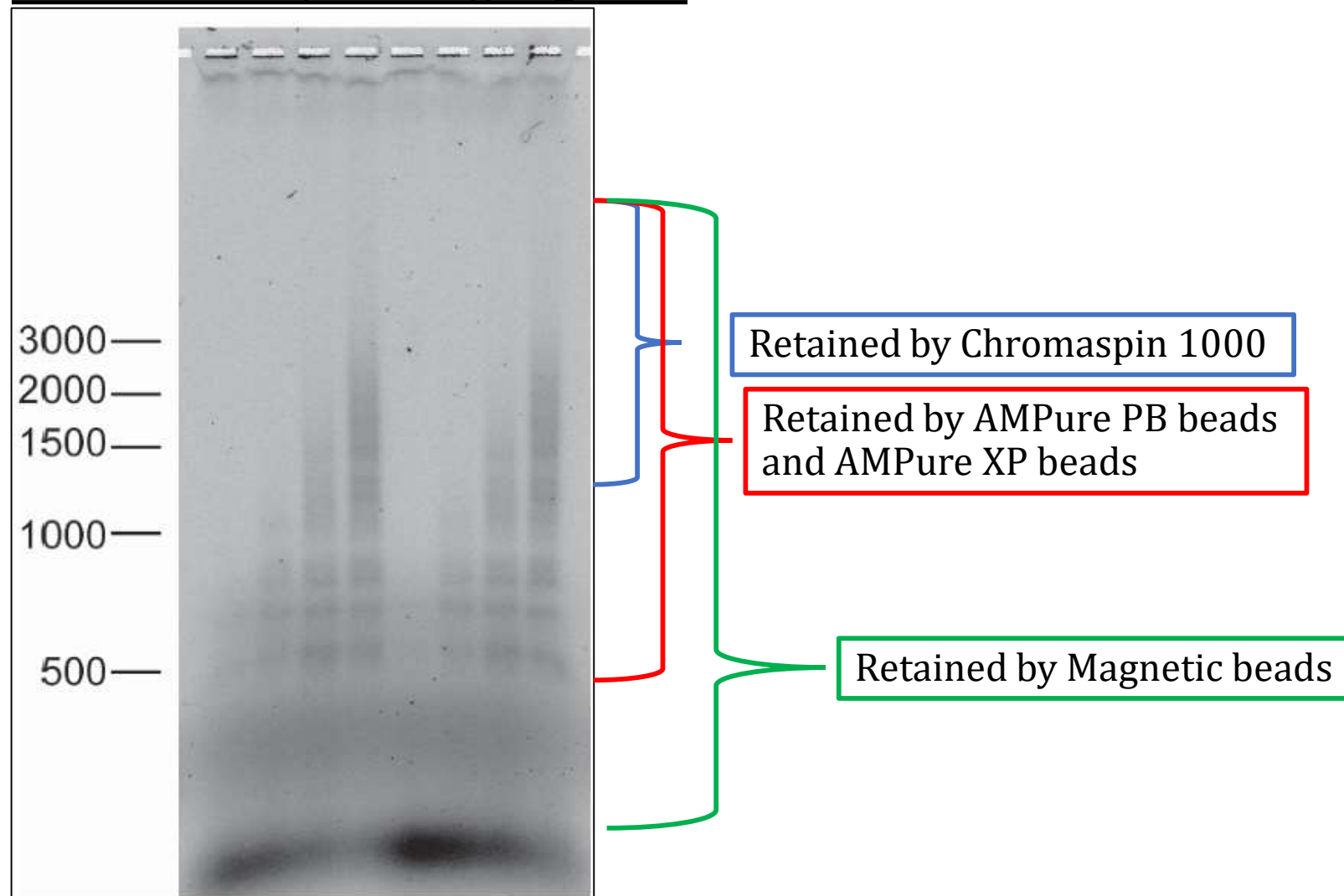
Guardant's new proposed size selection methods	Removes	Retains
ChromaSpin 1000	Products smaller than 300 bp	DNA larger than 1,350 bp
Magnetic beads	Hairpin dimers	DNA larger than hairpin dimers
AMPure PB beads	Products smaller than 400 bp	DNA larger than 400 bp
AMPure XP beads	Products smaller than 100 bp	DNA larger than 100 bp

Demonstrative Exhibit—not evidence

EX1018, ¶145; EX2072, 45:9-15, 48:1-8; 50:18-51:9, 108;
EX1035, 3, 24; EX1036, 12; Surreply, 24; Reply, 18-19

Guardant's size selection methods on Travers 2010 Figure 3

Travers 2010 (EX1021), Figure 3



Demonstrative Exhibit—not evidence

EX1021, Fig. 3; EX2072, 45:9-15, 48:1-8; 50:18-51:9, 108;
EX1035, 3, 24; EX1036, 12; Surreply, 24; POR, 33.

POSA would not have used gel electrophoresis as a size selection technique because it exposes DNA to intercalating dyes and UV radiation

PacBio Template Preparation and Sequencing Guide (EX1035)

Pacific Biosciences' template preparation process does not use amplification techniques. As a result, input DNA quality will be directly reflected in sequencing results. Any DNA damage (e.g., abasic sites, nicks, interstrand crosslinks) or contaminants (e.g., single-stranded DNA, RNA, proteins, dyes, or salts) present in the input material will impair performance of the system.

Therefore, ensure that your DNA sample:

- Is double-stranded. Single-stranded DNA will not be made into a SMRTbell template in this template preparation process and can interfere with quantitation and polymerase binding
- Has undergone a minimum of freeze-thaw cycles
- Has not been exposed to high temperatures (> 65°C for 1 hour can cause a detectable decrease in sequence quality)
- Has not been exposed to pH extremes (< 6 or > 9)
- Has an OD_{260/280} ratio of approximately 1.8 to 2.0
- Does not contain insoluble material
- Does not contain RNA
- Has not been exposed to intercalating fluorescent dyes or ultraviolet radiation

Demonstrative Exhibit—not evidence

EX1035, 5; EX2072, 52:8-53:15, 127;
Surreply, 25

Travers 2010 did not perform size selection using gel electrophoresis

Travers 2010 (EX1021), Figure 3

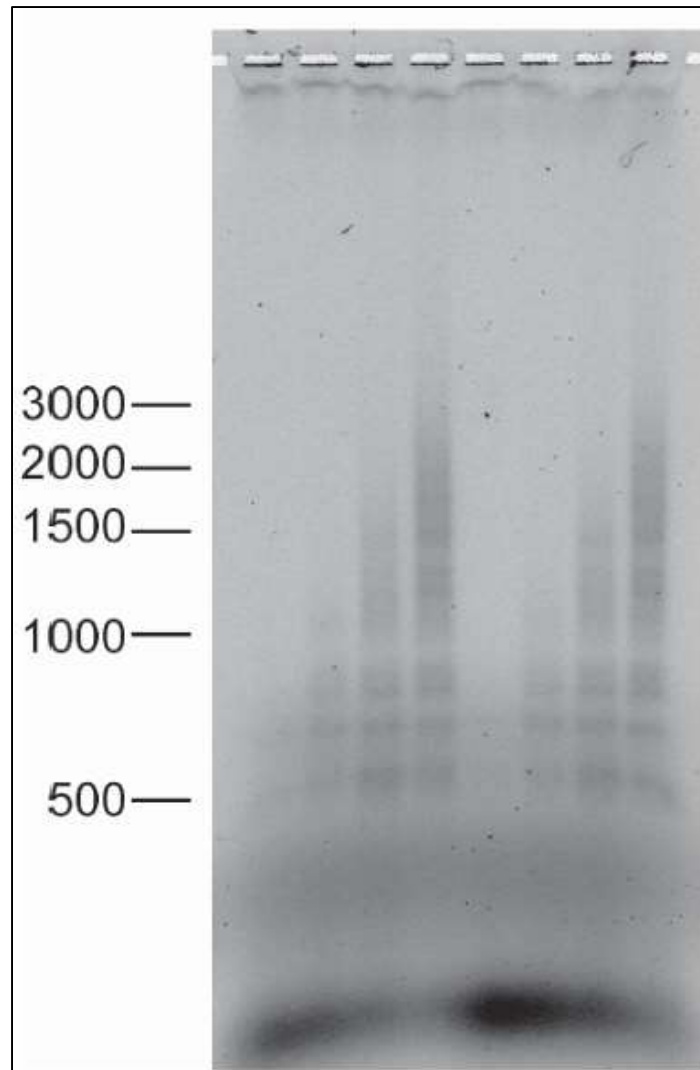
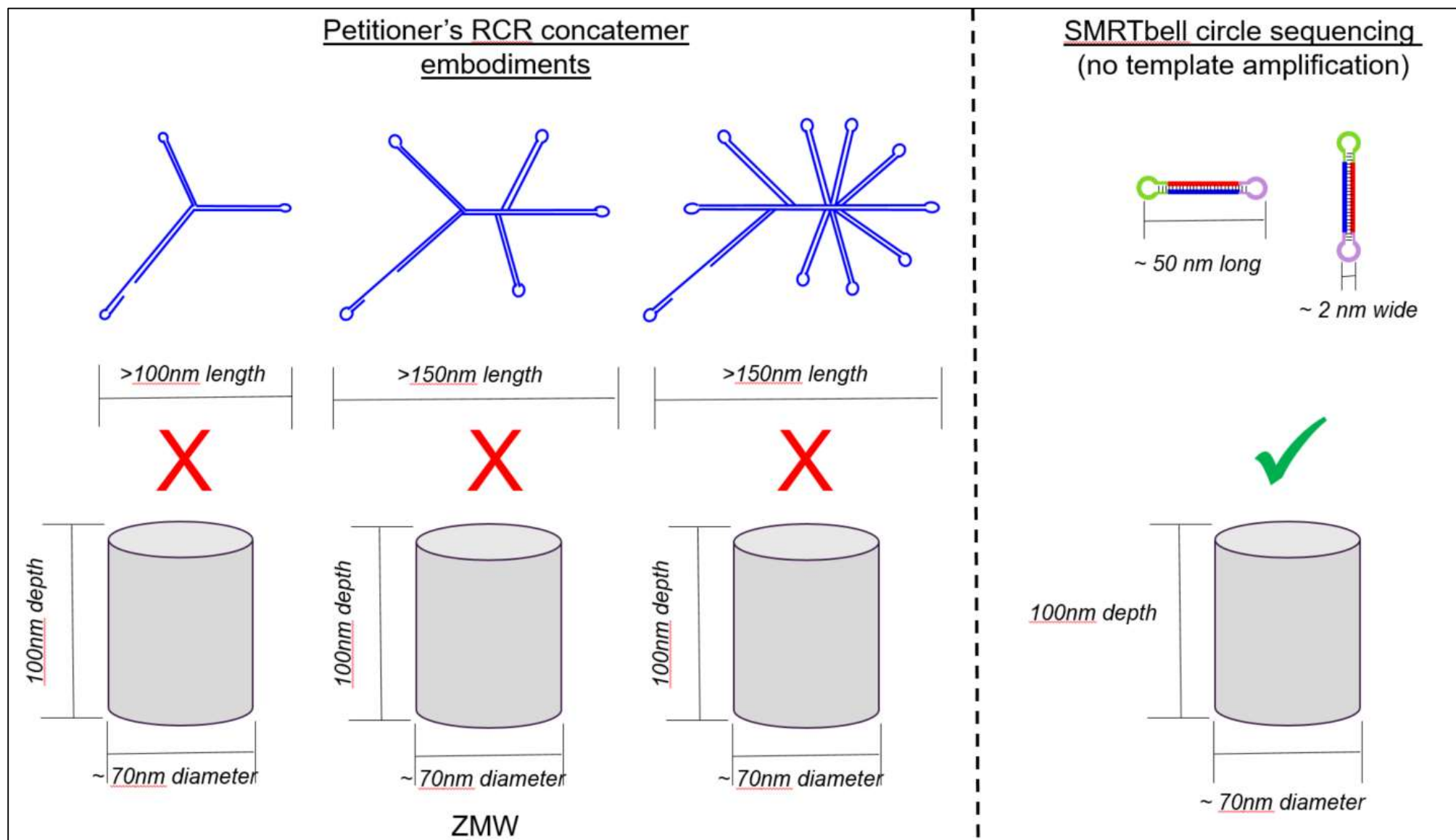


Figure 3. Bulk extension products of two SMRTbell templates. Lanes 1–4 contain the product from a template derived from strain FDA 209 (the ‘T’ allele) at timepoints of 2, 10, 30 and 60 min. Lanes 5–8 contain the product from a template derived from strain Mu50 (the ‘C’ allele) at timepoints of 2, 10, 30 and 60 min. Approximate sizes of products were determined relative to a 1 kb molecular weight ladder (indicated on the left). The position of the sequencing primer is indicated with an arrow.

EX1021, 4, Fig. 3; Surreply, 18, 24-25

Problem 4: large linear concatemers would form complex secondary structures and be unable to fit into ZMW wells

Problem 4: The geometry of the ZMWs posed physical constraints on Petitioner's RCR embodiment



Demonstrative Exhibit—not evidence

EX2014, ¶188-189; POR, 50-51

Guardant's evidence of "large templates" pertain to long, linear SMRTbells, not large concatemers with complex secondary structures

Reply

The Travers Publications disclose that much larger templates would fit into a ZMW and even provide examples of sequencing much larger templates. For example, Travers '075 explains "templates that are from about 200 to about 50,000 bases in length may be used." EX1018, ¶83; *see also id.*, ¶85. Travers '075 further

Reply, 22

Travers 2010 also contradicts PO's argument. Travers 2010 discloses that templates with "inserts as short as 40 bp, and as large as 25 000 bp [have been created], and we currently see no evidence of an intrinsic limit in the size of template." EX1021, 1. *Converting Travers templates expressed in bp into*

Reply, 22

The Template Preparation Guide similarly undermines Dr. Satija's argument. It describes "sequencing large insert libraries (e.g. 20 kb library) for generating long read lengths." EX1035, 35; *see also id.*, 6. *Converting the*

Reply, 23

Demonstrative Exhibit—not evidence

Each only discuss the ability of SMRTbell templates to enter the ZMW, not RCR concatemers

Surreply, 26

Guardant's argument that RCR concatemer structures are "flexible" would only exacerbate Problem 1

Petitioner does **not** dispute:

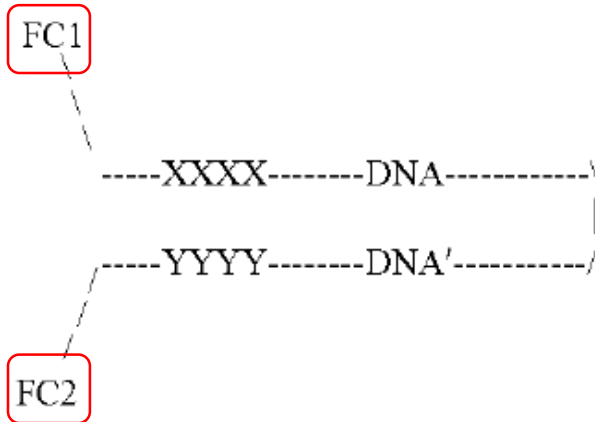
- RCR concatemers would indeed form secondary structures.
- RCR concatemers would have numerous polymerase binding sites.
- Secondary structures of RCR concatemers would fluctuate in solution.

Surreply

regard to Problem 4, but it would have only exacerbated Problem 1. Such flexible, fluctuating structures would increase the likelihood that multiple biotinylated-polymerases would bind the bottom of the streptavidin-coated ZMW and produce interfering signal. EX2072, 37:2-9; EX2014, ¶¶170-197.

The '127 Patent does not disclose Petitioner's RCR embodiment; Product I contains Illumina flow-cell binding sites

Product I. Adaptor 1-----DNA-----Adaptor 2, which yields the desired product:



EX1001, 9:55-65; Surreply, 2-3

According to the embodiments described herein, the SMI adaptor molecule may include at least two PCR primer or “flow cell” binding sites: a forward PCR primer binding site (or a “flow cell 1” (FC1) binding site); and a reverse PCR primer binding site (or a “flow cell 2” (FC2) binding site).

EX1001, 8:12-31; Surreply, 2-3

Demonstrative Exhibit—not evidence

Dr. Larrea Deposition Transcript (EX2072)

Q. (By Mr. Powers) Does the SMRT sequencing described in Travers 2010 use a flow cell?

A. Travers 2010 does not use a flow cell.

Q. (By Mr. Powers) Okay. This PacBio's SMRT sequencing described in Travers doesn't use binding sites on DNA to attach the template to a zero-mode waveguide. Correct?

A. Correct.

EX2072, 35:18-37:1; Surreply, 3

Petitioner's RCR embodiment is not encompassed within the claimed methods

The '127 Patent (EX1001)

detailed in the Example below. Product I contains a self-complementary hairpin sequence that can impair polymerase extension during amplification, however, this type of amplification has already been enabled in the technique of “Hairpin PCR” [50] which involves linking of the two strands followed by amplification with gene-specific primers. Amplification conditions that are compatible with amplification of hairpin DNA are thus already established. Moreover, ligation and amplification with circularizing “linkers” (i.e. hairpin linkers affixed to both ends of a fragment) has been demonstrated as a step in the Pacific Biosciences sample preparation workflow [49]. ← As the

**Travers 2010
(EX1021)**

EX1001, 10:55-66; Surreply, 3

Petitioner's RCR embodiment is not encompassed within the claimed methods

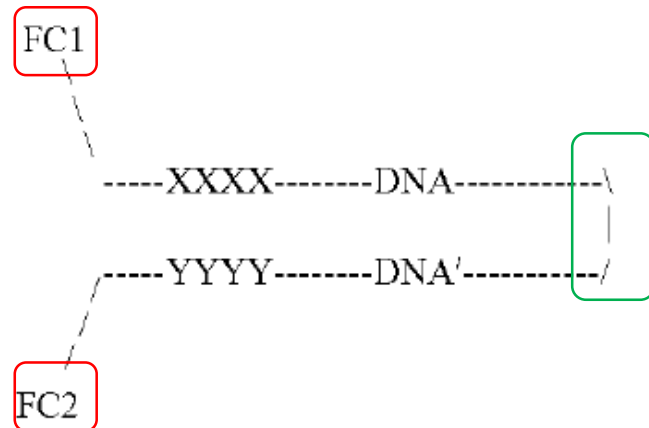
The '127 Patent (EX1001)

Biosciences sample preparation workflow [49]. As the sequence of the linker itself does not matter in the workflow, the published linker sequences from either of these references would be adequate for use in the assay.

EX1001, 10:66-11:2; Surreply, 3-4

The specification is pointing to a sequence in a hairpin adapter design that would be suitable in the specific assay for Product I

Surreply, 4



EX1001, 9:55-65

Demonstrative Exhibit—not evidence

Petitioner's RCR embodiment is not encompassed within the claimed methods

The '127 Patent (EX1001)

fragment may be desirable. Producing closed circles of captured material may help facilitate removal of non-captured DNA by exonuclease digestion given that circularized DNA will be protected from digestion by such enzymes. Additionally, closed circles may be pre-amplified using rolling circle amplification or serve as the substrate for continuous loop sequencing [49]. Recognition sites for restriction endonuclease digestion could be engineered into these adaptors to render closed loops open once again if more convenient for subsequent steps.

EX1001, 11:8-18; Surreply, 4

The specification is pointing out that U-shaped adapters are for protection from digestion by exonuclease and can be opened up later, i.e. not for SMRT sequencing

Demonstrative Exhibit—not evidence

Surreply, 4

Petitioner's RCR embodiment is not encompassed within the claimed methods

The '127 Patent (EX1001)

Additionally, closed circles may be pre-amplified using rolling circle amplification or serve as the substrate for continuous loop sequencing [49]. Recognition sites for

EX1001, 11:8-18; Surreply, 4-5

Surreply

rolling circle amplification. Petitioner also ignores the fact that using “closed circles” as the substrate “for continuous loop sequencing” is an explicit reference to PacBio’s SMRT sequencing as an alternative for closed-circle constructs *but not within the scope of the challenged claims*, which require a template amplification step after ligation but before sequencing. Paper 14, 18.

Demonstrative Exhibit—not evidence

Surreply, 4-5

Petitioner's RCR embodiment is not encompassed within the claimed methods

The '127 Patent (EX1001)

Additionally, closed circles may be pre-amplified using rolling circle amplification or serve as the substrate for continuous loop sequencing [49]. Recognition sites for

EX1001, 11:8-18; Surreply, 5

Surreply

PacBio's SMRT sequencing. Rather, a POSA would have understood that these “pre-amplified” products would need to be *re-fragmented* (as the patent indicates) and then *PCR-amplified to add flow-cell binding sites*. EX1001, 11:12-17, 3:61-64, FIG. 1; EX2014, ¶¶214-216. Thus, the specification never discloses making

Petitioner wrongly alleges that Dr. Satija confirmed the claims encompass Travers' amplification embodiment

X. DR. QUACKENBUSH FAILS TO ADDRESS ALL LIMITATIONS OF THE CHALLENGED CLAIMS.

C. A POSA would have understood that rolling circle replication is incompatible with the SMRT sequencing method of Travers '075 and Travers 2010 on a zero mode waveguide (ZMW) chip.

Surreply

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

Demonstrative Exhibit—not evidence

Claim 10 does not encompass Travers '075's RCR embodiment

Satija Dep. Tr.

Q. So one key difference you identified was that Claim 10 is not limited to Travers's '075 rolling circle replication embodiment; is that correct?

A. Just to be absolutely specific, I listed two reasons that followed from that statement. Because it's not limited to the '075 rolling circle embodiment, it's possible for a person of ordinary skill in the art to do two things.

One is to use any suitable method known in the art for downstream sequencing steps, and the other is to include downstream subsequent processing steps which include introducing recognition sites for restriction endonuclease digestion.

Demonstrative Exhibit—not evidence

EX1037, 108:5-10; Surreply, 5

Missing element:
“first and second strand sequence reads”
(claims 1-21)

Claim 1 recites obtaining “first and second strand sequence reads”

U.S. Patent 10,760,127



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 sequence reads and the reference sequence to identify a sequence variation.

Demonstrative Exhibit—not evidence

EX1001, claim 1

Dr. Satija testified that “first and second strand sequence reads” refer to the products of multiple, distinct sequencing reactions

“First and second strand sequence reads”



multiple and distinct sequencing reactions, each resulting in a sequence read, rather than a single sequencing reaction producing a single sequence read containing multiple subparts, i.e. “subreads.”

Dr. Satija (UW)

POR, 9; EX2014, ¶60-65

thus also include this limitation. EX1001, claims 2-4, 16, 18, 19. A POSA reading this claim would understand that a “sequence read” refers to a contiguous set of DNA nucleotides that correspond to the output of a DNA sequencing reaction, such as the sequencing-by-synthesis process depicted in Figure 1. EX1001, Fig. 1. In other words, a POSA would understand “first and second strand sequence reads” to mean a distinct sequence read of the first strand and a separate, distinct sequence read of the second strand.

“First and second strand sequence reads”

'127 Patent

5'-3' direction. When these molecules are amplified with PCR and sequenced, they will yield the following **sequence reads**: The top strand will give a read 1 file of TAAC- - - and

EX1001, 4:45-49; POR, 9; EX2014, ¶62

FIG. 3 illustrates error correction through Duplex Consensus Sequencing (DCS) analysis according to one embodiment. (a-c) shows **sequence reads** (brown) sharing a unique set of SMI tags are grouped into paired families with members having strand identifiers in either the $\alpha\beta$ or $\beta\alpha$ orientation. Each family pair reflects one double-stranded

“First and second strand sequence reads”

’127 Patent

This product is then PCR amplified. The reads will yield:

Read 1:

XXXX- - - -DNA- - - -

Read 2 (note that read 2 is seen as the complement of the bases sequenced:)

XXXX- - - -DNA- - - -

The sequences of the two duplex strands seen in the two sequence reads may then be compared, and sequence information and mutations will be scored only if the sequence at a given position matches in both of the reads.

EX1001, 9:1-14; POR, 9; EX2014, ¶62; Surreply, 8

Travers 2010 and Travers '075 do not disclose “first and second strand sequence reads”

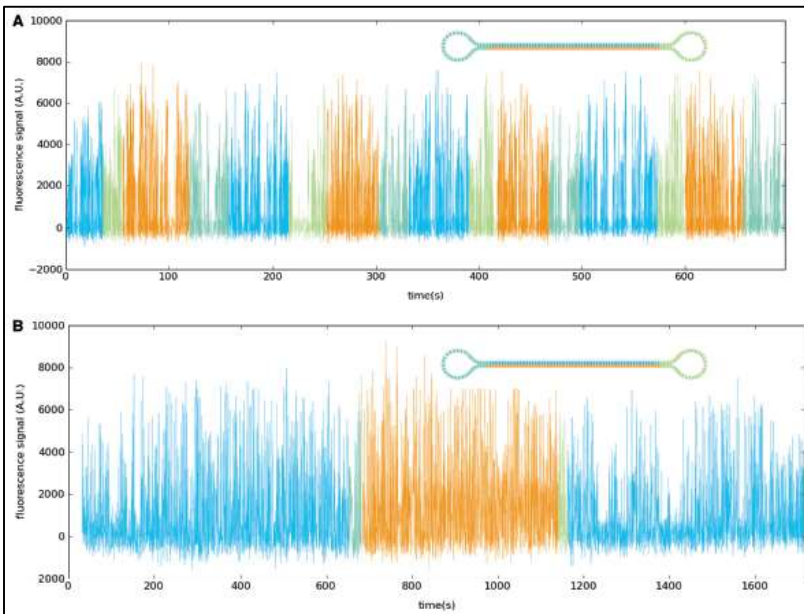
Travers 2010 (EX1021)

modified from (8). The first step is to classify the different regions in the raw circular molecule reads into adapter and insert subreads. This is done by aligning a raw read sequence to the known adapter sequence and a putative reference sequence of the insert regions. Once all subreads are identified, we test at each base position whether the subreads are generated by the putative reference sequence of the template or some variation of that sequence (e.g. a single-nucleotide polymorphism or an indel).

EX1021, 2; POR, 12; EX2014, ¶76

Travers 2010 and Travers '075 do not disclose “first and second strand sequence reads”

Travers 2010 (EX1021)



EX1021 (Travers 2010), Fig. 4

To detect the potential single-nucleotide polymorphism at a given location of the template, we align all the insert subreads identified from a single-molecule raw read to four different sequences representing the four possible SNP candidates using a probabilistic sequence aligner

EX1021, 2; POR, 11-12; EX2014, ¶77

short template. We call the set of called bases corresponding to the insert region a subread. For example, Figure 4A

EX1021, 5; POR, 11-12; EX2014, ¶77

Guardant has not shown that Travers teaches separate sequence reads derived from each of the original first and second strands

Petition

¶¶54, 83); *see also* EX1001, 10:63-11:18, 15:29-39. Travers discloses that either SMRTbell templates or replication products therefrom (*i.e.*, concatemers) may be sequenced using the disclosed template-dependent sequencing process. EX1018,

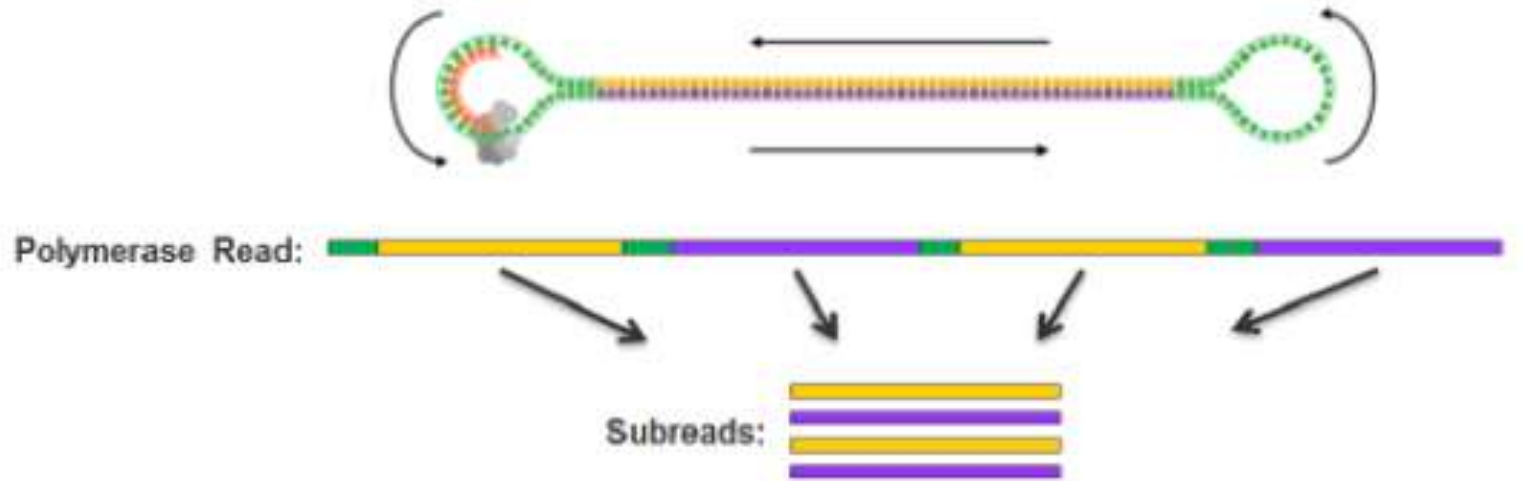
Dr. Quackenbush parrots the language in the Petition:

Dr. Quackenbush (Guardant)

81. Travers discloses that either SMRTbell templates, or their replication products (*i.e.*, concatemers), may be sequenced using the disclosed template-dependent sequencing process. EX1018, ¶122 (“...structurally circular nucleic acid

PacBio differentiated between sequencing read and subreads

PacBio Glossary of Terms



Travers '075's "sequencing"

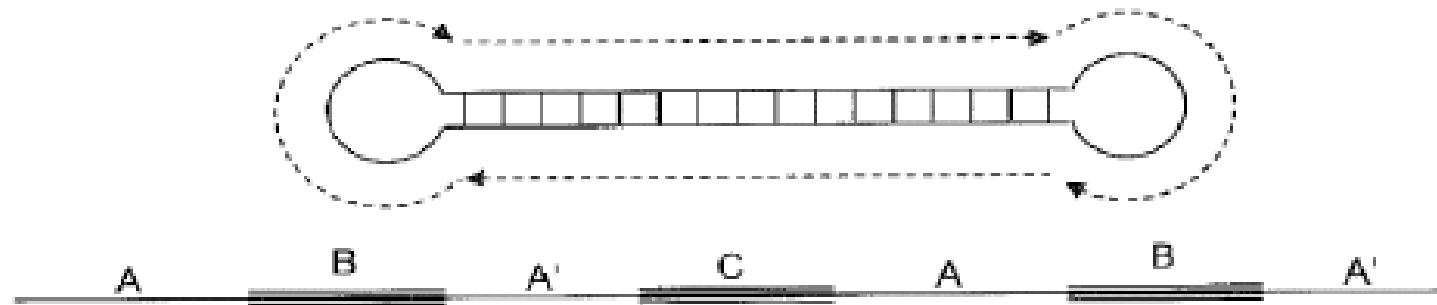


Figure 3B

Demonstrative Exhibit—not evidence

Surreply, 9; EX2072, 39:20-42:24; EX1018, Fig. 3B, ¶55

Dr. Larrea admitted that PacBio's subreads were portions of a sequence read

Dr. Larrea (Guardant)

Q. And this is PacBio's glossary of terms.

So subreads says: Each polymerase read is partitioned to form one or more subreads which contain sequence from a single pass of a polymerase on a single strand of an insert within a SMRTbell template and no adapter sequences.

Did I read that correctly?

MR. MILLS: Objection to form. Outside the scope.

A. You read that correctly.

Q. (By Mr. Powers) Okay. And you don't disagree with that definition, do you?

MR. MILLS: Objection to form. Scope.

A. Subreads were a convenient way of describing portions of the read.

Dr. Larrea admitted that PacBio sequencing generates a single contiguous output of sequence data from one sequencing reaction

Dr. Larrea (Guardant)

Do you agree that a polymerase read can include sequences from adapters and from one or multiple passes around a circular template?

MR. MILLS: Objection to scope.

A. In PacBio sequencing, a read is the nucleotides that come from an individual polymerase going through the incorporation events. So it may have, yeah, the parts that you describe.

Guardant alleges that UW's arguments are "limited" to certain embodiments

Reply

Like much of the POR, PO's analysis (8-9) is limited to discussion of non-limiting embodiments utilizing Y-shaped adapters, PCR amplification, and sequencing on the Illumina sequencing platform. But Dr. Satija conceded the

Reply, 7

'127 Patent

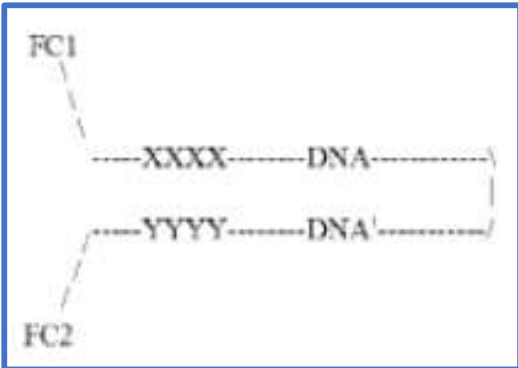
This approach greatly reduces errors by independently tagging and sequencing each of the two strands of a DNA duplex. As the two strands are complementary, true muta-

"Product I"

'127 Patent

EX1001, Abstract; Surreply, 7

Distinct PCR primer binding sites (or flow cell sequences FC1 and FC2) will flank the DNA sequence corresponding to each of the two SMI adaptor molecule strands, and a given sequence seen in Read 1 will then have the sequence corresponding to the complementary DNA duplex strand seen in Read 2. Mutations are scored only if they are seen



Demonstrative Exhibit—not evidence

EX1001, 6:20-30, 8:54-65, 9:51-65; Surreply, 7

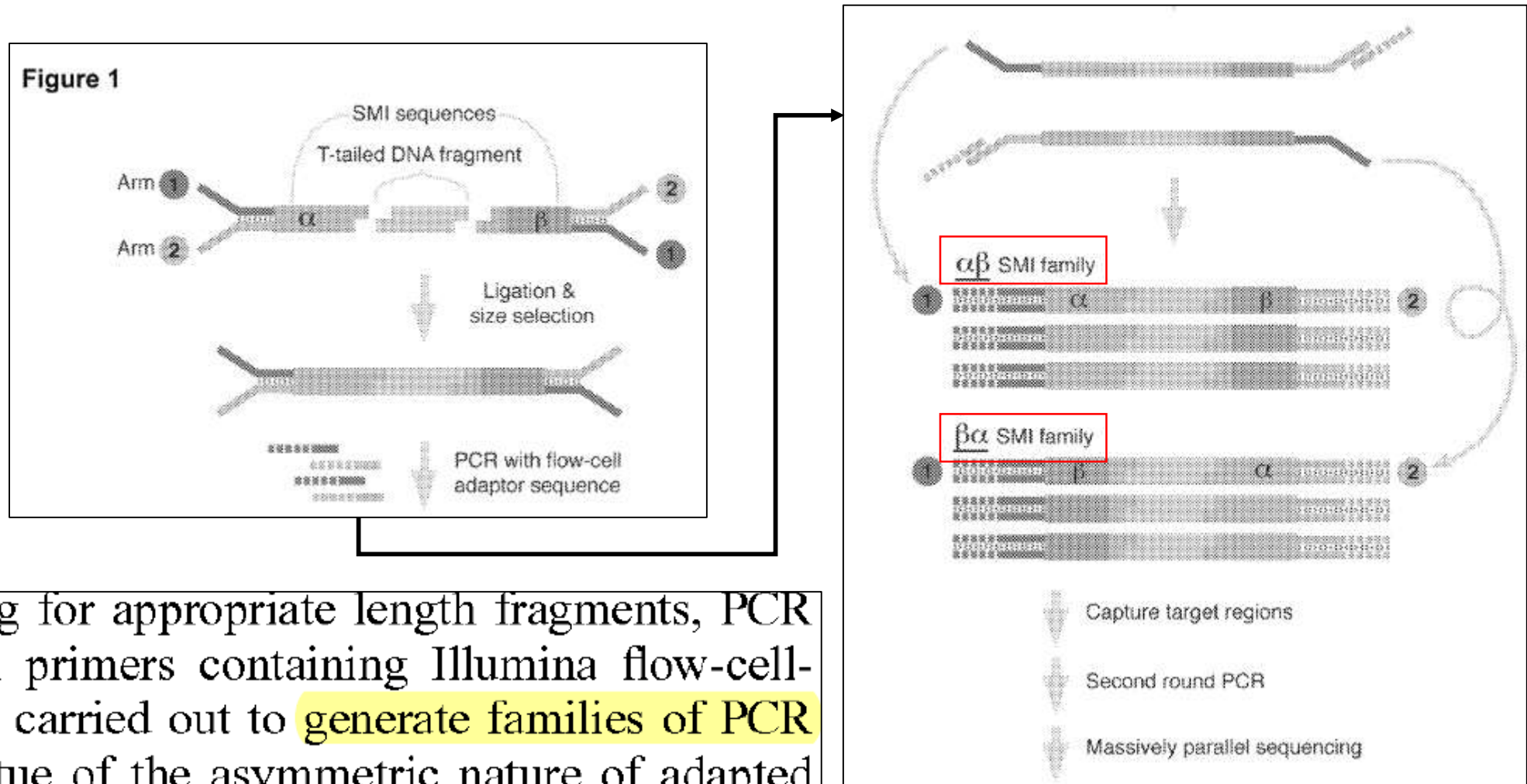
Missing Element:
**Grouping strand sequence reads into
families (claims 22-30)**

Claim 22 recites grouping the sequence reads into families

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.

Family grouping is grouping sequence reads derived from the same original molecule



After size-selecting for appropriate length fragments, PCR amplification with primers containing Illumina flow-cell-compatible tails is carried out to generate families of PCR duplicates. By virtue of the asymmetric nature of adapted

'127 Patent Figure 3

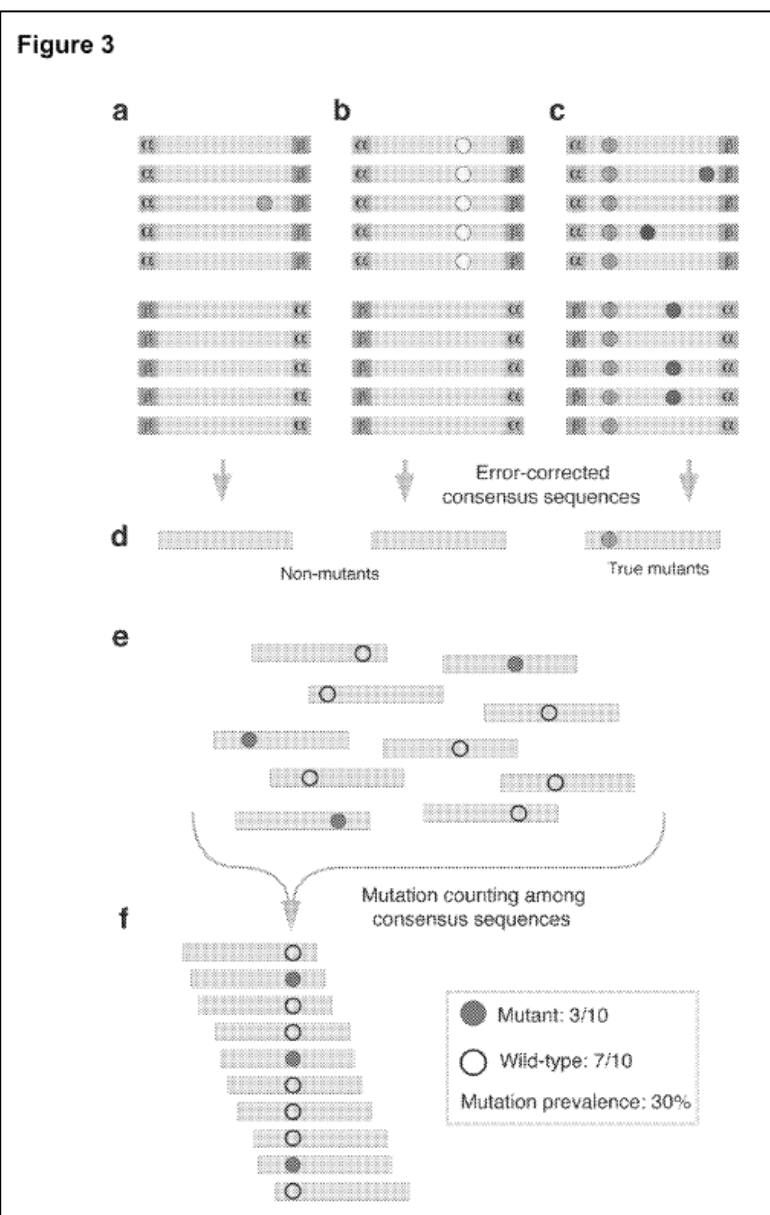


FIG. 3 illustrates error correction through Duplex Consensus Sequencing (DCS) analysis according to one embodiment. (a-c) shows sequence reads (brown) sharing a unique set of SMI tags are grouped into paired families with members having strand identifiers in either the $\alpha\beta$ or $\beta\alpha$ orientation. Each family pair reflects one double-stranded

Dr. Quackenbush previously testified that the specification teaches family grouping using molecular barcodes

Dr. Quackenbush (Guardant)

33. Schmitt, for example, uses a molecular barcoding approach to error correction. In this method, individual polynucleotide molecules are tracked through the sample preparation and sequencing processes. Molecular barcoding allows for identification and grouping of sequence reads derived from PCR duplication of a sample polynucleotide molecule. *E.g.*, EX1011, Fig. 3, 4:4-29. These groups of sequence reads are typically referred to as “families” and represent the PCR progeny of a common parent polynucleotide molecule in the original sample.

EX2073, 311, ¶33; Surreply, 11

'127 Patent Disclosures:

orientation. Each family pair reflects one double-stranded DNA fragment. (a) shows mutations (spots) present in only

EX1001, 4:17-18; Surreply, 11

After size-selecting for appropriate length fragments, PCR amplification with primers containing Illumina flow-cell-compatible tails is carried out to generate families of PCR duplicates. By virtue of the asymmetric nature of adapted

EX1001, 3:61-64; Surreply, 11

In the method described above, a set of sequenced SMI-DNA products generated in the methods described above may be grouped into families of paired target nucleic acid strands based on a common set of SMI sequences. Then, the

EX1001, 16:40-41; Surreply, 11

Dr. Quackenbush points only to Travers' sample barcodes

Dr. Quackenbush (Guardant)

Specifically, Travers describes collectively analyzing multiple reads of the target molecule. EX1018, ¶55 (describing assembly of “replicate sequence read data” for determining consensus), ¶58 (“...assembling the sequence data from multiple reads of a given sequence ... to provide an overall consensus sequence for that segment ...”); ¶100 (describing the use of “oligonucleotide tags” or barcodes to “pool[data] for analysis”). Travers further discloses that the assembled reads are used to

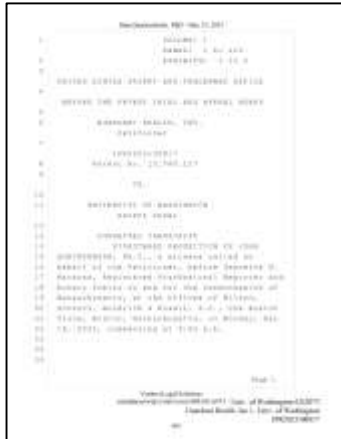
EX1002, ¶113

What Travers '075 actually discloses:

sample mixture. In particular, one can utilize connecting oligonucleotides in the template constructs that include sequence markers like a barcode, to indicate the origin of a given template sample. Different template samples including distinguishable connecting oligonucleotide tags could then be pooled for analysis in a single sequencing process. Sequence data derived from individual templates is then attributable to the originating sample preparation process through the identification of the connecting oligonucleotide tag.

Demonstrative Exhibit—not evidence

EX1018, ¶100; POR, 14



Travers '075's "pooling" of indexed barcodes is different from the claimed family "grouping" step

Indexing barcodes



Molecular barcodes



Dr. Satija (UW)

barcode and DNA fragment-specific information. Indexing barcodes or sample barcodes are short, unique sequences of DNA added to all molecules from a specific *sample* so samples can be pooled, then processed and sequenced in parallel with each resulting sequence containing information to determine the source material (starting sample). EX2034, 4. Pooling of indexed barcoded samples is very different from molecular barcoding as recited in claims 22-30, where each target molecule has a barcode sequence so that reads from each specific target molecule can be identified. Moreover, claims 22-30 require grouping strand sequence reads based on the barcode sequence and DNA fragment-specific information, which is not disclosed in Travers '075.

Guardant previously argued that index sequences are different from molecular barcodes

Guardant Response to Notice of Opposition (EX2019)

hand column as follows: *“This index sequence enables the PCR products from multiple different individuals to be simultaneously analyzed in the same flow cell compartment of the sequencer”* (see also **D16**, top of p.36). Thus the exogenous UID is not used when generating a consensus sequence, but rather is used to permit multiplexing of several different samples in a single sequencing experiment.

Travers '075 (EX1018)

Guardant ignores Claims 22's requirement to use both barcode sequence and "DNA fragment-specific information" to group reads into families

Dr. Quackenbush (Guardant)

reads are then assembled or compared to provide a consensus ..."). That is, Travers expressly describes determining consensus sequences based on assembled (*i.e.*, grouped) redundant sequence reads.

EX1002, ¶113

Dr. Satija (UW)

Second, the sample barcodes disclosed in Travers '075 must be identical for all template molecules within a sample, and therefore are not fragment-specific by definition. As such, Dr. Quackenbush has not explained how the subreads in either

Guardant ignores the specification's description of a grouped "family" of strand sequence reads

In its Reply, Guardant only describes sample grouping, not family grouping, as claimed:

Reply

... to [] provide an overall consensus sequence." EX1018, ¶58. Where multiplexing is employed, distinguishing sequence reads based on sample origin (index or multiplex barcodes) is a bioinformatics component to Travers' process of assembling the sequence data from multiple reads to determine consensus sequence. EX1002, ¶¶111-115; EX1039, ¶18.

Reply, 11

Surreply

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

Surreply, 11

Demonstrative Exhibit—not evidence

Travers does not use its index barcodes in any grouping step

Surreply

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

Surreply, 11

Travers '075

VI. Sequence Alignment

e.g., as a landmark or registration sequence. Further, even without knowledge of the sequence of the connecting oligonucleotide, one can derive the sequence by observing that portion of the overall sequence that does not possess a complementary portion elsewhere in the sequence data. In

EX1018, ¶98; Surreply, 11

Travers '075's index barcodes serve a different purpose than the '127 patent's molecular barcodes of claim 22

Surreply

Travers-075's index barcodes serve a completely different purpose than the '127 patent's molecular barcodes of claim 22 (referred to as "SMIs" throughout the specification). EX1037, 89:16-20 (testifying that "the use of *indexed barcoded*

Surreply, 12

Dr. Satija (UW)

Q. So you used the term "indexing barcode"; is that correct?

A. For example, I say in paragraphs 84 that the use of indexed barcoded samples is very different from the claim step of grouping the strands of sequence reads into families based on the barcode and DNA fragment-specific information.

Travers '075's sample barcodes cannot be used in claim 22

'127 Patent

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

EX1001, claim 22

Dr. Satija (UW)

16. Second, Travers '075 and Travers 2010 do not teach the grouping of multiple sequence reads into families based on barcode sequences and fragment-specific information, as recited in claim 22. While Dr. Quackenbush argues that Travers '075 teaches the use of *sample barcodes*, enabling researchers to simultaneously obtain sequencing data from multiple *samples*, these barcodes are *unrelated to the limitations in claim 22* (and its dependent claims 23-30). Moreover, these barcodes must be identical for all template molecules within a *sample*, and therefore are not fragment-specific.

EX2014, ¶16; POR, 13-15

very different from *molecular barcoding* as recited in claims 22-30, where each target molecule has a barcode sequence so that reads from each specific target molecule can be identified. Moreover, claims 22-30 require grouping strand sequence reads based on the barcode sequence and DNA fragment-specific information, which is not disclosed in Travers '075.

Demonstrative Exhibit—not evidence

EX2014, ¶84; POR, 13-15

Missing Element:

Using asymmetry of asymmetrical double-stranded adapter-DNA molecules (claim 19)

Claim 19 uses asymmetric adapters to differentiate the first and second strand sequence reads

U.S. Patent 10,760,127

first strand

19. The method of claim 1, wherein the [↑]sequence reads derived from a particular original adapter-DNA molecule can be differentiated from the second strand sequence reads derived from the same particular original adapter-DNA molecule at least in part by an asymmetry of the asymmetrical double-stranded adapter-DNA molecules.

Demonstrative Exhibit—not evidence

EX1001, claim 19

Guardant fails to meet its burden in its challenge of claim 19

Petition

xiii. Claim 19

19. The method of claim 1, wherein the sequence reads derived from a particular original adapter-DNA molecule can be differentiated from the second strand sequence reads derived from the same particular original adapter-DNA molecule at least in part by an asymmetry of the asymmetrical double-stranded adapter-DNA molecules.

As discussed above, Travers discloses adapter-DNA molecules within the scope of “partially-complementary, asymmetrical double-stranded adapter-DNA molecules.” *See* Section V. Travers further discloses that the asymmetry of adapter-DNA molecules imbued by the hairpin linker allows the first and second strands of an original adapter-DNA molecules to be distinguished. EX1018, ¶54; EX1021, Figure 1, Figure 4; *see also* EX1002, ¶¶171-73.

xiv. Claims 20, 27, and 28

**Entire discussion of
claim 19 in Petition**

Claim 19 leverages asymmetric adapter DNA to differentiate first and second strand sequence reads

Dr. Satija (UW)

89. A POSA would understand that the method of claim 19 recites *using the asymmetric nature of the adapters to differentiate the first strand sequence read and second strand sequence read*. Indeed, the specification of the '127 patent

EX2014, ¶89; POR, 16; Surreply, 12-13

'127 patent

duplicates. By virtue of the asymmetric nature of adapted fragments, two types of PCR products are produced from each capture event. Those derived from one strand will have the α SMI sequence adjacent to flow-cell sequence 1 and the β SMI sequence adjacent to flow cell sequence 2. PCR products originating from the complementary strand are labeled reciprocally.

Demonstrative Exhibit—not evidence

EX1001, 3:64-4:3; POR, 16; Surreply, 12-13

Travers '075 does not disclose using adapter asymmetry to distinguish first and second strands

Dr. Quackenbush (Guardant)

DNA molecules.” *See* Section V. Travers further discloses that the asymmetry of adapter-DNA molecules imbued by the hairpin linker allows the first and second strands of an original adapter-DNA molecules to be distinguished. EX1018, ¶54; EX1021, Figure 1, Figure 4.

EX1002, ¶171-173; POR, 16-17; Surreply, 12-13

What Travers '075 actually discloses:

process, the presence of linking segment 206 also provides an opportunity to provide a registration sequence that permits the identification of when one segment, e.g., 202, is completed and the other begins, e.g., 204. Such registration

Travers '075 does not disclose using adapter asymmetry to distinguish first and second strands

Travers '075 (EX1018):

antisense counterpart. As noted, because the B sequence may be exogenously provided, and thus known, it may also provide a registration sequence indicating a point in the sequence determination at which the sequencing reaction, and thus, the sequence data being obtained from the overall template construct, transitions from the sense to the antisense strands.

EX1018, ¶54; POR, 16-17; EX2014, ¶92; Surreply, 12-13

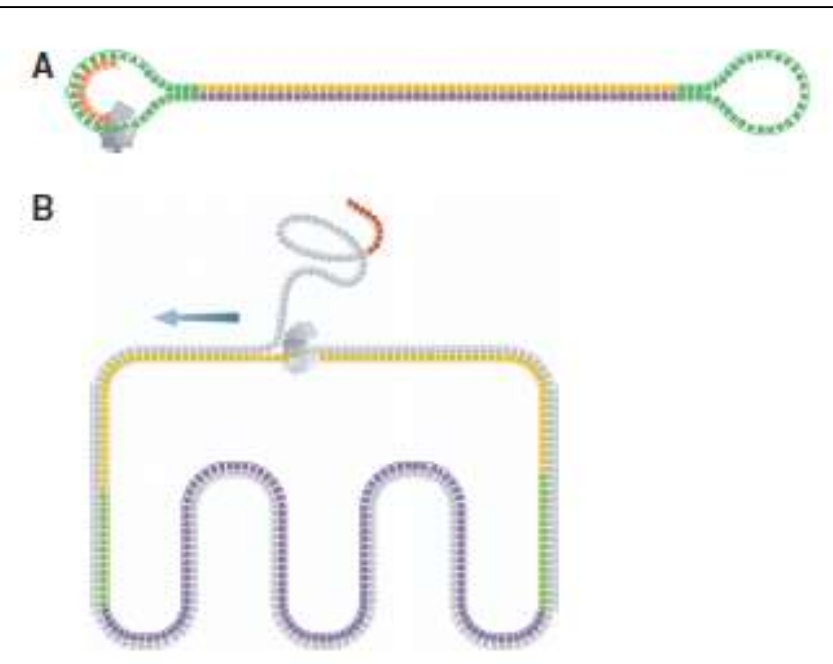
the same or identical templates. In particular, because the connecting oligonucleotide is known or knowable, one can readily exploit this pre-known sequence in aligning long strings of sequence data from such template or templates, e.g., as a landmark or registration sequence. Further, even

Demonstrative Exhibit—not evidence

EX1018, ¶98; POR, 16-17; EX2014, ¶92; Surreply, 12-13

Travers 2010 also does not disclose using adapter asymmetry to distinguish first and second strand sequence reads

Travers 2010 (EX1021):



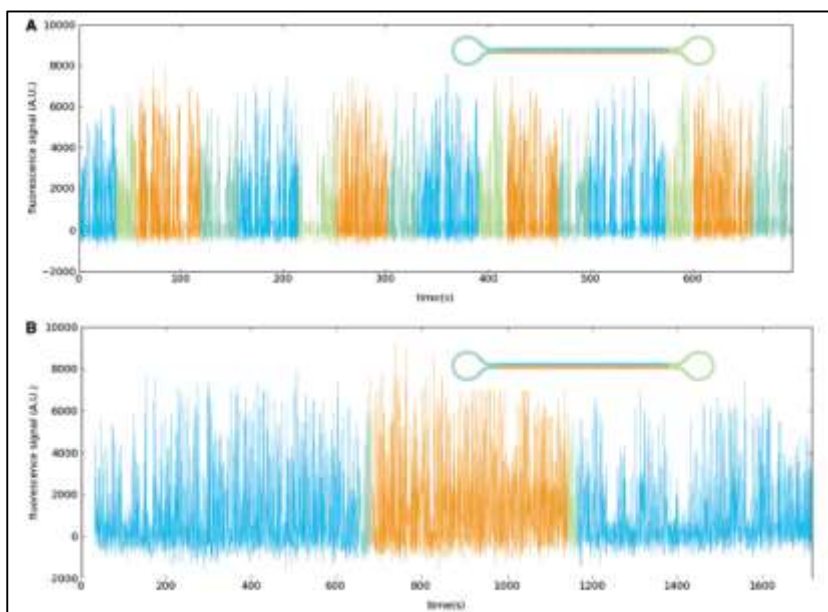
EX1021 (Travers 2010), Figure 1

Dr. Satija (UW)

However, Figure 1 in Travers 2010 says nothing about using the asymmetric nature of adapters to distinguish strands. Figure 1 only discloses a schematic of the SMRTbell template without any further disclosure regarding how the asymmetric nature of the hairpins are used to differentiate the first and second strand of the template molecule. EX1021, Fig. 1. And Travers 2010's Figure 4 only discloses

Travers 2010 also does not disclose using adapter asymmetry to distinguish first and second strand sequence reads

Travers 2010 (EX1021):



EX1021 (Travers 2010), Figure 4

Dr. Satija (UW)

template molecule. EX1021, Fig. 1. And Travers 2010's Figure 4 only discloses using the adapter sequences as landmarks to identify when one target strand ends and the next target strand begins. In fact, Travers 2010's Figure 4 depicts single-molecule traces of both the sense and antisense strands, and notes that the pulses within the sequencing traces are colored according to location within the template, with blue corresponding to the sense strand, orange corresponding to the antisense strand, and light blue and green corresponding to the hairpin adapters. EX1021,

EX2014, ¶93

Travers '075 or Travers 2010 does not teach differentiating the first and second strand reads using asymmetric adapters

Dr. Quackenbush (Guardant)

DNA molecules.” *See* Section V. Travers further discloses that the asymmetry of adapter-DNA molecules imbued by the hairpin linker allows the first and second strands of an original adapter-DNA molecules to be distinguished. EX1018, ¶54; EX1021, Figure 1, Figure 4.

EX1002, ¶172

Dr. Satija (UW)

claimed in claim 19. In addition, claim 19 is a method claim, and Dr. Quackenbush has not sufficiently shown that Travers '075 and Travers 2010 teach *why* or *how* to differentiate the first and the second strand using the asymmetric nature of the hairpin adapters. All Dr. Quackenbush states is that “the asymmetry of adapter-DNA molecules imbued by the hairpin linker *allows* the first and second strands of an original adapter-DNA molecules to be distinguished.” EX1002, ¶172. EX2014, ¶94

Demonstrative Exhibit—not evidence

POR, 17-18; Surreply, 12-13

Attaching U-shaped adapters in Travers does not read on Claim 19

Reply

As was explained by Dr. Quackenbush in his first declaration, the U-shaped adapters of Travers are asymmetric, are encompassed by the '127 patent claims, and generate asymmetric double-stranded adapter-DNA molecules. *E.g.*, EX1002, ¶¶49-52, 69. Independent claim 1 requires attaching adapters to the DNA molecules to make “partially-complementary, asymmetrical double-stranded adapter-DNA molecules.” Accordingly, the claims would be reasonably understood to encompass adapter-DNA molecules generated by attachment of Travers’ U-shaped adapters comprising barcodes to each end of double-stranded DNA molecules. PO does not dispute any of this, nor could it. EX1001, 10:63-11:2; *see also* DI, 8; EX1039, ¶22.

Reply, 12

Guardant has not shown that the art actually teaches a method of using the asymmetric nature of the adapter-DNA molecules to differentiate first and second strand sequence reads, as claimed.

Demonstrative Exhibit—not evidence

Dr. Satija (UW)

second strand sequence reads. Rather, Travers '075 discloses identifying only the presence of adapter sequences as landmarks or “registration sequences” that mark the portion of the sequence read where one strand ends and the next strand begins.

EX2014, ¶91

template molecule. EX1021, Fig. 1. And Travers 2010’s Figure 4 only discloses using the adapter sequences as landmarks to identify when one target strand ends and the next target strand begins. In fact, Travers 2010’s Figure 4 depicts single-

EX2014, ¶93

POR, 16;

Surreply, 13

Guardant fails to explain how any adapter-DNA asymmetry would be maintained in its linear rolling circle replication (“RCR”) concatemers

Reply

corresponding to the sense and antisense strands. PO argues Travers describes using adapter sequences as landmarks or “registration sequences” that mark the portion of the sequence read where one strand ends and the next strand begins.” POR, 17 (quoting EX1018, ¶54). This argument offers no distinction from what is claimed. That is, PO acknowledges Travers describes asymmetric adapter-DNA

Reply, 13

- Claim 19 relies on the asymmetry to differentiate first and second strand reads, so the asymmetry must be *maintained* in the amplified product and *used* to differentiate first and second strand reads.
- Guardant’s proposed RCR embodiment *loses asymmetry* when the molecule is replicated and becomes linear and single-stranded.

Objective indicia support patentability

Demonstrative Exhibit—not evidence

The '127 Patent's duplex sequencing technology

Relating and distinguishing strands; comparing strands

'127 Patent

vidually tagged strands are then PCR amplified. Every duplicate that arises from a single strand of DNA will have the same SMI, and thus each strand in a DNA duplex pair generates a distinct, yet related population of PCR duplicates after amplification owing to the complementary nature of the SMIs on the two strands of the duplex. Comparing the sequence obtained from each of the two strands comprising a single molecule of duplex DNA facilitates differentiation of sequencing errors from true mutations. When an apparent

EX1001, 21:46-52; POR, 68

Using *asymmetry* of adapter-DNA

'127 Patent

duplicates. By virtue of the asymmetric nature of adapted fragments, two types of PCR products are produced from each capture event. Those derived from one strand will have

EX1001, 3:64-65; POR, 68

The '127 Patent claims embody duplex sequencing

2. The method of claim 1, wherein the sequence variation is either (i) a processing error or a site of DNA damage, or (ii) a true variant, and wherein, for at least some of the adapter-DNA molecules, the method further comprises:

comparing the confirmed first strand sequence read and confirmed second strand sequence read;

identifying nucleotide bases that are not consistent between the confirmed first and second strand sequence reads; and

identifying nucleotide bases that are consistent between the confirmed first and second strand sequence reads, wherein—

if the sequence variation is not a consistent nucleotide base, then categorizing the sequence variation as (i) a processing error or a site of DNA damage, and

if the sequence variation is a consistent nucleotide base, then categorizing the sequence variant as (ii) a true variant.

3. The method of claim 2, wherein prior to comparing the confirmed first strand sequence read and confirmed second strand sequence read, the method comprises associating the confirmed first strand sequence read with the confirmed second strand sequence read using one or more of an adapter sequence, a sequence length, sequence alignment information and original strand information.

16. The method of claim 1, wherein prior to the comparing step, the method comprises associating the confirmed first strand sequence read with the confirmed second strand sequence read using one or more of an adapter sequence and original strand information.

18. The method of claim 1, wherein the first strand sequence reads derived from a particular original adapter-DNA molecule and the second strand sequence reads derived from the same particular original adapter-DNA molecule can be related based on a barcode sequence, a fragment-specific feature, or a combination thereof.

first strand

19. The method of claim 1, wherein the [↑]sequence reads derived from a particular original adapter-DNA molecule can be differentiated from the second strand sequence reads derived from the same particular original adapter-DNA molecule at least in part by an asymmetry of the asymmetrical double-stranded adapter-DNA molecules.

Summary of UW's Evidence of Objective Indicia

Industry Praise

- Kirsch (EX2007) praise for Duplex Sequencing
- GEN Edge (EX2065) praise for Duplex Sequencing

Long-Felt Need

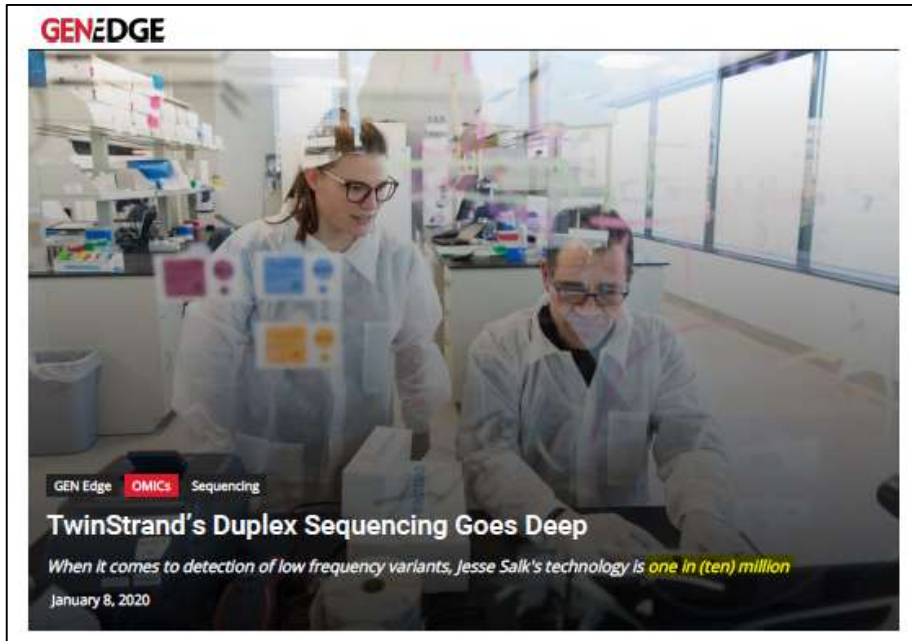
- GEN Liquid Biopsies (EX2051)
- GEN Sequencing Stars (EX2052)
- BusinessWire (EX2053)

Unexpectedly superior results

- Schmitt's Duplex Sequencing (EX2050)

Petitioner only challenges nexus of Kirsch and Schmitt

Objective Indicia: Industry Praise



GEN Edge: "one in (ten) million" technology

To do this, the technique independently tracks both strands of individual DNA molecules and compares the results to identify and eliminate errors. This concept, TwinStrand notes, is borrowed from the molecular machinery used by cells throughout the natural world to replicate their genomes with high accuracy.

other once separated. In addition to the UMI, an asymmetric portion of the adapters—the strand defining element (SDE)—distinguishes the strands so that each can be recognized as the original reference or anti-reference strand of the duplex. Together these elements create a data structure where every single

The limit of detection that duplex sequencing offers—below one in 10 million—is not always necessary. But, for those applications where finding low frequency mutations is critically important, it may be a game changer. Applications where

Objective Indicia: Industry Praise

Kirsch:

The Gordian knot in sequencing accuracy has apparently been cut by the duplex sequencing approach.

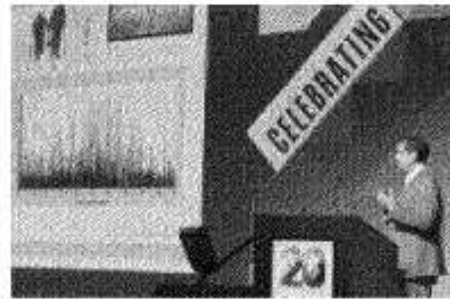


Schmitt et al. (1) may pave the way to explore the full power of NGS in answering fundamental questions and particularly through its application to cancer research. This enthusiasm is warranted because duplex sequencing reportedly reduces the error rate of NGS up to 10 million-fold.

The authors do so by simply exploiting the redundant sequence information contained in the complementary DNA strand of double stranded genomic DNA molecule. They add a unique random yet complementary double-stranded nucleotide sequence to both strands of duplex DNA before amplification. This approach

Objective Indicia: Long-Felt Need

GEN Sequencing Stars:



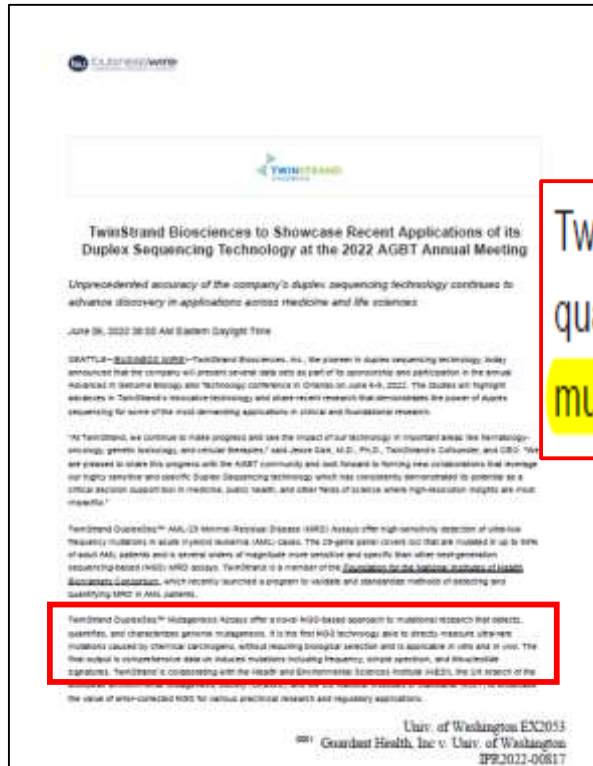
Jesse Salk, MD, PhD, CEO of TwinStrand Biosciences, presented duplex sequencing technology data to attendees of the annual meeting of Advances in Genome Biology and Technology. The information generated—mutation frequencies, simple mutation spectra, and trinucleotide mutation spectra—can be used together to detect, quantify, and characterize induced DNA mutagenesis. [AGBT]

TwinStrand has developed **duplex sequencing technology** to improve sequencing accuracy, making it possible to find low-frequency variants at a **level of detection that has not been achievable before**. At AGBT, Salk spoke about two of the primary applications where their product could be useful, the first of which is cancer—more specifically, the detection of minimal residual disease in acute myeloid leukemia (AML) patients. The hope is to be able to assess how well treatment works or if cancer remains after treatment. This information could spare patients additional, unnecessary treatments and allow drug companies to run smaller, safer, faster clinical trials.

Why did the company start in this area? Salk, who maintains a part-time position as an oncologist at a University of Washington–affiliated VA hospital, explained to *GEN*, “This is the area where I live.” He added that he wants to focus on something that would bring an immediate benefit by **addressing this particular unmet need**, which is one that he sees on a daily basis. He said, “It’s not just nice, it’s necessary.”

Objective Indicia: Long-Felt Need

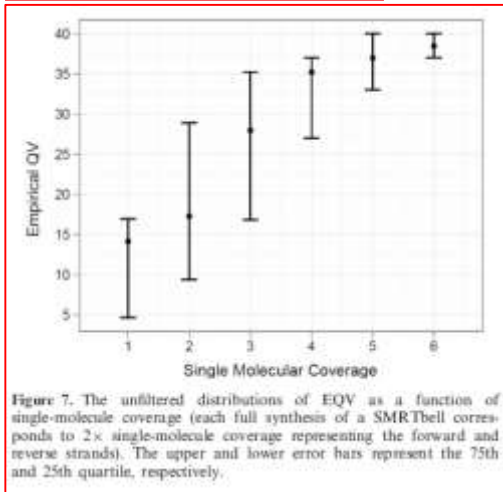
Business Wire:



TwinStrand DuplexSeq™ Mutagenesis Assays offer a novel NGS-based approach to mutational research that detects, quantifies, and characterizes genome mutagenesis. It is the first NGS technology able to directly measure ultra-rare mutations caused by chemical carcinogens, without requiring biological selection and is applicable *in vitro* and *in vivo*. The

Objective Indicia: Unexpectedly Superior Results

Travers 2010



EX1021, Fig. 7

Dr. Satija (UW)

Travers 2010 discloses that SMRT sequencing provides its highest empirical quality value (EQV) at 6x sequencing depth which provides an error detection of about 1×10^{-4} (0.0001). EX1021, Fig. 7. As discussed above, this means that the probability of an incorrect base call was nearly 1 in 10,000. EX1021, Fig. 7; EX2055, 1.

EX2014, ¶241

Demonstrative Exhibit—not evidence

Schmitt 2012

Based on the SSCS background error frequency of 3.4×10^{-5} from the M13mp2 DNA sequencing experiment, the error frequency of DCS can be approximated as: $(3.4 \times 10^{-5}) \times (3.4 \times 10^{-5}) \times 1/3 = 3.8 \times 10^{-10}$. This calculated error frequency represents a 10 million-fold improvement over the 3.8×10^{-3} value we obtained by standard methods. Of note, the calculation simplistically assumes

EX2050, 5

Dr. Satija (UW)

EX2050, 1. Moreover, Schmitt 2012 taught that based on the background error frequency of 3.4×10^{-5} from its disclosed single strand DNA sequencing experiments, “the error frequency of DCS can be approximated as... 3.8×10^{-10} .”

EX2050, 5. These surprising and dramatically superior results from the '127 patent are over six orders of magnitude greater in sensitivity than the accuracy of the methods of Travers 2010, which is far more than a difference in degree. Indeed,

EX2014, ¶242

POR, 73; Surreply, 27-29; EX2014, ¶¶241-242; EX2050, 5

Objective indicia are not exclusively tied to DCS methods

Petitioner:

Reply

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2019). PO's claims are not directed to DCS of the Schmitt reference—as discussed in the Kirsch reference—and, as such, its evidence uniformly relates to unclaimed features. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006) ([I]f the commercial success is due to an unclaimed feature of the device, the commercial success is irrelevant."). Moreover, the broad claims of '127 patent

Reply, 27-28.

***But see*
GEN Edge:**

GEN Edge

To do this, the technique independently tracks both strands of individual DNA molecules and compares the results to identify and eliminate errors. This concept, TwinStrand notes, is borrowed from the molecular machinery used by cells throughout the natural world to replicate their genomes with high accuracy.

EX2065, 1

Guardant completely ignored GEN Edge

Demonstrative Exhibit—not evidence

POR, 69-72; Surreply, 27-29; EX2065, 1

Petitioner's Reply Evidence Falls Short

Petitioner:

Reply

Furthermore, the Board has previously found that Kinde (EX1006) in view of Craig (EX1038) teach each limitation of claim 1 of the '127 patent. IPR2022-00816, DI, 13. That the claims recite only features found in the prior art is further confirmed by Kirsch. Kirsch explains Kinde's Safe-SeqS, like DCS, uses tags (i.e.,

Reply, 25-26.

Board

genomic DNA regions. Ex. 1007, 3, 18. Thus, based on the current record, we find Petitioner has shown sufficiently that the combination of Kinde and Craig teaches each limitation of claim 1. We adopt Petitioner's detailed accounting of each limitation as our own findings. See Pet. 25-35.

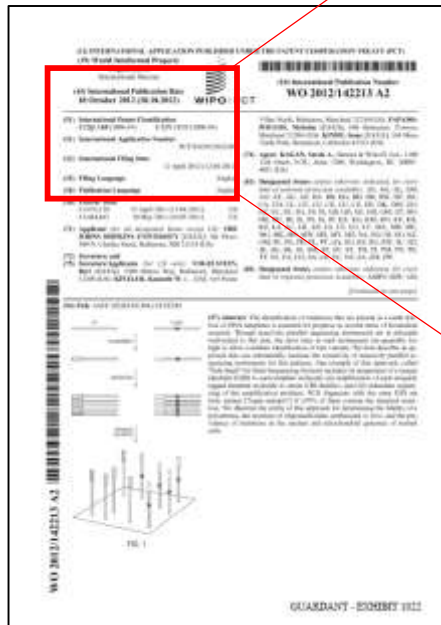
IPR2022-00816, DI, 13

Did not address claims 2-9, 16, 18, 19

**IPR2022-00816
DI: only
addressed claim 1**

Petitioner's Reply Evidence Falls Short

Vogelstein



EX1022

(43) International Publication Date
18 October 2012 (18.10.2012)



(51) International Patent Classification:
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(21) International Application Number:
PCT/US2012/033207

(22) International Filing Date:
12 April 2012 (12.04.2012) **(74)**

- Petitioner relies on Vogelstein to argue that tracking and comparing strands “was known in the art” Reply, 27
- Petitioner never established that Vogelstein is prior art

Opposition to Guardant's Motion to Exclude

Demonstrative Exhibit—not evidence

Guardant's Motion to Exclude Dr. Satija's Declaration (EX2014) is an improper attempt at additional merits briefing

Guardant

Dr. Satija's argument essentially collapses into a frivolous attack on enablement based on alleged inoperability of this disclosed embodiment. *See, e.g.,*

Pet. Motion to Exclude, 4



UW

obviousness theory. At best, Petitioner's arguments go towards weight of evidence, not admissibility. And that is not enough for a motion to exclude. *Found. Med., Inc. v. Guardant Health, Inc.*, IPR2019-00652, FWD, 8-11 (PTAB Aug. 18, 2020).

PO Opp. Motion to Exclude, 2

Guardant fails to identify “legal error” in Dr. Satija’s opinions

Guardant’s Motion to Exclude EX2014

- Guardant alleged legal error regarding operability
- Guardant alleged legal error regarding construction of “barcode” and “first and second strand sequence reads”

Pet. Motion to Exclude, 10

- Nowhere does Guardant identify any legal error in Dr. Satija’s declaration
- Guardant’s arguments, at most, go to weight and not admissibility

PO Opp. Motion to Exclude, 7-8

Each exhibit was used to impeach or test the declaration testimony of Drs. Larrea and Quackenbush

- Each of the exhibits introduced was for impeachment or to elicit cross-examination testimony directly related to Drs. Larrea's and Quackenbush's declarations
- Guardant's Reply witnesses offered new opinions that in fairness Patent Owner could only address during cross-examination



Ascend Performance Materials Operations LLC, v. Samsung SDI Co., IPR2020-00349, Paper 53, 12 (PTAB July 15, 2021)

“if exhibits are introduced during a deposition for the purposes of testing the witness’ testimony, a party should be able to submit those exhibits with the transcript, so the Board has the full context available in order to evaluate the testimony.”

Deposition exhibits used in Drs. Larrea and Quackenbush's depositions were highly relevant to evaluating their testimony

Exhibit:	Content:	Why relevant?
Exhibit 1 of EX2072	Table of contents listing all documents Dr. Larrea brought to deposition	Demonstrates materials that Dr. Larrea brought to deposition
Exhibit 2 of EX2072	Annotated drawing of SMRTbell template in Travers 2010	Impeach Dr. Larrea's declaration testimony regarding Dr. Satija's "Problem 1"
Exhibits 3-5 of EX2072	Annotated drawing of RCR products	Impeach Dr. Larrea's declaration testimony regarding Dr. Satija's "Problem 1"
Exhibit 6 of EX2072	PacBio Glossary describing "productivity" from ZMWs	PO elicited testimony that multi-polymerase-occupied ZMWs are not conducive to base-calling

Demonstrative Exhibit—not evidence

PO Opp. Motion to Exclude, 10-11

Deposition exhibits used in Drs. Larrea and Quackenbush's depositions were highly relevant to evaluating their testimony

Exhibit:	Content:	Why relevant?
Exhibit 7 of EX2072	CHROMA SPIN Columns User Manual teaching that it removes DNA molecules "<300 bp" and retain all molecules ">1,350 bp"	Demonstrates that Guardant's size selection argument would not work to remove concatemer products
Exhibit 8 of EX2072	Article teaching about gel electrophoresis (Li)	Dr. Larrea acknowledged that gel electrophoresis as a size selection technique would expose DNA to UV light
Exhibit 9 of EX2072	US2009/0024331 to "Tomaney"	Dr. Larrea admitted he did not consider Tomaney, which Travers '075 cites and incorporates by reference

Deposition exhibits used in Drs. Larrea and Quackenbush's depositions were highly relevant to evaluating their testimony

Exhibit:	Content:	Why relevant?
Exhibits 1-2 of EX2073	Dr. Quackenbush's declaration and deposition transcript from district court litigation	Dr. Quackenbush testified that claim terms were indefinite in district court, contradicting his positions in this case
Exhibit 3 of EX2073	Dr. Quackenbush's declaration from IPR2019-00652	Dr. Quackenbush testified that patent sharing '127 patent's specification used "family grouping" step, inconsistent with what is disclosed in Travers references
Exhibit 4 of EX2073	Excerpt of Dr. Quackenbush's expert report from district court litigation	Dr. Quackenbush provided contradictory claim construction opinions regarding '127 patent claim 1

Demonstrative Exhibit—not evidence

PO Opp. Motion to Exclude, 12-13

Thank You

Demonstrative Exhibit—not evidence