

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH INC.,
Petitioner

v.

UNIVERSITY OF WASHINGTON,
Patent Owner.

IPR2022-00817
Patent 10,760,127 B2

Record of Oral Hearing
Held: June 15, 2023

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

APPEARANCES:

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The above-entitled matter came on for hearing Thursday, June 15, 2023, commencing at 1:00 p.m. EDT.

P-R-O-C-E-E-D-I-N-G-S

1:01 p.m.

COURT CLERK: All rise.

JUDGE YANG: Please be seated. Good afternoon. This is the hearing for IPR2022-00817 involving Patent No. 10,760,127. I'm Judge Yang. Joining here with me is Judge New and Judge Hulse is joining remotely today and appearing on the screen.

Now, Counsel, please introduce yourselves. Let's start with Petitioner, please.

MR. ROSATO: Good afternoon, Your Honors. Mike Rosato on behalf of Petitioner and I have with me at counsel table, Sonja Gerrard.

JUDGE YANG: Thank you. Welcome. And Patent Owner please.

MR. POWERS: Good afternoon, Your Honor. Ralph Powers, III from Sterne, Kessler, Goldstein & Fox on behalf of Patent Owner, University of Washington. With me at counsel's table is Tyler Liu and behind us is David Holman.

JUDGE YANG: Thank you and welcome everyone. As we stated in the trial order each party has 60 minutes to present its argument, but for Patent Owner, we have a LEAP practitioner joining us, so Patent Owner gets an additional 15 minutes for a total of 75 minutes.

But both parties may, if you want, reserve no more than 15 minutes for rebuttal. Before the arguments start, I'll go over just a couple of housekeeping matters.

First, most importantly, please clearly identify the record. That way we can follow the transcript later. And also, as you see, Judge Hulse is joining us remotely and she cannot see what you put on the screen.

1 But she has the demonstratives so if you point out your slide number,
2 and when you are referring to the record, if you point out the paper number
3 and page number, she will be able to follow.

4 We recognize there is a Motion to Exclude and a Motion to Strike
5 from Petitioner's side. For today's argument, you are free to proceed
6 however you see fit as we haven't ruled on those motions. I'll just say that
7 bear in mind, if we decide the evidence or your arguments are new, we will
8 not consider it.

9 Also for today's argument, if you have any objection, please wait until
10 the other side is finished. You can present your objection after that.

11 Any questions? No? Very good. Petitioner, would you like to
12 reserve any time for your rebuttal?

13 MR. ROSATO: I'll reserve 15 minutes, Your Honor.

14 JUDGE YANG: 15 minutes. That gives your 45, let me see if I know
15 how to set this. All right, I learned how to set that timer. You may begin
16 whenever you're ready.

17 MR. ROSATO: Thank you. And I've been told that the Panel has
18 copies, electronic copies of the demonstratives?

19 JUDGE YANG: Correct.

20 MR. ROSATO: Because we have paper copies if either of you would
21 like one.

22 JUDGE NEW: No, we're fine. We've got it.

23 MR. ROSATO: Okay.

24 JUDGE YANG: Thank you.

25 MR. ROSATO: Thank you. Thank you for your time here today,
26 Your Honors. May it please the Board. We'll turn first to Slide 2 of the

1 demonstrative exhibits. And, you know, point out that all grounds of
2 challenge here revolve around the Travers references.

3 And these are two publications from the same authors describing the
4 same technology which includes U-shaped adapters, pardon me, amplifying
5 adapter DNA complexes and sequencing using the Pacific Bio sciences
6 sequencing platform or PAC Bio platform. We know that the claims of the
7 '127 Patent --

8 JUDGE YANG: Let me stop you there. I know this is really early in
9 the argument. I just want to clarify one thing. In the DI on Page 19, we said
10 as we understand it, these molecules, meaning the SMRTbell molecules,
11 they may be subject to SMRT sequencing directly, or they may be amplified
12 to produce concatemer molecules, which are then subject to SMRT
13 sequencing.

14 And then we said Petitioner relies on the latter in this case, and we
15 find that showing sufficient for each institution purpose. I just want to make
16 sure we did understand your argument correctly, that is, you use the
17 SMRTbell template, you amplify that to obtain these concatemer molecules.
18 And then use the SMRT sequencing. Is that the correct understanding from
19 the Board?

20 MR. ROSATO: Correct. I think what you're referring to is those two
21 identified embodiments, one where it, where the adaptors are ligated and the
22 SMRTbell is sequence, another embodiment where adapters are ligated.
23 There's an amplification step or pre-amplification step and the amplified
24 product is then sequenced.

25 JUDGE YANG: Okay, I want to emphasize the sequencing part. So
26 the first embodiment, if I understand this correctly, is subject to the SMRT

1 sequencing. The second embodiment after the amplification, are we still
2 talking about SMRT sequencing?

3 MR. ROSATO: We're talking about sequencing on the Pacific Bio
4 Sciences --

5 JUDGE YANG: Okay.

6 MR. ROSATO: -- sequencing platform.

7 JUDGE YANG: All right. Thank you for that clarification.

8 MR. ROSATO: Yes, sure. So turning back to the claims, we know
9 that the '127 Patent claims encompass the subject matter that I just described
10 briefly as in Travers. We know this because the claims expressly tell us that
11 they encompass this.

12 The '127 Patent itself in the specification expressly tells us they
13 encompass this. And the '127 Patent specification even cites to this subject
14 matter from Travers as 112 support in its specification. I mention these
15 because these are two critical issues which the Patent Owner really never
16 grapples with and really ignores in many instances in its responsive
17 arguments.

18 It doesn't grapple with the scope of its claims and it doesn't grapple
19 with the acknowledgments and plain disclosure in its own specification.
20 And we'll go through those issues. Pardon me. Turn to Slide 4 please.

21 So starting with a review of the '127 Patent claims and specification,
22 this confirms that there really are no differences between what's claimed and
23 what's in the prior art. And this starts by identifying what's listed in the '127
24 Patent as the alleged point of novelty.

25 What's clearly identified in the '127 Patent as an alleged point of
26 novelty is this process referred to as Duplex Consensus Sequencing or DCS.

1 This is a process that's described as pairing single stranded consensus
2 sequences for a duplex and matching those for an additional error correction
3 step in this process.

4 That's the alleged point of novelty. And I point this out for a couple
5 of reasons. One, it's not recited anywhere in the claims. And also, because
6 this was not the basis by which these claims were allowed.

7 These claims were allowed based on the mistake which has been
8 acknowledged in this proceeding and not disputed that asymmetric adaptors
9 were unknown in the art. We know that's not true. They were known.

10 They're demonstrated here and that aspect is not in dispute. So the
11 alleged point of novelty isn't recited in the claims. And the component that
12 did lead to allowance we all now know was in error.

13 JUDGE YANG: So can we just have an explanation of the
14 asymmetric adaptors? You just referred to what is in the, what is in the '127
15 Patent. Can you explain to us? I think perhaps Figure 1 would be a good
16 place to start?

17 MR. ROSATO: Well, I mean and we can talk about Figure 1. I guess
18 the first thing I would say about Figure 1 is we specifically asked Patent
19 Owner's expert whether the claims were limited to the process depicted in
20 Figure 1 and he unequivocally answered that no, they were not.

21 JUDGE YANG: All right.

22 MR. ROSATO: So that may be an embodiment that's encompassed,
23 but that embodiment certainly does not limit the claims. Okay? I do want to
24 and I will walk through as very pertinent aspects of the specification. Let's
25 turn to Slide 5.

1 And starting with the claims here, this is Claim 1 shown on Slide 5
2 and what's clear is these claims are exceptionally broad. They require
3 attaching adapters, but no particular type of adapter is recited. There's
4 amplifying without any restriction on the type of amplification.

5 There's sequencing without restriction on the type of sequencing. And
6 what we don't see recited here is duplex consensus sequencing. And Patent
7 Owner's expert confirmed during cross-examination that consensus
8 sequencing is not required to this claim and duplex consensus sequencing is
9 not required by any claim in this Patent.

10 Let's turn to Slide 6. Briefly, we'll look at Claim 22 which is even
11 broader in some respects, but similarly has no recitation for duplex
12 consensus sequencing. This claim, just like Claim 1, generically recites
13 adapters amplifying and sequencing.

14 But it doesn't limit those aspects to any particular type of adapters or
15 any particular type of amplification or any particular sequencing. Turn to
16 Slide 7 and turn to the specification of the '127 Patent. I'll go through a
17 couple of key and relevant points of disclosure.

18 We turn to the specification, the specification confirms that the claims
19 are indeed quite broad and as broad as they appear at face value. And this
20 starts with looking at the claimed adapters which even the claims themselves
21 confirm encompass U-shaped adapters.

22 As we look to Column 10 of the '127 Patent, the Patent explains that
23 the sequence of the linker itself does not matter in the workflow. And the
24 specification expressly cites to Reference No. 49 which is the Travers
25 reference stating that U-shaped adapters as disclosed in Travers are suitable
26 for its method. So --

1 JUDGE NEW: Excuse me.

2 MR. ROSATO: Yes, sir.

3 JUDGE NEW: Does the '127 Patent, I believe it does, but I just
4 would like to make certain of your position, that linkers and adapters are
5 synonymous in these terms.

6 MR. ROSATO: They do use those terms.

7 JUDGE NEW: Thanks. I just thought I'd check.

8 MR. ROSATO: Yes, thank you. So the breadth of the claims
9 regarding the adapters is confirmed by the undisputed construction of the
10 challenged claims which is addressed at Slide 8. So as the Petition explained
11 at Pages 13 through 15, the claims encompass Travers's U-shaped adapters
12 which when attached produce asymmetric adapter DNA molecules as
13 claimed.

14 And this interpretation was adopted in the Institution Decision that's
15 not been disputed. In fact, Patent Owner has never disputed this
16 interpretation and there is also no dispute as to one of the aspects of the
17 claims. And that is Travers's disclosure of adapters comprising bar code
18 selected from a plurality of bar codes.

19 So that construction and that disclosure of Travers is not a point
20 dispute. Turn to Slide 9 please. So Slide 9 illustrates the claimed
21 amplifying and sequencing and that those claimed terms also are very
22 broadly defined specification.

23 Column 10 of the specification as we've seen acknowledges disclosure
24 of amplifying as being a known step in the Pacific Bio Science's workflow
25 and cites specifically to Travers. Column 11 continues this

1 acknowledgement and discusses attaching U-shaped adapters to the ends of
2 the fragment to produce closed circles.

3 And then discusses pre-amplifying those closed circles and again
4 specifically cites to the Travers reference. I mention this because these are
5 critical acknowledgements that are in the specification and these
6 acknowledgements are not addressed anywhere, certainly not in the Patent
7 Owner Response.

8 They're addressed, Column 10 is addressed nowhere in Patent Owner's
9 expert's declaration.

10 JUDGE YANG: So my understanding is Patent Owner doesn't
11 dispute the rolling circle replication as it is part of Claim 10. But if I
12 understand their argument correctly, they're saying after you use this rolling
13 circle amplification, one skilled in the art would not, as Petitioner argues,
14 use the Pacific Bios platform to perform the sequencing step because these
15 are incompatible and there are many let's just say technical difficulties.

16 So it's not that they don't dispute anything at all. They are saying the
17 patent acknowledges, and it is clear in Claim 10, that there is rolling circle
18 replication. But I think they're saying your specific argument using the
19 Pacific Bios sequencing platform as you explained earlier wouldn't work for
20 this rolling circle amplification. Can you still address that please?

21 MR. ROSATO: Yes, that's I think they argue their case slightly
22 differently, but the reason we're pointing to this disclosure right in Column
23 10 for one reason is to look at what it acknowledges. It's acknowledging that
24 close circles amplification have been demonstrated as a step in the PAC Bio
25 or Pacific Bio site.

1 We can call that PAC Bio for ease, have been demonstrated as a step
2 in the PAC Bio workflow.

3 JUDGE YANG: Can you repeat what you just said.

4 MR. ROSATO: Sure. So I'm referring to Column 10 and I'll read the
5 exact verbiage. Ligation and amplification with circularizing linkers, i.e.,
6 hairpin linkers affixed at both ends of the fragment has been demonstrated as
7 a step in the Pacific Bio Sciences sample preparation workflow.

8 And there's a citation, a reference No. 49 which is Travers. I point
9 this out for several reasons, but one of them is it's an acknowledgement by
10 the inventors who are presumed persons of ordinary skill and have been
11 acknowledged by the Patent Owner's expert as skilled artisans.

12 But this is an acknowledgement that this subject matter has been
13 recognized as actually disclosed in a workflow. So this isn't an indication of
14 recognition of actual reduction of practice. This is relevant for a couple of
15 reasons, but one of the reasons is what you alluded to.

16 And that's Patent Owner's argument that somehow none of this would
17 work. That's not what Column 10 in the Patent says. Column 10 in the
18 Patent says this has been, you know, a recognized step in a known
19 workflow.

20 JUDGE YANG: Correct, so where you were referring to, it talks
21 about a ligation and amplification. And I'm looking at Claim 1, challenged
22 Claim 1. Let's just say generally speaking, ligation corresponds to step A
23 which is attaching the adapters that and amplification refers to the step B
24 that is amplifying.

25 We still need to talk about the sequencing part. I imagine you are
26 going there?

1 MR. ROSATO: The specification answers that question too, Your
2 Honor. And on this slide, we have referenced the Column 15 which lists
3 what are identified as sequencing according to their invention using any
4 suitable sequence method known in the art including, but not limited to, and
5 one of the listed sequencing approaches is sequencing using the Pacific Bio
6 Sciences sequencing platform.

7 So there is no doubt about it that sequencing according to PAC Bio
8 and using that platform is within the scope of this claim.

9 JUDGE YANG: Is it within the scope of what you allege, that you
10 use the SMRTbell template as a starting point and produce a concatemer and
11 then use the Pacific Bio? This specific combination, would the '127
12 specification support that?

13 MR. ROSATO: I'm not really clear what you're asking me. Is the
14 first question is, do the claims encompass U-shaped linkers of Travers? The
15 answer is yes. We know that because the claims have, because the
16 specification tells us so and the claims specifically recite U-shaped linkers.

17 Do they recite rolling circle amplification as their amplification step?
18 We know the answer to that is yes because Claim 10 specifically identifies
19 rolling circle amplification. And if the next question is do the claims
20 encompass then continuous sequencing out of PAC Bio sequencing
21 platform?

22 The answer there is unequivocally yes because the specification tells
23 us that and because there is nothing in these claims that limits --

24 JUDGE YANG: That's a very smart answer because all three
25 elements indeed are in the '127. I guess my question wasn't too smart.

26 MR. ROSATO: Oh, no.

1 JUDGE YANG: Because I was trying to find out as you said,
2 attaching a U-linker, amplifying it, and then, as you pointed out in Column
3 15, it talked about suitable sequencing methods, would the Pacific Bio's
4 sequencing method be suitable for sequencing the amplified concatemer?

5 MR. ROSATO: Yes, it would.

6 JUDGE YANG: I understand that is one of the main disputes. That
7 is, even if you can use the SMRTbell template and amplify it and thus
8 satisfying the first two steps, would the SMRT sequencing or the PAC Bios
9 platform be suitable for further sequencing that product?

10 MR. ROSATO: Yes, the short answer to that question is yes. And
11 there are multiple reasons we know the answer is yes. One, because the
12 claims encompass it and so if the claims are to be enabled, it has to, the
13 answer has to be yes.

14 But second, this specification tells us the answer is yes because in
15 multiple places, the specification is specifically talking about precisely what
16 we're envisioning. And that is U-shaped linkers on each end, a circular
17 template, that template being amplified and that amplified product being
18 sequenced on the Pacific Bio Sciences sequencing platform.

19 We see this in Column 10 with reference to Travers. An
20 acknowledgment that this is exactly what's in the Travers reference. We see
21 this again at Column 11 that we're, there's discussion of U-shaped linkers, a
22 circular, a closed circle, pre-amplification and then again citation to Travers.

23 And Travers is a PAC Bio. Both Travers references are a PAC Bio
24 publication. So we can approach this from three levels. One is a claim
25 scope issue or a claim scope perspective and understand the claims do
26 indeed encompass the subject matter.

1 The second is guidance in the specification. And while we look at the
2 guidance in the specification, we see guidance that indicates unequivocally
3 that these claims do in fact encompass that process. And then third, we look
4 at the art, the Travers references here and we see, and we haven't gotten to
5 that yet, but we will.

6 We see a description of this sequence of events. And we can rest
7 assured that this is in fact disclosed in the reference because it's expressly
8 stated in the reference, but also because the inventors of the Patent
9 application have told us it's in there.

10 And that is precisely what they're citing to for their own 112 support.
11 So this sort of all come, no pun intended, but full circle around. Right? So
12 the answer, that's the long version of answering your question.

13 JUDGE YANG: No, I appreciate that.

14 MR. ROSATO: Yes. But thank you for the questions. I'm going, you
15 are cutting to the chase on a lot of these issues and I appreciate that. But
16 moving ahead, let's go to Slide 10. And I just want to point out a few more
17 details on the claim scope issue.

18 And that is we made sure to really question Patent Owner's expert on
19 what was the perceived scope because, you know, sometimes these
20 arguments, it looks like Patent Owner is arguing details of an Illumina
21 sequencing process or details of a PCR based amplification or as you
22 pointed out, Your Honor, details of what's illustrated in the embodiment of
23 Figure 1 of their Patent.

24 So it made sure to go through and clarify these points with their expert
25 and he confirmed unequivocally that the claims are not limited to the process

1 of depicted in Figure 1 of the Patent. The claims are not limited to PCR
2 amplification.

3 And the claims are not limited to sequencing on any particular
4 platform and specifically not limited to the Illumina sequencing platform.
5 So this as I mentioned, is reflective of the breadth of the claims and the
6 breadth of the claims is one aspect that informs the prior art analysis.

7 As I did turn to the Travers references starting at this section begins at
8 Slide 11, but it is a general matter. Again, given the scope of the claims, the
9 guidance and the specification, it then comes as no surprise that the Travers
10 references do in fact disclose exactly what the specification tells us they
11 disclose.

12 That includes U-shaped adapter molecules. That includes forming
13 circular templates resulting in an asymmetric adapter DNA complexes with
14 these U-shaped adapters amplifying those complexes and sequencing,
15 including sequencing using the Pacific Bio Sciences sequencing platform.

16 And some miscellaneous outcomes of that including sequence reads
17 corresponding to sense and anti-sense strands that are analyzed and used to
18 build consensus. Let's turn to Slide 12 please. So briefly on the Travers
19 references again, as I mentioned earlier in our discussion, these are
20 references by the same authors, the same Pacific Bio Sciences scientists
21 describing the exact same technology.

22 And there's no dispute on this. There's probably at least a dozen
23 instances in the Patent Owner's own briefing where they acknowledge these
24 are the same authors describing the same technology.

25 And as identified, recognizing the Institution Decision, this is also not
26 an instance where the modification is being proposed as specifically

1 identified in prior art which, Your Honor, I appreciate you drawing out in
2 your questioning. It is not being sought to be modified, but identified and
3 applied to the claims.

4 JUDGE YANG: So another dispute is about the motivation to
5 combine these two references. Let's just say if you don't need a reason to
6 modify it because it is there, then what's the use of the other reference?

7 MR. ROSATO: Well there's certainly a rationale to, I prefer the term
8 rationale as rather than motivation as Patent Owner argues. It's more
9 consistent with the case law, but there's certainly a logical rationale as to
10 why a person of ordinary skill would look to two publications by the exact
11 same authors describing the exact same technology.

12 In fact, we are prescribed to understand the perspective of a person of
13 ordinary skill as someone presumed knowledgeable about the relevant prior
14 art. So certainly a person of ordinary skill knowing about one, is going to
15 know about one of the references if they're presumed familiar. They're also
16 going to know about the other.

17 So there's no reason why a POSA would disregard one publication by
18 the same authors on the same thing. Which is essentially what's being
19 described that there has to be some super motivation to go to both.

20 This is a simple logical reason why a human being who is a person of
21 ordinary skill wanting to know about a particular piece of technology would
22 logically look at two writings by the same author. So it doesn't, you know,
23 there's no magical or remarkable reason necessary why scientists would look
24 at publications on the same subject matter.

25 We expect that they do. And sorry, was there a second part of that
26 question? Thank you.

1 JUDGE YANG: No.

2 MR. ROSATO: And they're, you know, actually there's a second part
3 of my answer that I want to get to and that is I also want to disentangle. We
4 can get back to this, but there's a lot of argument about, you know, it seems
5 to be a suggestion that superiority should be established when there are
6 multiple embodiments of this requirement that, you know, one has to be
7 demonstrated as superior to the other.

8 And that's the only one that we're allowed to consider. Obviously
9 that's not sustainable. I think the Board recognized that in the Institution
10 Decision that remains true. So let's turn to Slide 13 and I'll touch on a few
11 key disclosures of Travers and we can certainly come back to it as the Board
12 pleases.

13 But starting with Slide 13 here, you know, and sort of running through
14 an organization that reflects the components of the claim, certainly Travers
15 is disclosing the U-shape linkers that the specification says they disclose and
16 discusses attaching those adapters to the ends of the fragment that results in
17 an asymmetric adapter DNA molecule.

18 Travers at paragraph 92 even uses the terminology asymmetric to
19 describe its linker complexes and as far as I understand, there's no dispute
20 that this is the case. And we can turn to Slide 14 please. So as we've been
21 talking about Travers discloses several approaches to its sequencing.

22 One approach and as shown here in paragraph 122 of Travers, one
23 approach discussed in Travers is that the adapter DNA complexes
24 themselves can be sequenced and as Your Honor pointed out, an alternative
25 approach is that the adapter complexes can be amplified and then the
26 amplified product sequenced.

1 So I know we talked about this, but one thing, you know, to make sure
2 we identify is this paragraph also is citing to another PAC Bio publication as
3 the 503 Patent and incorporating that by reference for additional discussion
4 of amplifying template complexes and then sequencing them. There is quite
5 a bit of discussion in the 503 Patent regarding that approach.

6 And that is entirely consistent with what we see and we discussed
7 being mentioned at Column 10 of the Patent which again talks about
8 amplifying and sequencing and cites to Travers. So sort of keeping a score
9 card on this that leaves us with four different references that are talking
10 about templates, amplifying those templates, sequencing those templates on
11 PAC Bio sequencing platform.

12 That includes Travers at 075, Travers 2010, the 503 Patent that's
13 referenced here, the '127 Patent itself which identified Travers as disclosing
14 this subject matter, and to your point, Your Honor, the operability issues that
15 are alleged.

16 There was zero references, zero references of record that ever indicate
17 that an amplified template is not amenable to sequencing on the PAC Bio
18 sequencing platform. So that's important when you've got four prior art
19 references that talk about doing exactly what is going on here and what's
20 discussed in Travers at paragraph 122.

21 And zero references that say otherwise. There's little reason to doubt
22 that what's being discussed is indeed operable. Especially when the Patent
23 itself talks about us having been done and a recognized component. So let's
24 turn to Slide 15.

1 JUDGE HULSE: Counsel, before you move on, just a quick question.
2 So you do not dispute that the amplification step has to be performed and
3 completed before the sequencing step?

4 MR. ROSATO: That's a good question. For the, you're asking a
5 claim interpretation question, Your Honor? Yes.

6 JUDGE HULSE: Yes.

7 MR. ROSATO: That is the interpretation that we've followed in
8 mapping to the prior art, yes. Let's turn to Slide 15 please. So another piece
9 of disclosure I want to point out about Travers and that is that it's expressly
10 discussing its sequencing and generating sequence reads, corresponding to
11 the sense and anti-sense transit, the DNA molecule.

12 And as we'll discuss, Patent Owner ignores this disclosure in Travers
13 075 when arguing, you know, this argument that Travers 2010 is using the
14 term sub-reads and therefore, you know, there's an absence of sequence
15 reads.

16 Again, this is discussed in the briefing, but important to point out that
17 Travers 075 is specifically referring to the same reads as sequence reads and
18 that's a disclosure that's ignored in Patent Owner's arguments, but certainly
19 informative on the point.

20 And I'm sure we'll come back to that. Lets turn to Slide 16. So again,
21 just walking through some pertinent points of Travers. Travers additionally
22 discusses grouping and comparing the sequence reads of the sense and anti-
23 sense strands in order to build the consensus sequence and Travers
24 specifically describes using barcode sequences in its grouping in
25 distinguishing molecules.

1 And there's fairly extensive discussion of bar codes and using bar
2 codes to parse out sequence reads from its sequence data at paragraphs 100
3 to 102 of Travers.

4 JUDGE YANG: So about this grouping disclosure, the only claim
5 that specifically recites this is Claim 22. I imagine you probably will get to
6 it later, but I'm just very curious so I want to ask my question now.

7 MR. ROSATO: Sure.

8 JUDGE YANG: Claim 22 talked about grouping the strand sequence
9 reads into families based on, you know, two sequences. In the, in Patent
10 Owner's surreply, this is on Page 11 of the surreply, Patent Owners says,
11 "Petitioner ignores the specification's description of grouped 'family' of
12 strand sequence reads and its reply arguments address only sample grouping,
13 not family grouping as claimed."

14 According to Patent Owner, family grouping is a fundamentally
15 different process from sample grouping. Could you address that because
16 later on the same page, Patent Owner cites to the specification of the '127
17 Patent. Everywhere they cited, they talked about family pair, families of
18 paired target sequence strands, PCR duplicates, so if you could address that,
19 that would be great.

20 MR. ROSATO: Yes. So this is an evolving argument. The argument
21 you see here is not the argument that was advanced in the Patent Owner
22 response. So we do have to address both arguments. So the argument in the
23 Patent Owner response was based on the barcode itself. Right?

24 The argument there was that Travers failed to meet the limitation of
25 the claim because the barcodes in Travers are sample barcodes rather than
26 fragment specific or molecular barcodes. And as we pointed out in our

1 reply, that argument does not in the least bit commensurate with the scope or
2 language of their claims.

3 Their claims generically recite barcode. They don't recite fragment
4 specific barcode or molecular barcode. And when we look at the generic
5 recitation of barcode, Travers meets that limitation as explained in Travers
6 and set forth in the Petition.

7 Travers does use barcode information. It also uses sequence
8 alignment to identify anti-sense strand reads and sense strand reads in its
9 process of building consensus sequences. So that was the argument in the
10 POR. That argument has been rebutted I think pretty effectively which is
11 why you see this different argument here which seems more like an
12 invitation in the surreply to read in some limitation on the term family. That
13 argument was never made in the POR.

14 There was no construction of the term family grouping advanced in
15 the Patent Owner response. What they seem to be doing is coming back and
16 asking the Board to adopt what their own expert disavowed and that is
17 interpret the claims as being specifically limited to the process depicted in
18 Figure 1 of their Patent which certainly does go through in conjunction with
19 Figure 3 which is the next step of that, of that process and describe a
20 particular type of grouping.

21 But the claims aren't limited to that type of grouping. And that's what
22 they're asking here. It's a new argument that came up in their surreply. It's
23 not commensurate with the scope of their claim just like many of their
24 arguments. And it doesn't, it's not supported by the language of the claim is
25 what I would say.

26 JUDGE YANG: All right.

1 MR. ROSATO: I have 11 minutes so I'm going forward, I'll just jump
2 to Slide 21. So, Your Honor, I really appreciate the questions, it's a far more
3 effective way to address the subject matter. Some of these, we've already
4 talked about.

5 But I do want to list out and identify the specific arguments that were
6 advanced in the Patent Owner response and make sure we're addressing any
7 of those. But there were essentially, you know, four key arguments.

8 There's a fifth argument about some dependent claims that look to
9 have been, I'm not sure if that's still pursued because it wasn't addressed in
10 the surreply materials, but the four main arguments and I'll briefly address
11 them, but the first argument was that Travers fails to teach sequence reads of
12 Claim 1 and the basis of that argument was pointing to Travers 2010.

13 And the usage of the term sub-read as we had pointed out in the
14 briefing Travers 075 discussion on this is completely ignored in Patent
15 Owner's response and particular, in particular discussion in Travers 075
16 where it's using the term sequence read to refer to the same read.

17 These are obviously sequence reads according to the reference and
18 Patent Owner's already been focusing on one of, one use of terminology in
19 one reference isn't sufficient. The second argument grouping, we thank you
20 for your question, Your Honor, I think we've talked about that.

21 There is this third argument about Claim 19. And I want to make sure
22 we address that because that also is an instance where they seem to be an
23 evolution of the argument as we went from the Patent Owner response to the
24 surreply.

25 But in the Patent Owner response, the argument about claim 1, or
26 excuse me, Claim 19 was Patent Owner was arguing that the adapters of

1 Travers are not asymmetric or not actually the asymmetry of the adapters
2 themselves wasn't used in the distinguishing as recited by Claim 19.

3 As we point out in our briefing and let me just, can we go to Slide 25?
4 As we pointed out in our briefing, adapter asymmetry is not what's recited
5 in Claim 19 so this is another instance of argument that's not commensurate
6 with the scope of their claims.

7 The language of Claim 19 is listed here. It refers to distinguishing
8 sequence reads at least in part by asymmetry of the asymmetrical double-
9 stranded adapter DNA molecule. So the Patent Owner's response is arguing
10 about the adapter for, you know, specifically whereas the claim is talking
11 about this asymmetry of the molecule.

12 That's important or pertinent point for several reasons. One, we
13 should talk about what the claim actually requires, but two, again as I
14 mentioned earlier, there's a construction that was advanced in the Petition
15 about that's pertinent to this aspect. It wasn't disputed.

16 And there's no dispute that the molecule that results from attaching
17 adapters of Travers is indeed asymmetric and that structure is in fact used by
18 Travers to distinguish reads of the sense strand and the anti-sense strand. So
19 those are --

20 JUDGE NEW: Excuse me.

21 MR. ROSATO: Yes, sir?

22 JUDGE NEW: Counsel, doesn't the double stranded asymmetrical
23 amplify DNA require that the adapter also be asymmetrical? In other words,
24 to get that asymmetric amplified DNA double strand you have to have an
25 asymmetric adapter as well?

1 MR. ROSATO: Well, given that Travers specifically describes its
2 adapters as asymmetric, I would say for purposes of this case, sure.

3 JUDGE NEW: Okay.

4 MR. ROSATO: Right? Because the, yes, if you have an asymmetric
5 adapter, you're certainly going to have an asymmetric adapter DNA
6 complex.

7 JUDGE NEW: Right, thank you.

8 MR. ROSATO: Thank you. Lets get to, I have six minutes left and I
9 want to observe time here, but turn to Slide 26 because I do want to talk
10 about these inoperability arguments. A whole lot of time is spent on these.

11 We touched on them, you know, earlier to a fair extent so I think the
12 Panel, you know, understands, you know, one of the concerns here is that
13 you have the Patent Owner that has broad claims that encompasses subject
14 matter and guidance in their specification that's acknowledging disclosure of
15 the subject matter in the references that are being asserted and even
16 describes those references as having reported this subject matter.

17 So indicating a recognition by the inventors that it's disclosed in these
18 references and even known to be in the, you know, commercial workflow.
19 So it's troubling to see, you know, that type of discussion, that type of claim
20 scope, that type of discussion.

21 And then sort of out of the other side of Patent Owner's mouth
22 attacking the same prior art disclosure that's relied on for 112 support as
23 somehow being inoperable which simply isn't true. And that's, there's a lot,
24 there's a lot of discussion about, you know, some technical details which,
25 you know, I'm happy to go into.

1 There's a lot of errors in those arguments. But I think at the high
2 level, these issues can be resolved by the simple fact that this ship has sort of
3 sailed for Patent Owner given their, the way they describe the subject matter
4 and their specification.

5 They're simply not in a position to come back and question or criticize
6 the prior art that they, that they acknowledge in their specification as
7 somehow being inoperable. And there's a, we'll turn to Slide 26. So another
8 aspect that I want to make sure, you know, comes through.

9 I'm sure it's recognized, but worth touching on and, you know, there's
10 sort of one, sort of one I would say meek attempt to address this issue of
11 what are the differences between the '127 specification and the prior art if
12 any?

13 As I mentioned earlier, the acknowledgements or discussions in
14 Column 10 of the '127 Patent are not addressed by their expert anywhere in
15 his declaration. I don't think they're even addressed in the Patent Owner
16 response.

17 But there is one, one sort of conclusory paragraph in the expert
18 declaration, paragraph 215 of Dr. Satija's declaration which mentions
19 Column 11, not Column 10, but mentions Column 11 of the '127
20 specification where he points to Column 11 mentioning restriction sites,
21 optionally engineered into the adapter sequences.

22 And this was in the context of the specification discussing closer pulls
23 and preamplification and citation of Travers. So the argument that they try
24 to advance here, again, it's very deep in expert declaration, but I do want to
25 make sure to address it.

1 The argument here is that this mention of the optional restriction sites
2 is pointed to by Dr. Satija as sort of self-solving the inoperability problem
3 according to his argument. And in one of the key aspects of his argument is
4 he says none of this is in Travers.

5 And that's not true. Paragraph 80 of Travers 075 which is listed here
6 on Slide 27 specifically discusses adapters having restriction sites
7 engineered in very similar to what's in the '127 Patent. In fact, in much more
8 detail.

9 And then at Slide 28, briefly, Dr. Satija was confronted with this
10 disclosure during his deposition. He really had no response to it. In fact, I
11 think he literally had no response to it. So this, I'm sort of repeating myself
12 here, but it comes down to this issue of, you know, inconsistency between,
13 you know, what Patent Owner would have to argue for enabling disclosure
14 versus how they're treating the prior art.

15 And that's just not a legally permissible path to take. Let's turn to
16 Slide 29. So briefly, I'm happy to get into any specific questions on this, but
17 there are these arguments about, you know, four alleged problems as to why
18 the technology wouldn't work.

19 I think this is addressed in the briefing at a high level. I mean, besides
20 the points that I've already made about the different, just the difference in the
21 argument given the disclosures, none of these are credible arguments and
22 there's, none of them are supported by evidence. They all conflict with
23 record evidence.

24 But none of these alleged problems are in fact problems that fall and
25 from a legal standpoint, they suffer from the defect of viewing a POSA as,

1 you know, either sort of inept to be honest or intent on sabotage or a
2 combination of both.

3 And that's just not the proper perspective by which a person of
4 ordinary skill should be defined. I'll jump, you know, briefly in the last
5 moments here to Slide 37, let's go to 37. I want to say a brief word about the
6 objective evidence, the evidence of secondary considerations that's been
7 advanced.

8 JUDGE YANG: Make it very brief because your time is up.

9 MR. ROSATO: And I'm happy to take, you know, give back any
10 rebuttal time. So these are argued for Claims 2 through 9, 16, 18 and 19.
11 What's very clear looking at these references and stated plainly in the
12 references themselves, these references Edge GEN and Kirsch are citing to
13 and discussing specifically the Schmitt 2012 paper that's using, you know, a
14 specific embodiment of randomized 12 nucleotide n-mers barcodes and
15 talking about duplex consensus.

16 You can see the particular approach. As we've talked about duplex
17 consensus sequencing, in fact, none of the aspects of Schmitt 2012 are
18 recited in the claim. But certainly duplex consensus sequencing is not
19 recited in the claims.

20 It's not recited in any claims. So to the extent there's any praise or any
21 evidence presented by these references, it's directed to Schmitt 2012 and
22 features that are simply not recited in the '127 Patent claims. Thank you.

23 JUDGE YANG: So can I first ask if you would like to reserve any
24 time and if so, how much?

25 MR. POWERS: Yes, Your Honor, 15 minutes for rebuttal please.

26 JUDGE YANG: All right, so you have 60. Whenever you're ready.

1 MR. POWERS: May it please the Board, Ralph Powers, III for Patent
2 Owner, University of Washington. And I'll be presenting today on
3 University of Washington's case in chief. My co-counsel David Holman, a
4 LEAP practitioner, will be presenting on objective indicia and any questions
5 about any ancillary motions or issues related to those motions. What we
6 heard from opposing counsel was based on a superficial view of the
7 technology at issue. Glossing over what the Patent actually says.

8 And like the Petition itself, counsel's argument attempts to get the
9 Board to ignore the many problematic details of its proposed embodiment
10 problems a skilled artisan would not have ignored. Indeed, a skilled artisan
11 would have viewed Petitioner's hindsight driven proposed approach to create
12 insurmountable problems leading to no reasonable expectation of success.

13 And I'd like to focus my time today on our no reason to combine and
14 no reasonable expectation of success arguments. And then I'd like to address
15 Petitioner's incorrect allegations of certain admissions allegedly made by the
16 specification. And then I will turn to some missing elements in the
17 combination. But first, I think it's important --

18 JUDGE YANG: Actually, I have a question. Just like I interrupted
19 Petitioner's portion --

20 MR. POWERS: Please, Your Honor.

21 JUDGE YANG: -- very early. I have a question that's the other side
22 of the same coin. I will say rolling circle replication is part of the disclosure
23 in the challenged '127 Patent. Is that correct?

24 MR. POWERS: That is correct.

25 JUDGE YANG: And a part of Claim 10 I believe. So let's say
26 starting from there, are you saying after the rolling circle replication, if you

1 use some other sequencing method as '127 somehow alluded to because it
2 said any suitable method, it will be just fine to reach whatever you claim
3 here.

4 But what Petitioner argued after the rolling circle of replication, if you
5 use the Pacific Bio's platform, then that's a no no because all the technical
6 issues. Do I understand your argument correctly?

7 MR. POWERS: I think so, Your Honor. At the end of the day, the
8 specification says use any suitable method. And our point was, and our
9 briefing extensively shows that a person of ordinary skill in the art would
10 not have viewed Petitioner's combination as suitable with the Pacific Bio
11 Sciences platform.

12 JUDGE YANG: Well thank you for that clarification.

13 MR. POWERS: You're welcome. Thank you. So I wanted to say I
14 think it is important for our no reason to combine and no expectation of
15 success arguments to actually understand how Pacific Bio Sciences work.

16 The sequencing method in Pacific Bio Sciences that's used by
17 Petitioner's combination and we didn't hear a single word about that really
18 from Petitioner. So they seem to want to gloss that over and I'd like to talk
19 about it.

20 If we go to Petitioner's Slide 18, I'd like to review how SMRT
21 sequencing works and how it works very differently from other next
22 generation sequencing technologies. The SMRT in SMRT sequencing refers
23 to Single Molecule Real Time sequencing.

24 And SMRT sequencing makes use of molecules that are linear, but
25 topologically circular because of their hairpins, their hairpin adapters. And

1 these molecules are called SMRTbells depicted from Travers 2010 up in the
2 upper left hand of this Slide.

3 And after the hairpin adapters are ligated onto the target DNA to
4 create SMRTbells, the SMRTbells are directly sequenced. In other words,
5 there's no amplification step after adapter ligation but before sequencing.
6 PAC Bio's method monitors a single polymerase incorporating fluorescent
7 dye linked bases one by one as the polymerase proceeds and synthesizes a
8 new strand off the template.

9 This all takes place in a tiny, tiny well called a zero mode wave guide.
10 Zero mode wave guide is between 50 and 70 nanometers in diameter. This
11 is super tiny. Both Travers documents incubate their SMRTbell templates
12 with polymerase and primer which binds to the SMRTbells.

13 And then they apply those SMRTbells to the complex, they apply that
14 complex rather to the zero mode wave guide arrays. When the correct
15 labeled nucleotide binds the polymerase, it's held there briefly as the
16 polymerase incorporates it and the nucleotide is read by the machine. Both
17 parties seem to agree to this.

18 This incorporation event is measured on the instrument and the
19 polymerase is free to incorporate the next nucleotide. That's why it's called
20 sequencing by synthesis and that's why it's called single molecule real time
21 sequencing.

22 Now, PAC Bio Sciences has by far the highest error rate of any next
23 generation sequencing technology. The way they overcome this is by
24 sequencing around and around the circular template to get multiple passes
25 through the circle.

1 This is all discussed in Dr. Satija's declaration and it's not disputed. If
2 we move to Slide 32 of Patent Owner's demonstratives, we see that the PAC
3 Bio Sciences system really exists on a knife's edge.

4 You don't want zero polymerases in the zero mode wave guide, but
5 you don't want more than one polymerase in the zero mode wave guide
6 either. You need one polymerase at the bottom of the zero mode wave
7 guide.

8 And this is from the Tomaney reference which is incorporated into
9 Travers 075 incorporated in its entirety and it says here that you do not get
10 useful data if a reaction, if more than one reaction enzyme is located in the
11 bottom of the zero mode wave guide.

12 You also don't get any useful data, of course, if there's no polymerase
13 located in the bottom of a zero mode wave guide. So if we move to Slide,
14 and by the way, on the left side here it says that if multiple polymerase are
15 sequencing, the data may be excluded from further analysis.

16 And I'll explain why that is in a moment. We go to Slide 21, and
17 here's --

18 JUDGE YANG: Patent Owner's or Petitioner's?

19 MR. POWERS: Of Patent Owner's, Your Honor. I'll stick on Patent
20 Owner's for a while.

21 JUDGE YANG: All right.

22 MR. POWERS: So there's a problem when you have multiple
23 polymerases bound at the bottom of the same zero mode wave guide
24 emitting signals at the same time. Why? Because a PAC Bio sequencer can
25 not resolve which signal comes from which polymerase at the bottom of the
26 zero mode wave guide and you get garbled inaccurate signal.

1 Moreover, these polymerases don't proceed at the same rate.
2 Sometimes they pause, sometimes they speed up. So imagine being in a
3 room with two different speakers playing different songs at different tempos
4 and try to decipher the notes. What you will hear is noise.

5 And the speaker, and the more speakers you add to the room, the
6 noisier it will get. Each polymerase at the bottom of a zero mode wave
7 guide is like a speaker playing its own song. If we move to Slide 22, this
8 requirement for a single polymerase at the bottom of a zero mode wave
9 guide is well established as disclosed in this art here on Slide 22.

10 Moreover Guardant's own expert, Dr. Larrea conceded in his
11 declaration that the key is that only a single DNA polymerase is immobilized
12 at the bottom of a zero mode wave guide. And that's at Exhibit 1033
13 paragraph 11. And this is exactly our point.

14 The key to the whole workflow is that only one polymerase is
15 immobilized at the bottom of the zero mode wave guide. If you get zero
16 polymerases, you don't get any data. If you get two or more polymerases,
17 you get noise.

18 So to sum up in PAC Bio sequencing, you have very small wells,
19 you're sequencing around and around these circular SMRTbell templates
20 created without any amplification step and it completely depends on being
21 on this knife's edge having only one polymerase in a zero mode wave guide.

22 So against that backdrop, let's look at the two independent claims and
23 then Petitioner's proposed embodiment. Let's go to Slide 12. I don't think it
24 was disputed, I think it was clear, but just to refresh everybody's memory,
25 these claims require attaching adapters then amplifying to produce copies of
26 those strands and then sequencing the first and second strand copies.

1 Okay, but that's not at all the way PAC Bio workflow works, but to try
2 to reach these claims using hindsight, Petitioner cherry picks some language
3 out of Travers 075. Let's go to Slide 5. And here is Petitioner's rolling circle
4 replication embodiment straight out of the Petition.

5 The SMRTbell templates from Travers are subjected to rolling circle
6 replication and then employed directly as template molecules impact Bio
7 sequencing. There are no other steps proposed, no processing, nothing else
8 just employed directly.

9 That's from the Petition. Slide 6 please. So the standard SMRTbell in
10 Travers is up here on the upper left-hand corner. But to try to reach these
11 claims, Petitioner proposes this rolling circle replication embodiment.

12 And when you conduct this kind of rolling circle replication, you get
13 an unresolved unresolvable smear of ticker tape linear products, linear
14 sequences of a huge range of sizes coming off the SMRTbell to generate
15 these linear concatemers.

16 Guardant does not dispute that this smear of vastly different sizes is
17 what you get when you do rolling circle replication off of SMRTbell. Now
18 in paragraph 122, Travers 075 does contain a reference to this embodiment.

19 But unlike every other portion of the Travers 075 document, there is
20 not description and there's certainly no enabling description in the Travers
21 075 of how to use these concatemers products in PAC Bio's method. We go
22 to Slide 7.

23 Guardant's own Dr. Larrea admitted that PAC Bio sequencing was
24 nascent and cutting edge technology in 2010. But the sparse disclosures in
25 Travers 075's paragraph 122 cannot and do not meet this standard.

1 Now I'd like to talk about our no reason to combine arguments. If we
2 go to Slide 9, Guardant unmistakably relies on a combination of two
3 separate references in the Petition for its Ground 1 and for every Ground.

4 These are the Travers references we've been talking a lot about them.
5 These are separate references. They happen to share the same first author,
6 but they are separate references and no one is combined within the other,
7 there's no reference incorporated, they're separate references.

8 And Guardant, if we move to Slide 10, is clearly relying on the
9 combined teachings of these references to try to reach the claims. You can
10 see for some claims and claim elements, they're using both. For some claims
11 and claim elements, they're only using one.

12 And for other claim elements, they're using the other. And if we move
13 to Slide 11, we see the entirety of the Petition's motivation or rationale to
14 combine. There's no discussion whatsoever about why anyone would excise
15 out any RCR embodiment from the Travers 075 and combine it in any way
16 or use it in any way with Travers 2010.

17 We get no why and we get no how. We're left with the inference,
18 Your Honors, that this is hindsight driven. The law requires more. If we
19 move to Slide 14, based on Travers 2010 a POSA would have understood
20 that a major advantage to the SMRT workflow was that it did not use
21 amplification and used a minimal number of steps. Guardant never disputes
22 this either.

23 In Slide 15 we see that many other references also taught that the no
24 amplification requirement in PAC Bio's workflow was a big advantage. And
25 Guardant never explains, if we go to Slide 18, Guardant never explains even

1 in reply why anyone would add an unnecessary amplification step to the
2 workflow in Travers 2010.

3 Guardant does not contest that this RCR embodiment would
4 necessarily introduce errors into the workflow moreover. Unlike other next
5 generation sequencing technologies, PAC Bio didn't require amplification,
6 but for sure, for certain, amplification, an amplification step will introduce
7 errors.

8 An unnecessary amplification step is going to cause errors. That's not
9 disputed and this demonstrates right off the bat that a POSA would have not
10 been motivated to implement the RCR embodiment in any combination as
11 articulated by the Petition in some amorphous way.

12 So in sum, Guardant is clearly relying on a combination of art. And
13 Guardant has failed to meet its burden to allege any reason, any credible
14 reason to toss aside the standard SMRTbell workflow and use this ticker
15 tape like concatemer based approach.

16 Now I would like to turn to if there are no questions on that, I'd like to
17 turn to no reasonable expectation of success. Now you don't need to
18 determine that Guardant's approach is not enabled to find that there's no
19 reasonable expectation of success.

20 The University of Washington relied on both arguments. But we
21 think they go hand in hand. And the technical problems that I'm about to
22 talk about certainly show that there's no expectation of success. We go to
23 Slide 19.

24 We have a quick summary of the problems that altering from a
25 SMRTbell to a linear concatemer would cause. Each of these problems is
26 enough to independently show that a person of skill in the art would have

1 had no expectation of success in making the proposed embodiment. But let's
2 start with problem one.

3 The many polymerase binding sites on the RCR template of
4 Petitioner's embodiment would cause significant problems and make the data
5 unreadable. Okay, if we go to Slide 24, let's set the table. Let's look again at
6 the output of Guardant's rolling circle replication embodiment.

7 Guardant hitches its wagon to this embodiment and this approach
8 fundamentally changes the substrate for sequencing from a circular
9 SMRTbell template to these large linear concatemers. Instead of the
10 SMRTbell from Travers, you get these linear concatemers that are depicted
11 in the second, third, and fourth structures down on the left side here.

12 And by the way, Your Honors, we looked for any evidence that
13 anyone has used this kind of approach in the past 13 years since Travers's
14 publications came out and we couldn't find anything. And out of tens of
15 thousands of publications on PAC Bio sequencing, not a single one uses this
16 approach.

17 JUDGE YANG: Counsel, I have a question based on this Slide 24.

18 MR. POWERS: Yes, Your Honor.

19 JUDGE YANG: So do I understand you correctly, earlier you said
20 the PAC Bio's ZM --

21 MR. POWERS: ZMW.

22 JUDGE YANG: Yes. They would only accommodate a single
23 polymerase template complex. Is that right?

24 MR. POWERS: They are, they only produce useful sequence. If
25 there's a single polymerase template combination, complex bound in that

1 zero mode wave guide. But if you get more than one polymerase operating
2 in that zero mode wave guide, you get noise.

3 JUDGE YANG: It is still bound, it's just the multiple reactions which
4 continue --

5 MR. POWERS: Exactly, Your Honor. That's exactly right. And that
6 is a huge part of our point. So Dr. Larrea when we asked as Guardant's
7 expert, we asked him to annotate on these ticker tape structures here, these
8 concatemer structures where the polymerase binding sites are. And he
9 annotated them with arrows.

10 You can see all these arrows on all these different sites. In one case
11 we're talking about seven binding sites and in another, eleven binding sites
12 and in another 21 binding sites. So instead of the SMRTbell where we have
13 two binding sites, we have a spread of many, many preliminaries binding
14 sites on these ticker tape concatemers.

15 And both sides' experts agree that the concatemers that would be
16 produced would have varied numbers of polymerase binding sites which is
17 another problem that we'll discuss. We go to Slide 25. These structures,
18 these concatemers that we asked Dr. Larrea about didn't come from thin air.
19 We didn't make them up.

20 These schematics correspond to the sizes that you would get based on
21 the Travers 2010 reference. Travers 2010 uses a bulk extension assay just to
22 see if it's sequencing enzyme can work on SMRTbells.

23 Its sequencing enzyme happens to be a rolling circle replication
24 enzyme, but I emphasize that Travers 2010 does not use these substrates for
25 sequencing at all. It was just seeing if its enzyme could work on SMRTbells
26 and proceed in them.

1 So Travers 2010 shows that experiment in Figure 3. When you get
2 this big smear of nonspecific products and the templates that Dr. Larrea
3 annotated correspond to these sizes from Travers 2010's Figure 3. It's also
4 undisputed that there's no way to monitor or control the rolling circle
5 replication process.

6 You just get a big smear of products of all different sizes. We go to
7 Slide 26. Dr. Larrea also testified that the polymerase binding would be
8 stochastic. And there's no way to control where a polymerase particular
9 polymerase binds at any site over any other site on these big, huge
10 concatemers. So this actually supports -- Judge New, do you have a
11 question?

12 JUDGE NEW: No.

13 MR. POWERS: Okay. This actually supports a position, a point
14 made in Patent Owner's POR that would be there would be no way to control
15 how much sequence data you can recover because a POSA would be unable
16 to control which polymerase binding site initiates the sequencing reaction.

17 In other words, if you go back one slide please, you wouldn't know
18 which binding site over any other binding site the sequencing reaction would
19 even start from. This introduces unpredictability and uncertainty. And this
20 is in our POR at Page 55. And of course, this assumes that you get any of
21 this to work which we'll show you in a minute. You wouldn't.

22 And it just goes to the unpredictability of this embodiment. If we go
23 to Slide 27. Now because Petitioner's linear concatemers we just saw
24 contain repeating portions of sense and anti-sense DNA which is
25 complimentary, these DNA sequences pair back on each other when they're
26 in solution. They pair back on themselves rather.

1 And they complex and they form these very complex secondary
2 structures as the DNA strands pair. Dr. Satija used software to predict these
3 secondary structures, show that they form, and Petitioner does not dispute
4 that these structures would form.

5 That's Exhibit 2014 paragraph 180 to 185 of Dr. Satija's declaration.
6 Now lets imagine how Dr. Larrea's polymerase binding sites would look on
7 these structures formed by Petitioner's RCR embodiment.

8 If we go to the next Slide, here's where we see all the polymerase
9 binding sites all over the place on these starburst structures from Petitioner's
10 RCR embodiment. They're bristling with polymerase binding sites so
11 naturally these types of structures are antithetical to the requirement in PAC
12 Bio sequencing of having one polymerase bound to the floor of the
13 sequencing well.

14 Additionally, both Travers 2010 and Travers 075 use biotinylated
15 polymerase and a streptavidin coated floor. What does that mean? That
16 means that if the biotinylated coated polymerase interacts at all with the
17 floor, touches the floor, it's going to stick there.

18 And if we go to Slide 29, you'll see Dr. Larrea admitted that this
19 interaction between biotin and streptavidin is a strong interaction. So again,
20 if the biotin bumps into the streptavidin, it's going to stick meaning you're
21 going to get multiple polymerases bound to the floor of a zero mode wave
22 guide and you're going to generate no useful data.

23 So because these starburst structures in Petitioner's embodiment have
24 binding cites all over them, there's no way to predict where a polymerase
25 will bind. There's going to be multiple polymerases bound to all of these
26 structures.

1 This is something the PAC Bio references specifically warn against
2 because they say if you have multiple polymerases in a zero mode wave
3 guide, you throw out the data. It would destroy the ability to produce useful
4 data.

5 And remember what Dr. Larrea said in his declaration. The key to the
6 workflow is that only a single DNA polymerase is immobilized to the
7 bottom of a zero mode wave guide. Let's go to Slide 35. Guardant's only
8 real rebuttal to this, we didn't hear that at all, is a single sentence taken out of
9 a PAC Bio document.

10 The stoichiometric optimum for the polymerase template ratio is two
11 polymerases bound to each template molecule, one to each hairpin adapter.

12 But this is clearly talking about SMRTbells. How do we know?
13 One to each hairpin adapter. That's where you have a possibility of only
14 two polymerase binding sites.

15 And that means that in the PacBio workflow, using SMRTbells
16 you have an optimum of being on that nice edge of having one polymerase
17 bound to the bottom of the zero mode wave guide when you have this
18 stoichiometric ratio.

19 That ratio is completely unknown for the smear of various
20 concatemers with the various large numbers of polymerase binding sites.

21 Also I'll point out that on the typical SMRTbell the polymerase
22 binding sites are very distant from each other. They're on opposite ends of
23 the molecule. That's not the case when you have these concatemer structures
24 that are all folded back on to each other. This polymerase binding site is
25 very close together.

1 So, while the optimum SMRTbell ratio might be two
2 polymerase molecules for a SMRTbell, it's just unknown for these
3 concatemers, much less a slurry of different concatemers with vastly
4 different numbers of polymerase binding sites.

5 So, additionally, Guardant makes an argument in reply, that you
6 could chop up and recircularize these concatemers. It's in the reply at 20.
7 That is a new argument, not at all proposed in the petition.

8 And it begs the question of why you'd start with a SMRTbell,
9 do an RCR step, chop it up and remake a SMRTbell. Talk about circular
10 logic.

11 If we go back to Slide 19 I'd like to talk about Problems 2 and
12 3. Slide, okay. So, if we, excuse me, Your Honors. So, these Problems 2
13 and 3 sort of are the flip side of the same coin. And they relate to the vastly
14 different sizes that you'd get out of this RCR embodiment.

15 If we go to Slide 38, so as we discussed, Petitioner's RCR
16 embodiment will produce this smear of vastly different sizes. They can't
17 even be resolved by gel electrophoresis.

18 If we go to Slide 40 we see that was known in the art that this
19 leads to a bias against larger molecules, where shorter truncated molecules
20 will out compete the larger molecules for occupancy in the zero mode wave
21 guide.

22 The problem is that sequencing just small molecules would not
23 generate sufficient redundancy to overcome the high inaccuracies known in
24 PacBio sequencing. And it wouldn't even meet the claims, which require
25 sequencing both first strand copies and second strand copies, even under
26 Guardant's construction of that term.

1 Travers 2010 states that it requires long sequencing reads. It
2 specifically states that.

3 If we go to Slide 42 we see the flip side of the coin. The larger
4 molecules would be out competed, and wouldn't even get into the
5 sequencing wells in the first place.

6 Now, Guardant's response to this is that you could just do size
7 selection. Size selection gets you around this problem. In reply Guardant
8 proposed four bead based size selection protocols, but none of them would
9 work.

10 Dr. Larrea admitted that these DNA sizes would, that the DNA
11 sizes that would be removed with each of these protocols would only be very
12 small fragments of DNA.

13 In other words, these bead based size selection protocols are
14 just for removing left over adapters after standard ligation. If we go to Slide
15 44, this is graphically represented in this figure.

16 In Guardant's proposed, newly proposed reply bead based
17 cleanup steps, everything that's in these brackets would remain as
18 concatemers to be sequenced allegedly in their proposed combination. So,
19 this simply wouldn't work.

20 I'll note that in Petitioner's own Exhibit, Exhibit 1035, it's the
21 PacBio sequencing guide, specifically says it's highly recommended to select
22 amplicons of the same size, plus or minus 10 percent, to minimize loading
23 bias.

24 And you can see from this slide that the differences in sizes left
25 over is way more than 10 percent. Again, not even meeting the standards set
26 forth in PacBio sequencing guide.

1 If we go to Slide 45 Guardant also proposed as a solution to
2 Problems 2 and 3 this gel electrophoresis as a size selection tool. But again,
3 Guardant's own exhibit, the PacBio sequencing guide says to avoid exposing
4 samples to UV radiation or intercalating dyes, which are used for doing gel
5 based size selection. Again, not a viable solution.

6 If we turn to Problem 4, I'd like to go to Slide 47. We talked a
7 little bit about this before when we talked about the multiple binding sites.
8 But the large linear concatemers would form these complex secondary
9 structures, and would be unable to fit into the zero mode wave guide in the
10 first place. At least, it would significantly inhibit their ability to fit.

11 If we go to Slide 48 we see that the structures that were, that
12 form when you do these linear concatemer, this linear concatemer approach,
13 and these structures are undisputed in the record, have a much greater size in
14 the tiny zero mode wave guide.

15 So, unlike the typical SMRTbell depicted on the right side of
16 this figure, which has a two nanometer wide, which is two nanometers wide,
17 and can readily fit into a zero mode wave guide, these large concatemers are
18 simply too big to fit effectively into a zero mode wave guide.

19 And if they did you'd still run into the problem described in
20 Problem 1, where you have multiple polymerase binding sites touching the
21 bottom of the zero mode wave guide.

22 Now, this is one of Guardant's reply arguments. If we go to
23 Slide 49.

24 JUDGE NEW: Counsel, before we move on, and perhaps this
25 is a naïve question. But you could help me with this.

26 MR. POWERS: Sure.

1 JUDGE NEW: You have these large complex structures
2 forming spontaneously because it essentially acts as strands lying to each
3 other. Couldn't you overcome that simply by heating the molecule? Would
4 a person of ordinary skill know that?

5 MR. POWERS: Well, Your Honor, you'd have to heat the
6 molecule up quite a bit to an unknown. It's not described in the art. And
7 PacBio --

8 JUDGE NEW: Well, isn't that the basis of PCR?

9 MR. POWERS: PCR gets heated up to a pretty high
10 temperature, as you know, Your Honor.

11 JUDGE NEW: Right.

12 MR. POWERS: But the problem is that PacBio's sequencing
13 takes place at room temperature. So, that wouldn't work.

14 JUDGE NEW: All right. Thank you.

15 MR. POWERS: No problem. If you go to Slide 49 I'd like to
16 talk about Guardant's reply arguments. Guardant in reply has two main
17 arguments to this issue.

18 First, Guardant relies on linear or SMRTbell templates, which
19 are essentially linear when they're paired. And says, these long SMRTbells
20 can get into zero mode wave guide.

21 But again, these are SMRTbells that are structurally linear.
22 And unlike these very large concatemers that you form when they pair back
23 on each other.

24 So, evidence of large molecules getting into a zero mode wave
25 guide that Guardant points to are really irrelevant to the concatemer complex
26 structure issue.

1 And next, on Slide 50 Guardant argues that the starburst
2 structures are flexible, and would fluctuate in solution. And that's not
3 something we dispute. Those structures, those starburst structures are
4 flexible. And Dr. Satija said so in his declaration. Those structures will
5 fluctuate.

6 But the problem is now Guardant's on a double edged sword. If
7 they're flexible enough to get into the zero mode wave guide, they're flexible
8 enough to exacerbate Problem 1 where you have multiple polymerases
9 coming in contact with the bottom of a zero mode wave guide. Thereby,
10 exacerbating Problem 1.

11 Now, I'd like to discuss two of our missing elements arguments.
12 And I'd like to start with Claim 22. If we go to Slide 72 we see here Claim
13 22. And there are two main parts to the claim that I'd like to draw your
14 attention to.

15 First, Step A requires attaching adapters, comprising barcodes
16 selected from a plurality of distinct barcode sequences to a bodily sample.
17 That means a plurality of distinct barcodes per sample.

18 And second, the method requires grouping the strand sequence
19 reads into families based on the barcode sequence and DNA fragment
20 specific information. You have to use the combination of that information.

21 Slide 73, please. Now, in the claimed method family grouping
22 is grouping sequence reads derived from the same original molecule. And
23 it's really a term of art. This is an active method step. And we see this
24 depicted in Figure 1 and its description. You generate families of PCR
25 duplicates.

1 If we go to Slide 74 we also see family grouping depicted in
2 Figure 3 of the patent, where separate sequence reads are grouping the
3 families, which means they represent amplified copies or progeny coming
4 from the same original parent molecule. That's why they're called families.

5 These are progeny sequences coming from the same parent. So,
6 grouping is a way of sorting which sequence, it's a way of sorting which
7 sequence copies came from Molecule A, and which sequence copies came
8 from Molecule B, and so on.

9 JUDGE YANG: So, on this issue I really need some help.

10 MR. POWERS: Yes.

11 JUDGE YANG: One is about the barcode part. I understand
12 the patent owner made the argument distinguishing the indexing barcodes
13 with the, I don't know, the barcode --

14 MR. POWERS: Molecular barcode.

15 JUDGE YANG: The molecular barcode.

16 MR. POWERS: Yes.

17 JUDGE YANG: But you are not equating molecular barcode
18 with the second recited element here, that is DNA fragment specific
19 information are you?

20 MR. POWERS: Yes, we are.

21 JUDGE YANG: Okay.

22 MR. POWERS: Because of the way, sorry, I got --

23 JUDGE YANG: No. So then I understood the Travers
24 references actually do disclose index barcode, right?

25 MR. POWERS: That is correct. So --

1 JUDGE YANG: So, would that index part, indexing barcode
2 meet the Roman numerals, the small Roman numeral one here saying the
3 barcode sequence in Claim 22?

4 MR. POWERS: No, Your Honor. It's not disclosed in Travers
5 at all. Because Travers doesn't use its indexing barcodes in any way to track
6 progeny molecules. Travers has no need to, because Travers' sequencing
7 output is one long sequence wreath. It's one long physically connected
8 thing, or electronically connected if it's a sequence file.

9 JUDGE YANG: Right.

10 MR. POWERS: So, there's simply no need to track progeny
11 back using any kind of molecular barcode. And indeed, Travers does not
12 disclose molecular barcodes. Travers does not disclose family grouping.
13 Because Travers doesn't need to.

14 JUDGE YANG: Okay. Can we step, take a long step back.

15 MR. POWERS: Yes, ma'am.

16 JUDGE YANG: The barcode sequence in D, Step D of Claim
17 22. I'm trying to figure out, excuse me, whether Travers discloses the
18 barcode sequence as disclosed here.

19 MR. POWERS: No, Your Honor. Travers discloses index
20 barcodes. But those are used for an entirely different purpose in Travers.

21 Now, I grant that this claim does not say index barcode. But it
22 does say barcode used in a very specific way, in a family grouping step, a
23 grouping into families. And that is a term of art which has specific meaning.

24 And that meaning is what we just discussed. It's grouping
25 progeny molecules that come from the same original parent molecule. And
26 Travers simply has no need to do that, because you already know what

1 molecule, what sub reads in Travers go together. Because they're all linked
2 in the same sequencing outlet.

3 JUDGE YANG: Right. I understand what you're arguing.
4 That is, they are physically, well, if sequences can be physically linked
5 together. But you know what I mean.

6 Sure, even if I agree with you to say Travers itself doesn't do
7 that, it doesn't mean you cannot use the, use the index barcodes there to do
8 the grouping as claimed here, right.

9 MR. POWERS: Well, Your Honor, it's simply not taught by
10 Travers. And I think that is our point. Neither of that is a missing element
11 in the art, that Travers doesn't have molecular barcodes. Travers only has
12 index barcodes.

13 And Travers is, assignment of its sub reads into, and collapsing
14 steps proceed the same way, whether or not Travers includes barcodes in its
15 sample. In other words, Travers does the same workflow whether or not
16 there are index barcodes present.

17 And you still wouldn't meet the first part of this claim,
18 which requires selecting from a plurality of distinct barcode sequence, sorry,
19 attaching a, sorry, attaching partially single stranded adapters comprising
20 barcodes selected from a plurality of distinct barcode sequences to a sample.

21 JUDGE YANG: I understand that part.

22 MR. POWERS: Okay.

23 JUDGE YANG: My curiosity remains with Step D, the
24 grouping step.

25 MR. POWERS: Sure, Your Honor.

26 JUDGE YANG: I'd like to try it again.

1 MR. POWERS: Okay.

2 JUDGE YANG: There is the indexing barcode, and there is the
3 molecular barcode. First of all, do I understand, when you say molecular
4 barcode you are saying that's the small Roman numeral two, the DNA
5 fragment specific information? Are you saying that?

6 MR. POWERS: No, Your Honor.

7 JUDGE YANG: Okay.

8 MR. POWERS: I'm saying that the Roman numeral one is --

9 JUDGE YANG: Okay.

10 MR. POWERS: -- a molecular barcode as it's used in the claim.

11 JUDGE YANG: Okay.

12 MR. POWERS: That is a barcode that's used in combination
13 with DNA fragment specific information to group the families. And if we
14 go to, I think if we go to Slide 75 it might shed some light on this.

15 This is Dr. Quackenbush, Guardant's own expert, in a different
16 IPR. But talking about the same specification as in the 127 patent, called
17 here Schmitt.

18 Quackenbush says that Schmitt uses a molecular barcoding
19 approach to error correction. And he says that molecular barcoding allows
20 for identification in grouping of sequence reads derived from PCR
21 duplication of a sample polynucleotide molecule.

22 These groups or sequence reads are typically referred to as
23 families, and represent the PCR progeny of common parent polynucleotide
24 molecules in a sample.

25 So, these barcodes are being used to track molecules, different
26 than an index barcode, which is the same as a sample barcode, which only

1 tracks, you know, did all these molecules come from Patient A versus
2 Patient B.

3 Travers only discloses using sample barcodes. And that's
4 because Travers has no need to use molecular barcodes. Because as Your
5 Honor understands, the sequencing output of Travers, both Travers
6 references, are already physically linked, or linked in the same sequence file.
7 Does that answer Your Honor's question?

8 JUDGE YANG: Okay, yes. Thank you.

9 MR. POWERS: Okay. And, Your Honor, the same
10 understanding of what a family grouping is, is also in the 127 patent
11 disclosure. We see several examples here.

12 And Counsel mentioned that we didn't raise this in our POR.
13 But I think that's just, he must have overlooked some information from our
14 POR where we specifically raised this.

15 For example, on Page 13 through Page 15, where we talk about
16 the differences between index barcodes and molecular barcodes, and Claim
17 22's requirement for molecular barcodes.

18 JUDGE YANG: And on that issue though I'm looking at Page
19 13 of the patent owner response. I agree with you. You are talking about
20 the difference between index barcodes versus the sample barcodes.

21 MR. POWERS: Yes, Your Honor.

22 JUDGE YANG: But I thought Petitioner's complaint about
23 your, at this time still alleged, new argument in the sur reply is about this
24 argument of grouped family. Where did your, did you mention this family
25 argument in the patent owner response that sort of would make you repeat it
26 in the sur reply?

1 MR. POWERS: Yes, Your Honor. In, at the very bottom of
2 Page 13 it says, in the proper context the POSA would have known that
3 Travers 075 discloses adding index barcodes to track sample origins, not
4 grouping the strands into families based on barcode sequence and fragment
5 specific information.

6 And then it goes on to describe additionally how Travers
7 doesn't need that limitation. And on Page 15 we say, Petitioner also ignores
8 Claim 22's requirement to use both the barcode sequence and DNA fragment
9 specific information for grouping the sequence reads into families.

10 In reply, and it goes on from there of course. In reply Guardant
11 completely ignored the requirement for grouping into families. In their reply
12 section addressing this issue there is not to be found the word family. They
13 don't say the word family except for in reciting the claim.

14 But their argument doesn't say anything about grouping
15 into families, which is a major shortcoming of their reply. And it's why we
16 clarified in our sur reply that the claims require grouping into families, just
17 as we said in the POR.

18 So, I guess in sum there's no need to track which sub read goes
19 with which sub read in PacBio sequencing. Because all of the sequence
20 output is already physically, or chemically, or electronically linked together
21 in one sequencing file.

22 So, there's no family grouping set. Travers doesn't disclose it.
23 And this is why the Travers 075 document also doesn't disclose, neither
24 Travers document discloses molecular barcodes.

1 Petitioner doesn't argue that they do disclose molecular
2 barcodes. But Travers simply has no need for molecular barcodes, because
3 all the sub reads are physically linked, electronically linked.

4 I think I'd like to just touch briefly on Slide 83. And then we
5 mentioned this before. But the barcodes are selected from a plurality of
6 distinct barcode sequences. And they're applied to a sample.

7 So again, this doesn't fit with index barcodes. Because index
8 barcodes would be the same for a given sample, not distinct for a given
9 sample. And Dr. Satija testified about this in, for example, Paragraph 16 and
10 Paragraph 84 of his opening declaration.

11 I'd also, while we're on the subject I'd like to turn to Ground 3.
12 Because we were just talking about how Travers has one connected
13 sequence file output. Can we go to Petitioner's Slide 35?

14 So, this slide sort of characterizes, it does attempt to
15 characterize what Dr. Satija said, that McCloskey deals exclusively with
16 PCR amplification, which is true. And that a POSA would understand
17 adding barcodes to track and identify separate PCR products would not be
18 needed. There would be no reason to combine that with McCloskey.

19 Now, on the right side of this slide Petitioner points out a few
20 different uses for McCloskey, like all these different methylation pattern
21 tests you can do, or authentication of mosaicism. That's all fine.

22 But McCloskey deals exclusively with molecular barcodes, not
23 indexing barcodes. And McCloskey still uses, and is all about using PCR to
24 track molecules. His barcodes are for tracking molecules.

25 So again, there's no reason, as Dr. Satija testified, a POSA
26 would have had no reason to use McCloskey's random molecular barcodes in

1 Travers 075's rolling circle replication embodiment. Because the Travers
2 075 rolling circle replication embodiment contains all the target DNA copies
3 physically linked together as a single concatemer molecule.

4 In other words, McCloskey's barcodes are designed and used
5 exclusively for amplicon products that are separate molecules, like PCR
6 products. And are used for an entirely different purpose that would not align
7 with Travers 075's rolling circle and application.

8 Now, there's no rebuttal testimony on this point at all, in either
9 of Guardant's two reply witness declarations. Dr. Quackenbush and Dr.
10 Larrea do not offer anything in response. And the reply merely points back
11 to the same flawed arguments in the petition.

12 Now, I'd like to turn to, unless there are any questions on that,
13 I'd like to turn to the alleged admissions in the specification. If you go to
14 Slide 51.

15 Now, it's very important to understand what the specification is
16 talking about here. The specification is talking about a structure it calls
17 Product 1.

18 Product 1 has a Y shaped adapter on one end and a U shaped
19 adapter on the other. This product is not for PacBio sequencing, because it
20 has flow cell binding sets.

21 Now, Dr. Larrea, Guardant's alleged expert on PacBio
22 sequencing admitted that PacBio sequencing doesn't use, make any use of
23 flow cell binding sets. So, we know that Product 1 is not about PacBio
24 sequencing.

25 JUDGE YANG: But the challenged claims do not recite flow
26 cell, do they?

1 MR. POWERS: No, Your Honor, they don't.

2 JUDGE YANG: Okay. So, why should we read this part into
3 them?

4 MR. POWERS: Oh, I'm not asking you to read this into the
5 claims. I'm just trying to put into context what Petitioner is taking out of
6 context about the alleged admissions in the specification.

7 JUDGE YANG: Okay.

8 MR. POWERS: Okay. So, I'd like to just point out that we're
9 talking about Product 1 here. And the specification is talking about Product
10 1, not related to PacBio.

11 And my overarching point is, the patent specification never says
12 to use Petitioner's rolling circle replication embodiment in any way.
13 Because that's not in the specification.

14 And what the patent, what the Petitioner is trying to do is take
15 little pieces from here and there in the specification to try to cobble together
16 this argument. And I'm just trying to clarify.

17 JUDGE YANG: I want to be precise here. You just said the
18 specification, well I heard the rolling circle replication. And then you said
19 the specification nowhere disclosed that. I missed something in between.
20 And I want you to emphasize that.

21 MR. POWERS: I will emphasize it. The specification never
22 says use rolling circle replication products directly in PacBio sequencing.

23 JUDGE YANG: Okay.

24 MR. POWERS; That is my point.

25 JUDGE YANG: Sure.

1 MR. POWERS: So, if we go to Slide 52 in this same section.
2 And this something that Petitioner pointed to without showing you the
3 context of Product 1.

4 In this section the 127 patent notes that Product 1 has a self
5 complementary hairpin sequence that can impair polymerase extension
6 during amplification. But there are enzymes that are out there that can
7 amplify through a hairpin.

8 Again, this is in the context of Product 1. And this has nothing
9 to do with PacBio sequencing methods. Remember, we're talking about
10 Product 1, which is designed for a different sequencing system.

11 And I note that Reference 49 here is Travers 2010. Travers
12 2010, even Petitioner doesn't allege that Travers 2010 has some sort of
13 rolling circle replication embodiment, which is then sequenced directly on
14 PacBio. That only comes from allegedly Travers 075.

15 So, the specification here is merely saying that hairpins can be
16 amplified. And again, these are hairpins designed for a different sequencing
17 system.

18 If we go to Slide 53. Okay, still talking about Product 1. The
19 specification says that linker portions, the linker portion doesn't matter in the
20 workflow with Product 1. Because what matters is the Y shaped adapter.

21 That's where you get the flow cell binding sites. That's where
22 you get the molecular barcode, depicted here as Xs and Ys. And that's
23 where the asymmetry is. So, any linker sequence at this portion of this
24 molecule will do. That's all this is saying.

25 Nowhere does the specification purport to enable Petitioner's
26 RCR concatemer embodiment. And Petitioner is making misleading

1 statements about quotes taken out of context. And we briefed this and
2 explained it pretty thoroughly in our sur reply.

3 With my remaining time I would like to discuss Claim 19.

4 JUDGE YANG: I want to remind you, you have seven
5 minutes. And we do have the LEAP practitioner.

6 MR. POWERS: Oh.

7 JUDGE YANG: Okay.

8 MR. POWERS. I'm very sorry. Yes, you're right. I will step
9 down and let my colleague go. Wait, do we have, did you set the, this is our
10 total time?

11 JUDGE YANG: This is for 60 minutes. You are free to
12 continue here. I just want to say the LEAP practitioner does have to make a
13 showing here.

14 MR. POWERS: And I'm happy to let him take over now,
15 unless there are further questions. Judge New, you look --

16 JUDGE NEW: No. Nothing further.

17 MR. POWERS: Okay. Thank you, Your Honor. Appreciate it.

18 MR. HOLMAN: May it please the Board. David Holman on
19 behalf of Patent Owner, University of Washington.

20 As my colleague Dr. Powers mentioned earlier I'm going to be
21 discussing Patent Owner's arguments regarding objective indicia of non
22 obviousness.

23 To the extent the Board has any questions on the additional
24 briefing related to Petitioner's motion to exclude and motion to strike, I'm
25 happy to answer those questions. But otherwise I'll focus on objective
26 indicia.

1 As this Board is well aware objective indicia play an important
2 role as a guard against hindsight bias, and obviousness in houses. And for
3 objective indicia to be given substantial weight of course must have a nexus
4 for the claimed invention.

5 If I could direct the Board's attention to Slide 98 please. The
6 Patent Owner presented evidence of industry praises, long felt but unmet
7 need and unexpectedly superior results.

8 And Patent Owner explained along with the supporting
9 testimony of Dr. Satija that in each case, in each piece of evidence here has a
10 nexus with the claimed duplex sequencing methods of the 127 patent.

11 Now, Petitioner never disputed any of the actual evidence
12 shown here on the slide. Rather, Petitioner's argument in his reply is
13 whether there's a nexus between the praise in the Kirsch reference by the
14 way of Schmitt reference and the challenged claims.

15 Indeed, Petitioner's reply failed to address any of the evidence
16 in the GEN Edge article, the Liquid Biopsies article, the Sequencing Stars
17 article or the Business Buyer article.

18 Now, I'll note that Petitioner does make a belated attempt to
19 address the GEN Edge article in his Demonstrative Slide 37. But, Your
20 Honors, that is a new argument presented here at oral hearing for the first
21 time.

22 The petition, neither the petition, the reply, not even the expert
23 declarations from Petitioner's side address the GEN Edge article, or Liquid
24 Biopsies, Sequencing Stars or Business Buyer article, for that matter.

1 If you turn to Slide 96 please. Now to assess presence of a
2 nexus we of course must look at the claimed invention. Here is the 127
3 patent is referred to as duplex sequencing.

4 As this slide demonstrates, at its core of duplex sequencing are
5 the key principles of relating DNA strands, distinguishing those DNA
6 strands, and comparing those DNA strands.

7 As the 127 patent explains, to do this to facilitate differentiation
8 of sequencing errors and true mutations. The patent also explains that these
9 processes are carried out using the asymmetric nature of the adaptive
10 fragments.

11 Can you turn to Slide 97, please? Patent Owner explained in its
12 POR that the claims of the 127 patent practice these key features of duplex
13 sequencing.

14 For example, as shown on the slide here, Claim 2 recites
15 comparing the first strand and second strand sequence reads. Claims 3 and
16 16 both refer to associating first and second strand sequence reads. Claim
17 18 recites, or refers to relating the first and second strand DNA sequencing
18 reads. And Claim 19 refers to differentiating the first strand and second
19 strand DNA sequencing reads.

20 Now, I'll note that independent Claims 1 and 22 also embrace
21 these key features, these aspects of duplex sequencing. However, Patent
22 Owner selected these claims, in particular Claims 2 through 9, 16, 18, and 19
23 for briefing, as Patent Owner's response for going nexus, because the nexus
24 is particularly strong for these claims.

1 Let's turn back to Petitioner's argument. Please look at Slide
2 104. Now, Petitioner's argument, Petitioner's dispute on nexus boils down to
3 this.

4 According to Petitioner the Patent Owner's objective indicia all
5 flow through, or all come from the Kirsch. Petitioner only addresses the
6 Kirsch paper. And according to Petitioner it all flows through the Schmitt
7 reference.

8 And therefore, all the evidence must be limited to Schmitt's
9 method of making single strand consensus sequences, and comparing those
10 single strand consensus sequences to generated duplex consensus sequence,
11 which Petitioner argues is an unclaimed feature.

12 But what Petitioner glosses over by this argument is that even
13 Schmitt's embodiment of making single strand consensus sequences and
14 comparing those to generated duplex consensus sequence, that process still
15 follows this, these fundamental concept, this fundament process of duplex
16 sequencing, relating the strands, distinguishing the strands and comparing
17 the strands.

18 Moreover, if you, if I could direct your attention to Slide 99.
19 As Patent Owner explained in its sur reply, the evidence is not exclusively
20 limited to Schmitt's teachings of comparing, making single strand consensus
21 sequences and comparing them.

22 For example, the GEN Edge article here refers to the duplex
23 sequencing technology as a one in ten million technology. It refers to it as a
24 game changer in applications for finding low frequency mutations.

1 But as you can see in the description of duplex sequencing
2 GEN Edge refers to it as independently tracking the strands, comparing the
3 results using asymmetry of the adapter DNA fragments.

4 Again, this evidence was unrebutted. It was not addressed in
5 the petition or the Petitioner's reply. I see I'm almost out of time. So, I'll
6 stop here. And I'm happy to answer any questions from the Board.

7 JUDGE YANG: Thank you.

8 MR. HOLMAN: Thanks.

9 MR. ROSATO: Thank you, Your Honor. For a start, in
10 response by this drawing on observation on one of the, to one of the sort of
11 deficiencies with Patent Owner's argument is failure to consider the state of
12 the art at the time, and evaluate the evidence from the perspective of a
13 person of ordinary skill in the art.

14 And we see this come into play in several ways. And I'll start
15 with PacBio sequencing. So just to the extent it's not clear, it is addressed
16 both in the petition as well as the expert declaration.

17 But Pacific Bio Sciences sequencing platform is one only a few
18 major commercially available sequencing platforms. I mention this because
19 there seems to be discussion about it like it's this, almost like scary music
20 has been cued when we talk about this.

21 But we're talking about a well established large company that
22 has been long producing one of the widely distributed and accepted
23 sequencing platforms.

24 I'm sure sequencing platforms are complicated. I'm sure if we
25 looked at the Illumina sequencing platform it's also extremely well known.
26 There are things about it that would be complicated.

1 Just because a piece of technology is complicated doesn't make
2 it unknown in the art. It doesn't disqualify it from the art. So, many times
3 technology, when convenient for Patent Owner, tends to be represented as if
4 it's daunting, when it's really not.

5 And this, you know, plays to things like a question, you know,
6 the question, Judge, you asked about denaturing DNA molecules. Again,
7 when convenient to Patent Owner it was a, you know, terribly complex thing
8 to heat up molecules enough for, to denature.

9 You are correct. This is a routine aspect of PCR. If we were to
10 assume that a person of ordinary skill forgot to plug in the PCR cyclers I'm
11 sure PCR wouldn't work. But these are the type, these assumptions we don't
12 make when we're evaluating the perspective of a person of ordinary skill.

13 And, you know, this is what I alluded to in the initial discussion
14 about, when it comes to these alleged problems of inoperability we see
15 Patent Owner treating a person of ordinary skill as if they're a person with a
16 degree of ineptitude. And that's obviously not the right standard.

17 Can you put up Slide 40, please? I want to talk about this
18 Product 1 argument. And maybe this is stating something readily apparent
19 to the Board.

20 I'm not exactly sure where Patent Owner is going with this.
21 They seem to concede that their claims are not limited to Product 1, which
22 they're in, there is no way those claims can be interpreted as limited to
23 Product 1. So, I'm glad to hear them concede that.

24 Other than that, if they're suggesting that the discussion at
25 Columns 10 and 11 are limited to a discussion of Product 1, that's

1 demonstratively false. Both Column 10 and 11 are discussing linkers on
2 both sides.

3 They're discussing circular products. This is not a circular
4 product. And the concession that discussions in those sections of the
5 specification are by no means under Product 1.

6 Can you turn to Slide 30? So, one point of distinction I want to
7 make, to the extent the Board's considering these arguments about alleged
8 issues of incompatibility, this is a really deceptive argument that's been
9 advanced here.

10 I want to make sure that two concepts are recognized. And
11 maybe you think I'm perhaps stating what's already recognized. But there
12 are two concepts. There's concepts going on with this alleged problem that
13 multiple polymerases render sequencing inoperable.

14 So, the two concepts are as follows. There is one concept
15 where we're talking about multiple polymerases, of having a single template
16 with multiple polymerase binding sites. That's one concept.

17 There's a different concept of having two different templates,
18 each of which have the remote polymerase binding sites. One is not a
19 problem for sequencing. The other is undesirable. We do, you know,
20 sequencing does not want to load different molecules into one sequencing
21 well.

22 As far as one template having multiple polymerase binding
23 sites, that is by no means a problem. And we know that, at least for a couple
24 of reasons.

25 One, there is not a single reference that's been identified that
26 states that a single template with multiple polymerase binding sites is not

1 amenable to sequencing. In fact, the references themselves talk about
2 putting two different adapters, even in their, in the standard non amplified
3 method, each of which have polymerase binding sites.

4 So, every molecule that goes into a well has multiple
5 polymerase binding sites. And that's not an issue. It's a completely separate
6 issue if we're talking about users overloading a plate with samples, such that
7 multiple molecules get into the well.

8 So, those are two completely different things. And Patent
9 Owner, you know, throughout really conflates and confuses those two
10 things, pointing to overloading a well as essentially representing that, you
11 know, the first concept is a problem, when it's not.

12 JUDGE YANG: Okay. Consider me confused.

13 MR. ROSATO: I think that was the intent, Your Honor.

14 JUDGE YANG: Let me ask you this. Let's just assume one
15 molecule, a long concatemer, do you agree that because of the multiple
16 adapter sequences there would be multiple polymerase binding sites in that
17 one concatemer molecule?

18 MR. ROSATO: Whether we're talking about your standard
19 SMRTbell --

20 JUDGE YANG: No.

21 MR. ROSATO: -- or that other --

22 JUDGE YANG: No, no, no.

23 MR. ROSATO: -- situation.

24 (Simultaneous speaking)

25 JUDGE YANG: I'm talking about the embodiment Petitioner's
26 relying on, which is not, if I understand it correctly, is not the

1 straightforward SMRTbell embed, correct? You're talking about amplifying
2 that to generate the concatemer. And then subjecting that product to further
3 sequencing, right?

4 MR. ROSATO: I'm not sure, let me make sure I, I'm not sure
5 what the question was. But in both instances, both the embodiment where
6 there is no amplification and the embodiment where there is amplification,
7 you have a template with multiple polymerase binding sites.

8 JUDGE YANG: So okay. That's, take that one step back. In
9 the one without amplification you have two hairpin adapters. And you
10 mentioned that in answering Judge New's question. The two adapters are
11 different, so to reach the asymmetric requirement.

12 And my understanding is there are two polymerases to bind to,
13 to adapter sites, right. So, that's where you are talking about the two, the
14 multiple, the one on one polymerase. Do I understand you correctly there?

15 MR. ROSATO: I think so. Can you put up Slide 18? It may
16 help with the discussion. What I'm saying, Your Honor, is their argument of
17 Problem 1 was the assertion that if you have a template molecule with
18 multiple polymerase binding sites, it won't work.

19 That assertion is demonstrably false for many reasons, one of
20 which is this, just your standard basic sequencing --

21 JUDGE YANG: Okay.

22 MR. ROSATO: -- which includes multiple polymerases.

23 JUDGE YANG: Let me say, I understand what you're arguing.
24 But I, maybe I'm misunderstanding Patent Owner's argument. But I thought
25 what they are saying is, when you have a, the DNA of interest is a smear of
26 products with varying sizes, where, you know, just like the, in the, in this

1 slide, the lower parts, where you have multiple repeats, and you have
2 multiple polymerases binding to it, any one of them could be the starting
3 point. And all of them could start your sequencing.

4 As a result you will have a very noisy signal. And therefore, it's
5 just not a suitable method.

6 MR. ROSATO: They make a couple of arguments. And they
7 conflate and confuse a lot of things. So, Problem number 1, as they assert in
8 their argument is, if you have multiple polymerase binding sites it won't
9 work.

10 And my response to that, and I'm glad I brought it up because
11 there's clearly confusion. They are confusing the situation where you get
12 multiple, you have multiple templates in a well. So, it's like having two
13 different samples in the same well. Versus a single molecule with multiple
14 polymerase binding sites.

15 The latter is not a problem. And there's not a single piece of
16 evidence that illustrates it's a problem, And there's plenty of evidence that
17 says, of course we want multiple polymerase binding sites.

18 There's the standard sequencing, which often has
19 multiple polymerase binding sites. There's the Pacific Bio Sciences'
20 sequencing guide we cited, which states that multiple polymerase binding
21 sites are optimal.

22 There's also the testimony of Dr. Larrea, who draws the
23 distinction between those two types of situations Patent Owner is confusing
24 in their argument, and says, multiple binding sites of one molecule is not an
25 issue. Putting multiple samples into the same well, yes, we don't want to do
26 that, right.

1 JUDGE YANG: Let me narrow the question on this then. One
2 sample, multiple polymerase binding sites. And this one sample is not your
3 straightforward SMRTbell template molecule. It's your amplified product,
4 which is a concatemer. Would that be a problem?

5 MR. ROSATO: No.

6 JUDGE YANG: Why not?

7 MR. ROSATO: And there's zero evidence that that is a
8 problem. You've got four references that tell us you can sequence that
9 product. You've got three PacBio references, and the Travers 2010, Travers
10 075, and the 503 patent. And you have the 127 patent pointing to it and
11 acknowledging that.

12 We have zero references, zero, that tell us that you can't
13 sequence an amplified product.

14 JUDGE YANG: Okay.

15 MR. ROSATO: Yes. As far as the, you brought it up, so I do
16 want to address it. There's the, this alleged Problem 2 and 3. By the way,
17 this is Travers 2010.

18 That Figure 3 is amplified product. So, when the 127 patent
19 points to Travers 2010 and acknowledges that they discussed amplifying and
20 sequencing their, you're sequencing the amplified product, it is disclosed in
21 here.

22 Back to Problems alleged 2 and 3. This relates to the size issue.
23 Can you put of their Slide, I forget the number, yes, here it is. Okay.

24 So, Your Honor, you touched on this. This is a separate alleged
25 problem which is, this is not credible arguments. But their own slide
26 demonstrates why this is not credible.

1 They've argued that if you amplify you get products of different
2 size, and you may not, you may have some that you didn't amplify enough
3 where you have a full copy of even one, of one template. And that would be
4 so small you would, if you sequenced it, it doesn't give you the sequence for
5 the whole molecule.

6 Our rebuttal to that is, your own, the commercial product
7 sequence guide tells you to do these routine cleanup steps, where you just
8 get rid of whatever fragments you don't want, including smaller fragments.

9 And that includes, for example the Chromaspin product that's
10 mentioned both in Travers, and I believe also in the sequence guide. This is
11 an example where the template is less than 400 nucleotides in length.

12 JUDGE YANG: What slide are you on?

13 MR. ROSATO: I'm sorry, Your Honor. This is Slide 44 of
14 Patent Owner's demonstrative exhibits.

15 JUDGE YANG: Thank you.

16 MR. HOLMAN: Thank you for noting that. So, Patent Owner
17 put this up saying, look, if you use Chromaspin like Travers tells you to, you
18 still end up with all the fragments over roughly 1,200 nucleotides in length.

19 Every one of those fragments is informative, because it includes
20 at least one copy of your template. So, they're whole argument that if you
21 amplify you get uninformative fragments, as, you know, as our experts had
22 argued in rebuttal is a non issue. Because it's something that's easily
23 resolved with very routine steps that are laid out in the sequencing guide.

24 Let's go back to our exhibits real quick.

25 JUDGE YANG: You might want to tell Judge Hulse which
26 slide this is.

1 MR. ROSATO: Yes. I need to figure that out myself.

2 JUDGE YANG: Okay.

3 MR. HOLMAN: Let's, okay, let's go to our, Petitioner's Slide
4 14. I just want to briefly identify something. The question is raised, why
5 the, why would we want to amplify? Like, Petitioner hasn't explained why
6 you would want to amplify.

7 The Travers reference itself, to the extent it's not readily
8 apparent, tells you exactly why you would want to amplify. It explains you
9 amplify to generate more copies of what you're looking at.

10 You would do this to have repeating copies, and to, he even
11 says, sequence more deeply. So, it's pointing to this embodiment and telling
12 you, you can do amplification because you'll get this result.

13 The other thing I want to point to is, can you go to our Slide 9?
14 Make sure this is clear. So, there isn't discussion by Patent Owner about, oh
15 you've only used suitable methods. And that would exclude.

16 I want to make sure it's clear what they're saying when they say
17 suitable method. This is Column 15, what's showing here on our Slide 9 is
18 Column 15, Lines 29 through 39.

19 But they first identify amplification with PCR or non PCR.
20 And then the very next sentence you say, it states, these products are then
21 sequenced using, you know, any suitable method. And it specifically
22 identifies the suitable method as PacBio's, one of them as being PacBio
23 sequencing.

24 So, it's specifically linking together non PCR plus PacBio.
25 There is no distinction. There's never anything in the specification that says,
26 this one method isn't suitable for this other type of situation.

1 JUDGE YANG: And now, I think you're out of your time.
2 And we'll just add the one minute --

3 MR. ROSATO: Thank you.

4 JUDGE YANG: -- and the 30 seconds to Patent Owner's
5 rebuttal time.

6 MR. POWERS: If we could start out with Petitioner's Slide 27?
7 Scratch that. Your Honors, Petitioner got up here and said that these are
8 well established sequencing methods. PacBio is well established. And
9 there's been a lot on it.

10 But it goes to show that nobody in this case, there is nothing of
11 record in this case that shows that the RCR embodiments imagined by
12 Petitioner could actually be used for sequencing. There is no evidence at all
13 that those ever provided any useful data.

14 And that's because of the problems that we've identified and
15 discussed with you today. There's no real credible response to that, except
16 for pointing to throw away sentences in the Travers 075, and a document
17 incorporated by reference therein, which just talks about basic PacBio
18 sequencing.

19 That's the 503 patent, which isn't even relied on in the petition
20 for doing any kind of processing steps, or any kind of steps with this rolling
21 circle replication embodiment.

22 Also, there's no ineptitude of a POSA going on here. When we
23 describe what a POSA would think, I think the evidence overwhelmingly
24 shows that there are significant issues with the proposed combination of
25 Petitioners.

1 We provide a lot of evidence. We have Dr. Satija, who is a
2 Rhodes Scholar, and Professor at NYU at the Genome Center there, and has
3 hands on experience in many sequencing technologies, including PacBio
4 sequencing technology, saying that this wouldn't work.

5 Let's go to Slide 32 of Patent Owners demonstratives. Now, I
6 think I heard Counsel say that overloading is a problem. But that having
7 concatemers, a single concatemer with lots of different polymerase binding
8 sites and polymerases bound to it is not a problem.

9 But that's not what PacBio's evidence, own patent application
10 shows. This is Tomaney again, incorporated by reference into the 075
11 Travers document. And it says that if multiple polymerases are sequencing
12 in a ZMW, in which case that, you can exclude data from that ZMW. That's
13 over on the left side.

14 And then it says, some of these reaction locations will not
15 provide useful data. This may occur if no reaction enzyme becomes located
16 in a particular ZMW, if more than one reaction is located in a ZMW, or if a
17 reaction enzyme is otherwise producing problematic data.

18 JUDGE YANG: I see that. But I also want to make sure, you
19 do recognize that for a SMRTbell template there will be two, or there can be
20 two copies of the polymerase, right?

21 MR. POWERS: There can be. And that is a different situation.
22 If we go to Demonstrative 48 of Petitioner's, I'm sorry, Patent Owners.
23 What you've got here, imagine the SMRTbell on the right side with the
24 polymerase at the bottom, and a polymerase at the top, far away from each
25 other, right.

1 Those polymerases are separated by space, a fair bit of space.
2 What you don't have is any separation like that when you have concatemers.
3 You have, again, these concatemers bristling with polymerase binding sites
4 all over the place.

5 So, while you may be on that sort of optimized, getting the most
6 data possible with a SMRTbell, when you have two polymerase binding
7 sites which are separated by plenty of space, there is no evidence that this
8 has ever been done, or that it would work if you have these kinds of
9 concatemer molecules.

10 And that's because you're going to have lots of polymerase
11 binding sites all over the place, including very close together. And that's
12 what we showed you previously on those slides. Petitioner --

13 JUDGE YANG: Counsel, I thought that the issue with having
14 multiple polymerases was because you end up with noise, like that speaker
15 analogy that you made earlier. Is that not, did I misunderstand you?

16 MR. POWERS: Yes. That's exactly correct, Your Honor. You
17 have noise.

18 JUDGE YANG: So, why wouldn't you have noise on the right
19 side, with the SMRTbell.

20 MR. POWERS: Oh, I see. Yes. Because the, one polymerase
21 is down at the bottom of the zero mode wave guide, at the bottom of the zero
22 mode wave guide where its emissions are read. And the other polymerase is
23 far away, up at the top of the SMRTbell, where it's not fluorescing.

24 In other words, the fluorescence intensity is only bright down at
25 the bottom of the zero mode wave guide. And what really matters is how

1 many zero, how many polymerases are at the bottom of the zero mode wave
2 guide making those fluorescent signals.

3 So, you're going to get a lot of those polymerases down at the
4 bottom when you have these concatemers with dozens of binding sites.
5 When you have a SMRTbell with one polymerase binding site far away at
6 the top, and one polymerase binding site down at the bottom you're not
7 going to have that, as great a problem.

8 But you still occasionally do have that problem in PacBio
9 sequencing. PacBio does encounter that. And it throws away the data when
10 multiple polymerases are binding, are down at the floor of a zero mode wave
11 guide, and sequencing is not, the sequencing is too noisy because of that.

12 Now, Petitioner tries to distinguish overloading as a problem,
13 which Petitioner acknowledges is a problem, versus the concatemers, which
14 Petitioner alleges are not a problem.

15 But we've analogized the overloading problem with these
16 concatemers, for the same simple reason that you're getting noisy data when
17 you're overloading, because you're getting multiple polymerases down in the
18 same zero mode wave guide.

19 The concatemers are going to work the same way. The
20 concatemers are going to get you multiple polymerases down in the zero
21 mode wave guide, to the extent they ever fit in the zero mode wave guide.
22 And that's going to create noisy data.

23 Now, Petitioner's evidence, and again all this is such hindsight
24 driven argument, because Petitioner's evidence of why its concatemer based
25 embodiment would work always comes back to SMRTbells. Petitioner's
26 only pointing to evidence from SMRTbells, very different structures, to

1 attempt to salvage its petition, and say that these concatemers would actually
2 work.

3 If we go to Slide 28, here we see again all the binding sites of,
4 for polymerases on these concatemers. Again, they're not far away like the
5 SMRTbell binding sites where there are only two. We have multiple
6 binding sites, including some that are very bunched up. And these structures
7 are not contested.

8 I'd like to take you to Slide 44. Now, Counsel for Petitioner
9 spoke about this slide for a while. And alleged that it was evidence of how,
10 it actually was evidence of how a person of ordinary skill could this all to
11 work.

12 But Counsel ignored that its own reference, Exhibit 1035, the
13 PacBio sequencing guide says very clearly that it is strongly recommended
14 that sequence templates are of the same size, plus or minus ten percent.

15 So, just look at these ranges of products here. These are their
16 reply proposed solutions to the problem that these massively varied sizes in
17 the RCR embodiment.

18 And you see that even the tightest one has a huge variance of
19 more than, I don't know, threefold, twofold at least, more than twofold.
20 That's not ten percent. That doesn't even fit with the PacBio sequencing
21 guidance about what works in PacBio system.

22 So, I submit that the evidence is that the RCR embodiment
23 proposed by Petitioner has never been done for a simple reason. And that is
24 that no one would be motivated to do it. And two, it wouldn't work.

25 We can go to Petitioner's Slide 31, just to emphasize this point.
26 Here it is. Exhibit 1035, on the right side, interesting it's not highlighted.

1 As I just told you, it's highly recommended to select amplicons of the same
2 size, plus or minus ten percent, to minimize loading bias.

3 And again, even Petitioner's reply based proposed solutions to
4 these problems don't even come close to meeting these requirements.

5 If we go to Slide, Petitioner's Slide 27, please. So, Your
6 Honors, there was no discussion of any nuclease activity in the petition at
7 all. And no hints that anyone would recircularize the template. That's a new
8 argument that was found for the first time in reply.

9 The petition clearly said, sequenced linear concatemers directly.
10 But Petitioner is wrong on the science here anyway. The cited portion of
11 Travers 075 is actually talking about releasing a SMRTbell template from
12 the sequencing by synthesis reaction, and then exposing it to exonuclease
13 activity to digest it and get rid of the sequence.

14 Exonucleases digest DNA. So, it's not the same thing as what's
15 in the specification of the 127 patent, where the specification in the 127
16 patent is talking about engineering recognition sites to chop up DNA for
17 further processing.

18 Here this late reply argument from Travers is completely
19 different. It's very clear from reading this language that it's about providing
20 in a nuclease recognition sites which can allow to release a given template
21 sequence from a synthesis reaction.

22 By linearizing it, and allowing the polymerase to run off the
23 linear template, that's in the context of stopping the sequencing reaction.

24 With that, Your Honors, I will leave you with our overall point,
25 which is that the Petitioner provided no reason to combine besides these are

1 just two Travers documents. This late reason to combine that you heard for
2 the first time today is insufficient.

3 And a person of ordinary skill in the art endeavoring to make
4 this RCR proposed embodiment would be challenged with a number of
5 unpredictable and unworkable problems that simply wouldn't work.

6 And that is demonstrated by the fact that over 13 years of
7 PacBio literature, since the publication of Travers 2010 makes no use of this
8 approach. It simply wouldn't work.

9 And Petitioner has not shown any reason to discard the tried
10 and true SMRTbell sequencing method described in Travers, and is still used
11 by PacBio sequencing today. These RCR concatemers would not work.
12 Thank you.

13 JUDGE YANG: Thank you. We would like to thank both
14 parties. Counsel from both sides did a great job throughout this case and
15 today's argument is very helpful. This case is submitted. And we will issue
16 a final decision in due course. And we are adjourned.

17 (Whereupon the above-entitled matter went off the record at
18 2:49 p.m.)

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