

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA INC.,
Petitioner,

v.

MOLECULAR LOOP BIOSCIENCES, INC.,
Patent Owner.

IPR2024-00964 (Patent 11,041,852 B2)
IPR2024-00965 (Patent 11,768,200 B2)

Record of Oral Hearing
Held: September 23, 2025

Before: ANNETTE R. REIMERS, SUSAN L. C. MITCHELL, and
ZHENYU YANG, *Administrative Patent Judges*.

IPR2024-00964 (Patent 11,041,852 B2)

IPR2024-00965 (Patent 11,768,200 B2)

APPEARANCES:

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The above-entitled matter came on for hearing on September 23, 2025 at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia in Hearing Room A, commencing at 1:00 p.m.

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

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3 JUDGE YANG: Good afternoon. This is a consolidated hearing
4 for IPR2024-00964 and 965. I am Judge Yang. With me here is Judge
5 Mitchell, and joining us via video is Judge Reimers. Now, Counsel, please
6 introduce yourselves. Let's start with Petitioner.

7 MR. RAICH: Bill Raich from Finnegan for Petitioner Illumina.

8 MR. MATTY: Good morning, Your Honor. It's Brian Matty from
9 Desmarais for Patent Owner Molecular Loop. And we have with us today
10 Dr. Greg Porreca, who's the inventor on the patents we'll be talking about
11 today, and also Pat Saunders from (INDISCERNIBLE).

12 JUDGE YANG: Thank you and welcome, everyone. As we stated
13 in the trial order, each side has 60 minutes to present your argument, and
14 each side could, if you like to, reserve at most 20 minutes for rebuttal. The
15 hearing is open to the public, and I understand there is at least one public
16 line open. So please, no confidential information. And the Court reporter
17 will provide a transcript for the hearing, and that will be the official record
18 of this one. To ensure we have a useful transcript, please do clearly identify
19 the record. And Judge Reimers cannot actually see what's on the screen, so
20 it would help her if you can identify the record. I see Counsel for both
21 parties are seasoned practitioners at the Board, so I don't think we need
22 much else introduction. Any questions?

23 MR. RAICH: I would be negligent if I didn't mention that Roland
24 Schwillinski and Marcus Burch from Illumina are here at the
25 (INDISCERNIBLE) today, Your Honor.

1 JUDGE YANG: Very good and welcome to all. So Petitioner,
2 would you like to reserve any time for rebuttal?

3 MR. RAICH: Fifteen minutes, please, Your Honor.

4 JUDGE YANG: Fifteen minutes. Okay. Can we set the timer?
5 And you may start whenever you're ready.

6 MR. RAICH: Good afternoon. Molecular Loop's related patents
7 are anticipated and/or rendered obvious over prior art, disclosing the claim
8 methods of reducing error when sequencing nucleic acids from multiple
9 samples. Specifically, prior art such as Parameswaran and Gloor taught
10 methods for reducing sequencing errors by adding distinct pairs of identifier
11 sequences for nucleic acids from a given sample, the same subject matter
12 that Molecular Loop now claims as its own. There are two patents being
13 challenged: the '852 and '200 Patents. As shown on Slide 2, they have the
14 same title. They're substantively identical. And for purposes of these IPRs,
15 we've used a provisional filing date of December 23rd, 2010.

16 I'd like to start with the '852 Patent. And turning to Slide 4, this
17 shows challenge Claim 1 of the '852 Patent. And it recites conventional
18 steps of sequencing multiple samples to reduce cross-over error. The steps
19 include incorporating at least two members of a plurality of identifier
20 sequences into template nucleic acids. That's shown with the green barcodes
21 attached to the samples and the pink barcodes attached to templates from a
22 different sample. Combining those templates into a single sample,
23 amplifying them on the surface of a flow cell as is contained in an Illumina
24 sequencing machine to form clusters. At least one of those clusters
25 comprises a chimeric sequence that has identifier sequences different than

1 any of the distinct pairs. That's the pink and the green identifiers that are
2 different than the assigned green and pink shown in step [a]. Sequencing
3 those and then discarding sequence reads that have identifiers that are
4 different than any of the distinct pairs.

5 Slide 5. How did Molecular Loop get this patent? Nearly identical
6 claims were rejected by the examiner over Parameswaran. And as the
7 examiner found, Parameswaran taught a method for reducing template cross-
8 over error introduced during the sequencing workflow. Molecular Loop did
9 not disagree with that characterization. Instead, they amended their claims
10 to recite amplification on the surface of a flow cell as used in Illumina
11 sequencing. Molecular Loop then argued that Parameswaran is all about
12 pyrosequencing, where amplification happens on the surface of beads
13 instead of on a flow cell. In other words, Molecular Loop distinguished
14 Parameswaran for doing multiplex sequencing on a different machine, a
15 pyrosequencer, rather than an Illumina sequencer. But it would have been
16 obvious to combine the barcoding method of Parameswaran with an
17 Illumina sequencer. And that's the basis of the ground set forth in Slide 6.

18 Now why would it have been obvious to use Illumina sequencing?
19 Slide 7. Well, Illumina sequencing was one of three major next-generation
20 sequencing platforms. Next-generation sequencing just refers to the
21 simultaneous sequencing of many template DNA samples. And as shown in
22 Parameswaran, Parameswaran identified Roche/454 Life Sciences -- that's
23 pyrosequencing as one of the major platforms as well as Illumina/Solexa
24 sequencing as another major platform. And the Gloor reference explains
25 that Illumina sequencing was an approximate order of magnitude cheaper

1 than the per-read cost of pyrosequencing.

2 Why was it obvious to reduce cross-over error? Slide 8. Well,
3 next-generation sequencing used PCR, the polymerase chain reaction, at
4 multiple sequencing stages. This is an enzymatic reaction that amplifies
5 DNA templates so that you'd have enough DNA to sequence. So shown on
6 Slide 8 is a standard prior art protocol for Illumina multiplex sequencing.
7 Multiplex sequencing just involves sequencing of multiple samples. And
8 what it shows is that it used PCR at multiple steps. It used PCRs to attach
9 barcodes, also called identifiers or sequence tags. It used PCR to amplify
10 the pooled libraries before adding those libraries to the sequencing machine.
11 And it used bridge PCR to create clusters on the sequencing machine. But
12 this created a problem. Slide 9. PCR was known to cause chimera
13 formation as stated in Exhibit 1017. And as Exhibit 1018 explains, chimeras
14 are molecules composed of parts of two different sequences that are
15 artificially combined during PCR. Exhibit 1019 explains that this is
16 sometimes called jumping PCR because one prematurely terminated product
17 jumps to another template, creating an in vitro recombination product. And
18 Exhibit 1020 explains that these chimeras can be generated during a single
19 round of primer extension. This means that chimeras can form at any stage
20 where PCR is used and multiple templates are involved.

21 JUDGE YANG: So on that issue, I think the parties actually
22 dispute whether it was recognized at the time of the priority date, in this case
23 December of 2010. Whether this cross-over error was a recognized
24 phenomenon in the Illumina sequencer. Could you discuss that issue a bit
25 please?

1 MR. RAICH: Yes, Your Honor. I'd be happy to. So I guess very
2 briefly and in the context of next-generation sequencing, this was called an
3 ideal breeding ground for recombinant DNA molecules or chimeras. And if
4 we could jump please to Slide 30. So the occurrence of chimeric molecules
5 created during cluster amplification was a known problem. So this is the
6 Gloor reference, which is one of the references in the ground. And it states
7 that, "Chimeric sequences can arise during PCR or because of overlapping
8 spots on the solid support." And this is a reference that is describing
9 multiplex sequencing on an Illumina machine. And it talks about these
10 chimeric sequences arising during PCR or overlapping spots. And in fact, it
11 detected chimeric sequences. And if you compare this language from the
12 Gloor paper to what's stated in the '852 Patent, the '852 Patent, which is the
13 Molecular Loop Patent, explains that nucleic acids from sample A and the
14 nucleic acid from sample B landed within a cluster radius on the solid
15 support. This is very similar to the language and Gloor which talk about
16 chimeric sequences forming because of overlapping spots on the solid
17 support.

18 And Petitioner's expert explained the, "incomplete PCR on the
19 surface of the flow cell would have been particularly problematic when
20 different templates were seeded nearby on the flow cell. Incompletely
21 extended templates were known to create an ideal opportunity for the
22 formation of chimeric molecules." Now, we addressed this quote from
23 Gloor in our petition. We addressed it in our opening Spellman declaration.
24 We addressed it in our reply paper at pages 2, 8, 9, and 16 and our
25 supporting reply declaration paragraphs 37, 51, and 66. Patent Owner never

1 addressed it in their Patent Owner response, didn't address it in their sur-
2 reply, and their expert, Dr. Adalsteinsson, did not address it in his
3 declaration. Chimeric molecules were a known problem on Illumina
4 sequencing.

5 JUDGE YANG: Okay. So I would like you to address two
6 sentences in the Gloor reference. One is on page 8 of the reference, where it
7 actually talked -- it said, "We concluded that chimeric sequence composed a
8 very small subset of the total number of ISUs." And later on it said
9 something very similar. On page 22 of the Gloor reference, it said, "We
10 observed very few chimeric sequences in our data set." So was it an -- I
11 understand what you're saying. PCR causes the chimeric sequence. But was
12 it an issue to the -- rising to the level that one skilled in the art would like to
13 address it?

14 MR. RAICH: I think the answer to that is absolutely, Your Honor.
15 It didn't say there was no chimeric sequences. It says that there were
16 chimeric sequences. And the evidence is undisputed that, depending on
17 what the purpose of your sequencing is, it can be incredibly important to
18 identify these chimeric sequences. If, for example, you're doing sequencing
19 to detect cancer in a particular patient, you want to make completely certain
20 that you're tracking it back to the original sample. And so I think the
21 evidence is very strong that a person of skill in the art would have been
22 motivated to remove chimeric sequences. Even if they didn't occur at a
23 particularly high amount in some reference, they still occurred. And they
24 were certainly known to be problematic.

25 JUDGE YANG: I have another question on this cross-over error.

1 That is on claim construction. At what stage does the cross-over error
2 occur? I'm sure you're aware that Patent Owner said it has to be during
3 amplification. And what's Petitioner's view? My understanding is you're
4 saying it can be anywhere. So where else during the process could this
5 cross-over happen?

6 MR. RAICH: I think anytime that there is a PCR step, it was well
7 established that it could occur when you do PCR. And so, for example, if
8 you are looking at the claims, these are comprising claims. So the steps
9 aren't just limited to specific things that are recited here. I just showed you
10 the PCR protocol for Illumina sequencing that was in the prior art. And
11 PCR was often done after samples were combined in order to just increase
12 the amount of DNA such that you could do sequencing. And that's certainly
13 a stage where cross-over error was known to occur. PCR was known to
14 cause -- and that is part of the method that is encompassed by these claims.

15 And I'll point over from a claim construction perspective, it says
16 specifically in this claim that the cross-over error is introduced during the
17 sequencing workflow. It doesn't require the chimeric sequences to be
18 created during cluster amplification. The claim is very broad in its language.
19 It says during sequencing workflow. And furthermore, if you look later in
20 the claim when it's talking about the clusters that have formed, it merely says
21 that one of which comprises a chimeric sequence. This is broad language. It
22 doesn't say that the chimera has to be created during cluster amplification. It
23 just has to be present at that stage. If the chimera was created before cluster
24 amplification, of course the chimera would comprise a chimeric molecule.
25 So I think the plain language of the claims is clearly broad enough to

1 encompass cross-over error, regardless of when it formed.

2 JUDGE YANG: So in Patent Owner's sur-reply, they pointed out,
3 or at least they allege, that even Petitioner doesn't dispute that this cross-over
4 error wouldn't have happened -- wouldn't happen before the combining step.
5 Is that correct statement on Patent Owner side?

6 MR. RAICH: I think that it could happen before the combining
7 step if there was just some kind of contamination between samples. So it is
8 possible that it occurred beforehand. That is something that certainly does in
9 fact occur. So it could occur before the combining steps. So we would
10 respectfully dispute that.

11 JUDGE YANG: Okay.

12 MR. RAICH: I think in terms of -- since we're on the subject of
13 claim construction, if we could have Slide 15, please. Yeah. So essentially,
14 Patent Owner is focusing on particular figures in their patent and making the
15 argument the claim should be limited to clusters created on the flow cell
16 despite this plain language of the claims, which I think is very clear. But the
17 case law is clear. You don't read limitations from the embodiments and the
18 specification into the claims. And furthermore, if you look at what the
19 specification says, it says that it's not -- they're not being limited by any
20 particular theory or mechanism of action. It explains repeatedly that the
21 figures are exemplary and not limited.

22 JUDGE YANG: On that, I have some questions too. So Petitioner
23 actually pointed out there were four instances in the specification where it
24 discussed the cross-over error. So when we look at the specification, Patent
25 Owner said in all those four instances, those errors were created during

1 amplification. And I would like to draw your attention specifically to
2 column 7 of the '852 Patent around line 20 where it says, "Unlike the single
3 barcode amplification reaction, the chimeric molecule formed in this
4 amplification reaction." I'm pretty sure Patent Owner emphasized that and
5 said look here. It's very clearly said the chimeric molecule was formed in
6 the -- during the amplification step. Could you please address that?

7 MR. RAICH: Sure. I mean, I think first of all, read in context
8 elsewhere in this same discussion, they're saying they're not being limited by
9 any particular theory or mechanism of action. Furthermore, I do think the
10 case law is very clear that you don't heed limitations from the embodiments
11 in the specification into the claims. Even if all of the embodiments or the
12 only embodiment disclose a particular thing, you don't -- a particular
13 example, you don't read that limitation into the claims.

14 Here the plain language of the claims says it's introduced during
15 the sequencing workflow. That is throughout the process of sequencing. If
16 they wanted to claim more narrowly, they could have done that. That's just
17 not what the plain language of the claim says. And I think that the
18 disclaimer language that I pointed to from the patent further indicates that
19 they did not mean when drafting the Patent to be limited to this particular
20 theory or mechanism of action. So the Hill-Rom case is certainly supportive
21 of the claim construction position. Thorner vs. Sony is another example. So
22 I think they should not benefit from one sentence in the specification when
23 there is other language in the specification that is much broader.

24 JUDGE YANG: Since we are on claim construction, I have just a
25 simple question. Petitioner's proposed construction doesn't include the word

1 error, and Patent Owner complained about that. Maybe complaint isn't the
2 right word here. Patent Owner said you should have included that. Any
3 reason error shouldn't be included in the proper claim construction?

4 MR. RAICH: It merely repeats a word from the claim, but it
5 doesn't affect either party's arguments. So we don't object to the inclusion of
6 the word error in the construction. I think the issue that we have is the
7 limitation created during cluster amplification because that's just not what
8 the claim says. Why don't we go to Slide 17, please. So Parameswaran and
9 Gloor together disclose each element of Claim 1. And what I'd like to do is
10 focus on the contested issues, including chimera formation and the
11 discarding step. And I want to start with Parameswaran.

12 So if we have Slide 19, please. So Claim 1 recites that at least one
13 of the clusters "comprises a chimeric sequence comprising a combination of
14 identifier sequences that are different." Parameswaran teaches various
15 erroneous sequences including what it calls perfect unexpected occurrences.
16 And these contain combinations of identifier sequences that are different
17 than any of the distinct pairs. Now what about the discarding step of Claim
18 1?

19 By calling these perfect unexpected occurrences as false
20 discoveries, which is stated several times in Parameswaran, a skilled artisan
21 would understand that they were discarded from the sequencing workflow.
22 And why is that? It's because they can't be assigned to any one sample. So
23 let me explain this. So in Parameswaran it has a variety of different
24 sequences, and some of the sequences are placed in the unassigned bin.
25 They don't have a barcode that matches to one of the original identifier

1 sequences. And then everything else goes into what they call the raw bin.
2 Sequences in the raw bin are then sorted into perfect expected, which have
3 two good barcodes, imperfect expected, which have one good barcode and a
4 non-conflicting barcode, and perfect unexpected sequences, which have two
5 good barcodes, but they conflict with one another informationally.

6 So what does this mean? So if you look in Parameswaran, the
7 perfect expected sequences are on the diagonal. Both of those sequences
8 map to, in this case, sample 69. So they have two matching pairs. The
9 imperfect expected have one good barcode which matches to sample 69 and
10 a second barcode which does not conflict with that information. But the
11 perfect unexpected sequences have conflicting information. One barcode is
12 matching to sample 69, and one barcode is matching to sample 67.

13 Therefore they cannot be assigned. They are discarded. So the perfect
14 expected occurrences, and this is Slide 22, are shown on the diagonal. They
15 can be assigned to samples. But the perfect unexpected occurrences cannot
16 be assigned to any one sample because of this conflicting information.

17 So briefly on Gloor, Slide 23. So Gloor discloses dual index
18 multiplex sequencing. So it's Illumina sequencing. So its amplification
19 occurs on the flow cell. And it also specifically detected chimeric
20 sequences. But instead of using the index tag to identify the chimeras, it
21 used a bioinformatic approach. Now a person in skill in the art would have
22 been motivated to combine Parameswaran and Gloor. Illumina sequencing
23 was faster, more efficient, and less expensive. It was a superior sequencing
24 platform. And while Illumina sequencing had low errors, chimeras were a
25 known problem. So Parameswaran's unique dual indexing could be used to

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1 efficiently discard those chimeric sequences to ensure that the DNA
2 sequences were assigned to correct samples.

3 But there's more. Slide 29 (sic). Parameswaran includes a
4 recommendation, and Parameswaran states that its barcodes may be
5 compatible with other sequencing platforms. And it specifically identifies
6 the Illumina/Solexa platform. Even the '852 Patent acknowledges that
7 unique dual indexing can be used with "essentially any sequencing method."
8 And under KSR, "if a technique has been used to improve one device," a
9 person of skill in the art "would recognize that it would improve similar
10 device in the same way, using the technique is obvious unless its actual
11 application is beyond his or her skill."

12 And Slide 26. There's no real dispute that the actual application is
13 beyond the reasonable skill of a person of skill in the art. There's no real
14 dispute that the adapters and protocols are interchangeable between
15 platforms. There's no real dispute that samples could be sequenced given
16 Illumina read lengths in 2010. And indeed Maughan, which is Exhibit 1038,
17 applied a unique dual-indexing approach using the same barcodes for both
18 454 and Illumina sequencing, strongly supporting a reasonable expectation
19 of success.

20 JUDGE YANG: I'm going to have to interrupt you there. Can we
21 go back to Slide 22 please? So I'm still on the discarding step. So these
22 grayed out, four of them, they are the perfect unexpected occurrence. Is that
23 correct?

24 MR. RAICH: Yes --

25 JUDGE YANG: And that's the --

1 MR. RAICH: -- they are.

2 JUDGE YANG: -- so perfect unexpected occurrence has -- try me
3 again. Two of the perfect tags just not assigned the -- they're from different
4 --

5 MR. RAICH: Different samples --

6 JUDGE YANG: -- samples?

7 MR. RAICH: -- that's right, Your Honor.

8 JUDGE YANG: Okay. So then I actually did understand it. And
9 then I have a question. So this Parameswaran reference, in the abstract and
10 later it talked about this. I'm reading from the abstract. It says, "We found
11 that over 99.8 of obtained sequences could be assigned to 25 independent
12 uniquely barcoded libraries based on the presence of either a perfect forward
13 or a perfect reverse barcode." You have to explain to me. If they assigned
14 these sequences based only -- based on only one perfect barcode, how did
15 they exclude this? I'm trying to reconcile these two. Here it at least appears
16 to me if there is one perfect barcode, it's been assigned. And yet you are
17 telling me here that is a perfect unexpected occurrence and therefore is not
18 assigned. Maybe I mixed up something. So please explain.

19 MR. RAICH: I think that there's two things going on here. So
20 first of all, if there are no appropriate barcodes, I think Patent Owner agrees
21 those are discarded sequences. But when you have conflicting pairs, as Dr.
22 Spellman explained, they cannot be assigned. So because you can't assign it
23 to, in this case sample 69 or sample 67 because they conflict with one
24 another. And the reference specifically calls those false discoveries or false
25 -- I think false discoveries is the term that they use. That is essentially a

1 discard step because it cannot be assigned to one of the originally assigned
2 samples because there's conflicting information.

3 And I think if you looked furthermore the sort of one of the
4 sentences that they're pointing to -- if I could have Slide 66, please. So it
5 does say that, "For our purposes, all sequences with a match to one of the
6 two expected sequence motifs were considered as true members of the
7 corresponding data set." We interpret that as referring to expected sequence
8 motifs, not sequences with mismatched barcode motifs that can't be
9 assigned. And furthermore, if you look at that sentence as we set forth in
10 our petition and reply, it says, "For our purposes, all sequences with a
11 match." So I think even if a person of skill in the art interprets
12 Parameswaran the way that they would like to interpret it, it's still
13 acknowledging that it's going to depend on sequencing purpose, and that
14 there are times when the sequencing purpose needs to be exceedingly
15 accurate, and you need to have sample assignment perfectly. So we think
16 both that Parameswaran is actually discarding based on the reading of the
17 paper and the way that it steps when you have perfect unexpected pairs. But
18 also that it would be obvious to discard those sequences which can't be
19 properly assigned if sample assignment is important.

20 JUDGE YANG: Let's put the for our purposes or for any other
21 purposes aside. I hear your argument. I read that part. I just want to make
22 sure that I understand both your argument and the reference. Here in this
23 sentence, it says, "all sequences with a match to one of the two expected
24 sequence motifs." It means you don't have to have perfect match on both
25 ends, correct?

1 MR. RAICH: At least for that step. But then there is, as I was just
2 walking through on Slide 21, there's this additional sorting that occurs that
3 once you have one good sequence, if you make it to the raw bin, that's not
4 the end of the analysis. And those sequences are still being analyzed, and a
5 subset of those sequences are specifically called out as perfect unexpected
6 sequences which have this conflicting information. So I think that's only
7 part of the story.

8 JUDGE YANG: Go ahead.

9 MR. RAICH: Let's talk about some of the arguments that Patent
10 Owner has raised. Why don't we look at -- if we could go to Slide 31,
11 please. And this is picking up on the issue that you raised previously, Your
12 Honor, about whether or not chimeras created during cluster amplification
13 were a known problem. Actually, if we could have Slide 29, please. So I
14 think it's clear that chimeric sequences are arising in Illumina sequencing
15 were a known problem, that Exhibit 1015 talked about jumping PCR in the
16 protocol for Illumina multiplex sequencing. That can form chimeric
17 sequences. Now, they also have a refinement of that argument where they
18 say that chimeric sequences created during cluster amplification was an
19 unrecognized problem. But just keep in mind that argument is 100 percent
20 dependent on their claim construction theory that would limit the claims to
21 creating during cluster amplification. So that is point one. And as I
22 mentioned, we think that it's factually wrong.

23 I discussed the Gloor reference. Let's briefly discuss the Campbell
24 reference. The Campbell reference reinforces that chimeric molecules
25 created during cluster amplification was a real problem. Here, they were

1 looking for biologic chimeras, molecules that could cause cancer, chimeras
2 that occurred naturally. But what they found was very few biologic
3 chimeras, but lots of what the paper called rearrangement that result from the
4 sequencing workflow. As Dr. Spellman explained, "A person of skill in the
5 art would have understood that many of these chimeric sequences arose from
6 chimeric molecules created during cluster amplification on Illumina's flow
7 cells."

8 If we could have Slide 33, please. Now, they also make the
9 argument that this problem wasn't recognized until 2011 in the public
10 domain, citing a paper, Exhibit 2004 of post-filing evidence. So if you look
11 at Exhibit 2004, it actually talks about chimeras resulting from PCR, and it
12 refers to jumping PCR. And it cites as Exhibits 17 to 20 the same evidence
13 that I walked through with you earlier, all prior art references talking about
14 the problem of chimeras in PCR. And it ignores that the same authors in
15 Exhibit 1015 had already published on Illumina sequencing, talking about
16 jumping PCR. And that was in the prior art. And furthermore, our expert
17 explains that, "There's no scientific basis for asserting that chimeric
18 molecules would not form during cluster amplification."

19 Slide 34. Now, beyond the claim construction and factual issues,
20 there's also a legal problem with Patent Owner's argument. Patent Owner
21 appears to argue that if it was unknown that chimeras form on the flow cell,
22 then the claims would be non-obvious. But that's just a problem that the
23 inventors focused on. And under KSR it's error to look only at the inventors
24 (sic) the Patentee was trying to solve. "Under the correct analysis, any need
25 or problem known in the field" and provide a reason to combine.

1 And here, a person of skill in the art would have recognized that
2 chimeras, regardless of where they form, would be problematic for sample
3 tracking and therefore would have been motivated to apply Parameswaran's
4 barcoding method to Illumina sequencing and would have had a reasonable
5 expectation of success. A person of skill in the art would have reasonably
6 expected to reduce all chimeric sequences using this method,
7 Parameswaran's method, regardless of how they were created, and that more
8 than suffices for a reasonable expectation of success under the law.

9 Now they also argue that Parameswaran -- this is Slide 35
10 -- doesn't specifically identify the mismatched barcode motifs as cross-over
11 errors. But obviousness has to be carried out from the vantage point of a
12 person of ordinary skill in the art. And here, chimeric sequences forming
13 during Illumina sequencing was a known problem. And as Dr. Spellman
14 explained, "a person would have understood that sequences would have been
15 -- these sequences with mismatched barcode motifs would have included
16 sequences from chimeric molecules."

17 Let's go to Slide 37, please. Now, they also argue that a person of
18 skill in the art wouldn't "have thought that Parameswaran's barcoding
19 methods would have utility in Gloor's Illumina sequencers because Illumina
20 sequencers did not have the same needs as pyrosequencing." But this just
21 ignores the prior art. And there are multiple references such as Pfrender and
22 Wu that specifically discuss Illumina sequencing and discuss the tagging
23 strategies of Parameswaran in the context of Illumina sequencing.

24 In Slide 38, and in fact even a co-inventor of the Molecular Loop
25 Patent published a prior art article and stated that an option would be

1 "effective technology to judiciously add sequence tags" then cited
2 Parameswaran and said, "this reduces the inefficiencies of ensemble-based
3 sequencing by synthesis architectures." And then the paper further -- this is
4 another excerpt -- discusses schemes for sequencing by synthesis and
5 specifically cites the Bentley paper. The Bentley paper is the other paper in
6 our other ground challenging the '852 Patent. Bentley discloses sequencing
7 by synthesis. It's Illumina sequencing. So even the inventor understood that
8 Parameswaran was not all about pyrosequencing as was argued in
9 prosecution.

10 Patent Owner argues that, "Parameswaran and Gloor pitch
11 combinatorial dual indexing as much more than a mere alternative or
12 choice." But as I mentioned earlier, a person of skill in the art "would have
13 understood that sample tracking and sequence fidelity are critical in many"
14 applications such as cancer research or molecular diagnosis. And they
15 acknowledge that in some applications of sample multiplexing you need to
16 be highly accurate. That would have motivated the use of unique dual
17 indexing as in Parameswaran as opposed to a combinatorial approach. And
18 furthermore, the law is on our side on this. The inquiry into the existence of
19 motivation assumes the person of skill in the art has common sense and
20 would know which is the appropriate barcoding scheme to apply.

21 JUDGE YANG: I'm sure you're going to get to it, but can we
22 address the prior art status of Gloor, please?

23 MR. RAICH: We can if you could have Slide 40, please. So
24 Gloor was published and is publicly available from a well-known archive.
25 It's called arXiv.org. It has a dedicated URL. That URL is active to this

1 day. We have two declarations from Dr. Gloor, the first author of the Gloor
2 publication, explaining that Gloor was publicly available as of July 29th,
3 2010.

4 JUDGE YANG: I have a very specific question. That is Patent
5 Owner's Exhibit 2008, which purportedly is a printout from the Wayback
6 Machine. According to Patent Owner, that printout shows that the earliest
7 availability was 2020. Could you explain the relevance of this exhibit to me,
8 please?

9 MR. RAICH: I think, if I'm remembering correctly, Your Honor,
10 that might have been a reference to some of the metadata that was available
11 and -- okay. Yeah. It's the capture from the Wayback Machine of 2018. I
12 think our response to that is simple. You have to look at the evidence as a
13 whole here. And we think that the evidence is really overwhelming in this
14 case. Wayback crawlers don't archive everything all the time. I don't know
15 why. In this case, the one that they submitted is from 2018.

16 But we literally have the publication policy that was in place at the
17 time for arXiv.org indicating that if it was submitted on a Monday, it was
18 made publicly available that same day and announced the next day. And if
19 you look at Slide 42, the evidence is that Dr. Gloor submitted it on July 28th.
20 And that's I think clear, and I think even they acknowledge this. And then
21 he received an email the very next day, a responsive email, stating that his
22 abstract was available. That the article was available, and that the abstract
23 would appear on July 29th, 2010. That's Exhibit E to 1002. It's consistent
24 with the publication policy, and it's consistent with Dr. Gloor's testimony.

25 Furthermore, the current website actually states that the paper was

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1 originally announced in July 2010. That's Exhibit 1051. So it's all
2 consistent. Furthermore, arXiv Technical Support confirmed that the article
3 appeared online July 30th after midnight or 1:00 a.m. UTC, which is July
4 29th, Eastern Time. Slide 40 --

5 JUDGE REIMERS: And I assume you have evidence that it's
6 searchable, that people that wanted to get to the article could if they needed
7 too.

8 MR. RAICH: Yes. Yeah. Absolutely, it's searchable. You can
9 search to this day. People did find it. In fact, if you go to Exhibit -- this is
10 Slide 45, Exhibit 1052, where in a sequencing forum someone cites the same
11 link that's printed on the paper and the same link that is active today. And
12 he says, "You can find the paper," and it gives that same URL. And
13 furthermore, Dr. Gloor responded to that link. So in fact, this shows that
14 someone did in fact access the paper. All of this evidence is consistent with
15 the Gloor paper being publicly available. And Gloor posted a response to
16 that same discussion forum, which confirms the existence of the forum and
17 its discussion regarding the Gloor publication. I just point out again, there's
18 extensive and repeated correspondence from arXiv Technical Support
19 service stating that Gloor was publicly available on July 29th, 2010. That's
20 on Slides 47, 48, 49, and 50.

21 JUDGE YANG: I'm just curious. I do see all the correspondences
22 from the archive personnel, but Petitioner couldn't obtain any direct
23 evidence on that point like Wayback Machine instead of the publication
24 policy? Actually, you couldn't show somebody got an email saying here is
25 the publication? None of that?

1 MR. RAICH: I mean, Dr. Gloor's email, the email that was sent to
2 Dr. Gloor, which is Exhibit E to Exhibit1002, states that at the time that the
3 paper is available, I think is the exact words that it used, and will be
4 announced later today. I think that's exactly what it says. So we don't have
5 Wayback Machine evidence except on the publication policy. But as the
6 Federal Circuit has explained in CQB, public availability should not
7 overstate the required degree of certainty. This is a preponderance of the
8 evidence standard. We think it's more than met in this case or is publicly
9 available prior art.

10 Let me very briefly discuss the '200 Patent, and I will keep this
11 brief. If we could have Slide 55, please. So these claims are similar to the
12 '852 Patent, but they're broader. For example, there's no reference to cross-
13 over error. It's just about validating the sequence. Individual identifiers can
14 be used with different samples. There's no reference to a flow cell, the thing
15 that they've harped on for the '852 Patent. You can exclude sequences. You
16 validate by excluding sequences that have only one identifier or an incorrect
17 pair of identifiers. And so what this means, consequently, is that there are
18 more different grounds available. And I just want to very, very briefly
19 discuss this.

20 There is a claim construction dispute here. They briefed it in their
21 sur-reply. And the question is, does the phrase, "two or more identifier
22 sequences that are uniquely associated with the nucleic acid of analyte
23 interest," is this combinatorial dual indexing or unique dual indexing? And
24 it should be construed as broad enough to cover both. It doesn't state that
25 each identifier sequence must be uniquely associated. It states that the "two

1 or more identifier sequences are uniquely associated." And if you look at
2 the specification of their patent, it repeatedly states that, "While pairs of
3 barcodes associated with any given template is unique, individual barcode
4 sequences can be used with multiple templates as long as no pair is used
5 across two different samples." So the term should be given its plain and
6 ordinary meaning as Dr. Spellman set forth.

7 And if we have Slide 60, once Patent Owner's erroneous
8 construction is rejected, there's no dispute that Gloor teaches every
9 limitation. And so what I'm going to do is focus on their unique arguments
10 for some of the dependent claims. If we go to Slide 62, there is a dependent
11 claim that says, "wherein the barcode sequences are designed to have no
12 homopolymer regions," and the barcodes in Gloor have no homopolymer
13 regions. Those are just repeated bases. And their expert admits this. They
14 nonetheless argue that, well, they didn't discuss not having homopolymer
15 regions, but the likelihood of the barcodes in Gloor having no homopolymer
16 regions by chance is exceedingly low. Dr. Spellman calculated lower odds
17 than a million times lower than the odds of winning the Powerball lottery, so
18 I think that Claim 5 is also anticipated by Gloor.

19 Parameswaran also anticipates all claims of the '200 Patent.
20 There's no dispute that Parameswaran taught all limitations except the
21 excluding step for Claim 1. But the argument there, we should win this for
22 the same reasons as we discussed earlier for the discarding step in the '852
23 Patent. They're literally described as false discoveries, and they are
24 therefore excluded. I think absent any further questions from the panel, I
25 will reserve my remaining time.

1 JUDGE YANG: While you are connecting there, Patent Owner,
2 would you let me know how much time if you would like to reserve for
3 surrebuttal?

4 MR. MATTY: I'll try to keep five minutes, Your Honor.

5 JUDGE YANG: Whenever you're ready.

6 MR. MATTY: Good afternoon, Your Honors. Brian Matty for
7 Molecular Loop. May it please the Board. We plan to focus our
8 presentation today on three fundamental shortcomings of Illumina's
9 petitions, and they affect all grounds in the 964 IPR and many of the grounds
10 in the related 965 IPR that we've heard about already today.

11 First, the petitions failed to show that it would have been obvious
12 to combine Petitioner's prior art to use Parameswaran's pyrosequencing
13 approach on flow cell based sequencers like those in Gloor and Bentley.
14 Here, Petitioner repeatedly stretches the disclosures of their prior art and the
15 additional references to suggest that they show widespread
16 acknowledgement of issues and problems in NGS that simply weren't there.
17 The shortcomings are particularly important here given the timing of the
18 inventions of the '852 Patent, which were developed at a time when these
19 next-generation sequencing machines were a nascent field with many
20 unknowns that people were still trying to figure out.

21 Second, the petitions failed to show a reasonable expectation of
22 success in combining the prior art to achieve the invention as claimed. This
23 issue centers on the lack of awareness of cross-over error causing problems
24 in next-generation sequencing machines. Those errors were not known, and
25 they were not acknowledged at the time of the inventions here. And a

1 person of ordinary skill simply could not have had a reasonable expectation
2 of successfully reducing errors when they simply were not aware that those
3 errors existed in the first place.

4 Then third, even with the combination here, the petition failed to
5 show that the prior art discloses or renders obvious the discarding step of the
6 '852 Patent. Petitioner argues that Parameswaran and Gloor discarded
7 certain sequences. We heard a little bit about that already. And their
8 support for that is Dr. Spellman's conclusory assertions that those
9 disclosures are in the prior art, but they're simply not supported by the
10 explanations and the references themselves. And Petitioner's fallback to
11 obviousness for this step, again, is based on hindsight, working backward
12 from the claimed invention to get there. We'll talk about the host of
13 supporting references that Petitioner has put in the record. But on the whole
14 they do not establish obviousness because they're, again, stretching the
15 disclosures to suggest this widespread knowledge of an issue that simply
16 wasn't there.

17 As Your Honors know and have addressed a little bit already
18 today, there's claim construction issues underlying all of those. So I'll start
19 with the claim construction issue and then move forward with those three
20 main arguments that we plan to highlight today. There's other issues and
21 other disputes that you're aware of in the papers, some specific to the '200
22 Patent. We'll see if we have time to get there. For anything we don't get to
23 today, we're happy to rest on the arguments that are in our briefs and in our
24 papers in this case.

25 So to put things in context here, I want to maybe reset a little bit on

1 what these Molecular Loop Patents are about. These patents date back to a
2 provisional application in 2010. And as I mentioned that timing is important
3 here in considering these inventions. The next-generation sequencing
4 platforms that we're talking all about, they're all over the place today.
5 They're widely used. But at the time of this invention, they were just
6 coming out. They were just being developed. They weren't commercial
7 systems yet.

8 People were trying to figure out how do these platforms work,
9 what are their ups and downs, and what's the best way of using them. And
10 the inventors here in this case were one of those groups. They didn't solve
11 every potential problem with the NGS machines early on, but what they did
12 come up with was a rather elegant approach that contributed to the ability to
13 increase efficiency and accuracy in these machines.

14 And on Patent Owner Slide 4, we highlight Figure 2 in the patent,
15 which highlights the inventor's approach. This shows how the invention
16 works during amplification on the surface of a flow cell. And when the
17 inventors were using this new NGS platform, they realized that there was
18 something going on on the flow cell that caused errors with traditional
19 sample tags getting mixed up. Now, they didn't have a camera or video to
20 show exactly what was going on on the nanoscale level of the flow cell. So
21 they were hypothesizing, trying to figure out what was going on.

22 And Figure 2 shows the thought that they came up with. Their
23 hypothesis was that during the cluster amplification step, chimeric molecules
24 were forming on the surface of the flow cell due to improper overlap, which
25 they showed in panel 3 of the figures. Then they figured out that that

1 overlap, that cross-over, caused barcode hopping that could mess up your
2 sample identification in your analysis down the road. So from that
3 foundational realization, they developed their barcoding scheme that would
4 make sure there were two barcodes on every genetic fragment so that cross-
5 overs like this could be sorted out and discarded from the analysis. So that
6 was the fundamental idea that the inventors described in this in these patents.
7 And it came from their experimentation and hypothesizing about this new
8 and nascent NGS platform that they were trying to figure out.

9 So with that fact, I'll jump ahead to the disputed issues here on
10 Patent Owner's Slide 12. For the 964 IPR, there's really six main issues that
11 are addressed in the parties' briefs, and we've put together this sort of list to
12 sort or guide our presentation to Your Honors today. And as I mentioned,
13 I'll start with the claim construction term. The term cross-over error here
14 should be construed as, "error from sequences of chimeric molecules created
15 during cluster amplification and made from template nucleic acids derived
16 from different samples." There were two disputes here in the briefing. I
17 think we've resolved one of them today. I heard Patent Owner no longer
18 objects to including error from at the beginning of the construction. So I'll
19 put that one aside and focus on the main dispute that's remaining between
20 the parties.

21 Turning to Patent Owner's Slide 16, the cross-over error in this
22 patent is repeatedly and consistently described as errors resulting from
23 chimeric molecules that form during cluster amplification. Every example
24 of cross-over error shown in the figures depicts error arising from a chimeric
25 molecule formed during cluster amplification.

1 JUDGE YANG: So I hear you there, Counsel. What about
2 Petitioner's argument that we shouldn't import limitation from the
3 specification? What's your answer to that?

4 MR. MATTY: Yes, Your Honor. We have to look at the
5 specification and make sure that we're defining the term consistent with how
6 it's used throughout the intrinsic evidence. And if you look here, actually, in
7 each of those four places where the patent talks about cross-over error,
8 there's two things that are true about every one of those places that it
9 describes it. It describes cross-over error as forming from chimeric
10 molecules that come from template nucleic acids from two different
11 samples. And it talks about that chimeric molecule forming during cluster
12 amplification.

13 Petitioner actually acknowledges for the first of those points that
14 should be included in the construction. We agree that we're talking about
15 chimeric molecules forming from template nucleic acids from two different
16 samples. But by the same token, to stay true to the way this cross-over error
17 is described throughout the patent, you have to also include that that chimera
18 is formed during cluster amplification. So it's not improperly reading an
19 embodiment from the spec. It's staying true to the way that the cross-over
20 error is described in every instance talked about in the step and including
21 both of those two requirements that all over it says are part of the cross-over
22 error. And again, that's exactly what is shown in the, I think the most
23 important figure in the patent, Figure 2. But it's also shown in every figure
24 in the patent. There is no figure in the patent that shows a cross-over error
25 from a chimera formed at some time other than cluster amplification.

1 Then, turning to Patent Owner Slide 17, the patent also
2 consistently describes the result of the overlap that occurs during cluster
3 amplification. As the patent describes at the paragraph at the end of column
4 5 and over to column 6, the point -- this is the point after the overlap has
5 occurred during cluster amplification, after the heteroduplex has formed,
6 what's shown in panel 3 of the figure -- at that point, that is when "a cross-
7 over has occurred." That's what the patent says. It's during the cluster
8 amplification.

9 It's after that overlap and that cross-over that happens during the
10 cluster amplification. And that's the first time in the flow in the depiction of
11 the invention here that there's a chimeric molecule, as shown at the bottom
12 right of the figure. We have a gene from template A1 tag from -- A1 from
13 that same template and then a second tag, tag B2, from a different template.
14 That's the first chimeric molecule that's shown in this flow depicting the
15 invention, and it's created during cluster amplification.

16 And again, this is the main figure to highlight the point. But it's
17 also consistent with everything else in the specification. All the other
18 figures, all the other places in the spec, including each instance of cross-over
19 error that's discussed that Petitioner cited in its citations at pages 22 to 23 of
20 the petition. That's where they said there's four places. Each of those four
21 places talks about molecules from different samples forming this chimera.
22 In those same places you'll see that it's talking about that chimera formed
23 during cluster amplification.

24 So I'll jump ahead to Patent Owner Slide 19. Here we address
25 Petitioner's argument on the timing issue. Here, Petitioner argued for their

1 broader claim construction by asserting that the cross-over error can be
2 introduced at any point during the sequencing workflow. They focus on that
3 claim language in the preamble in this argument, noting that the claim says,
4 "cross-over error introduced during sequencing workflow." And it is true
5 that language is in the preamble. There's no dispute about that.

6 But the key question here is what is the claimed cross-over error in
7 the first place? It's that question that limits this term to error from chimeric
8 molecules formed during cluster amplification when you take into account
9 the intrinsic evidence and the repeated description across all the figures and
10 all the embodiments in the patent. So in other words, it's the type of error
11 that is introduced during the sequencing workflow that's the important
12 question here.

13 And Petitioner's assertion regarding the claim language during
14 sequencing workflow essentially misses that point. It's pointing to other
15 language that's in the claim, but it's really ancillary to the main dispute here
16 of what is the cross-over error in the first place. Additionally, when you
17 look at the sequencing workflow that is claimed, as we've noted, even under
18 Petitioner's interpretation, the only place in these claim steps that chimeras
19 creating cross-over error could form is during the cluster amplification.

20 JUDGE YANG: I think you heard Counsel for Petitioner actually
21 dispute -- I hope I'm accurately describing your point here -- that it could
22 happen before the combining step. So I just want to point that out if you
23 want to address it.

24 MR. MATTY: Absolutely. And again, Your Honor, I think with
25 that hypothetical, we're departing from the intrinsic evidence. This notion

1 that there could be some other way that the cross-over error arises during a
2 sequencing workflow, if some hypothetical -- I think we heard
3 contamination in anything from a pipette early on in the process. There's
4 nothing like that in the patent. Certainly if we look at the four instances of
5 cross-over error in the patent, there's nothing like that described as giving
6 rise to a cross-over error. It's essentially a hypothetical of other ways that
7 chimeras could form in a laboratory. It's not true to the intrinsic evidence
8 and the description that's actually in the patent.

9 Then I'll turn to Patent Owner Slide 20. Petitioner also argues that
10 the specification identifies cluster amplification as merely one possible
11 theory for chimera formation. And again, it is true. The patent describes the
12 inventor's theory on the mechanism of action for the chimeras that create
13 cross-over error. Their theory was the formation of a heteroduplex, as is
14 described in the patent and shown in that panel 3 of Figure 2.

15 And what the inventors explained and what Dr. Adalsteinsson
16 highlighted at paragraph 29 of his declaration was that there might be
17 something else going on on the biochemical level on the surface of that flow
18 cell that's shown in the figure. Because again, they didn't have a video
19 camera or anything that could show them what's actually going on in real
20 time at the nanoscale of these nucleic acids. And Dr. Spellman actually
21 agreed the heteroduplex, like the one shown in the patent, "is one
22 mechanism for creating a chimeric sequence but not necessarily the only
23 mechanism." We show that quote at the bottom of our Slide 20.

24 But as Dr. Adalsteinsson again explained, while there might
25 potentially be other ways to form chimeric molecules during cluster

1 amplification, there might be other phenomena happening on the surface of
2 that flow cell. Just because other biochemical mechanisms might occur
3 during cluster amplification doesn't open this claim term up to a broad
4 reference to error created at any point in the sequencing workflow. Even in
5 the discussion of Figure 3, the portion of the patent that's shown at column 6,
6 line 25 that Petitioner is focused on, that's giving theories of the specific
7 mechanism that's happening during cluster amplification. It's not saying that
8 cross-over error also includes errors from these other hypothetical time
9 points in the sequencing.

10 So turning to Patent Owner Slide 21, at the end of the day, Patent
11 Owner's construction here is the one that stays true to the invention that is
12 laid out in the patent. It's consistent with the intrinsic evidence. The patent
13 figures and specification repeatedly explain that cross-over error arises from
14 chimaeras formed during cluster amplification. And it's not disputed that
15 every example of cross-over error actually described in the patent comes
16 from chimeras that are formed during cluster amplification. So we'd ask the
17 Patent Owners construction be adopted.

18 JUDGE REIMERS: Should we look at your claim construction
19 issue as if the Patent Owner is his or her own lexicographer? Is that sort of
20 what you're asking us to do? We've explained it repeatedly in the spec the
21 same way, and we should look at that as the definition.

22 MR. MATTY: Yes, Your Honor, I think so. And I think that both
23 parties agree here. This is not a term of art. We're not trying to depart from
24 some known meaning of a term. I think the parties acknowledge this was
25 not a term of art.

1 JUDGE REIMERS: So there's no plain and ordinary meaning out
2 there that I can ask an expert, and they would have a definition for that term
3 at the time.

4 MR. MATTY: That's certainly correct and certainly not in any of
5 the evidence in this case. No one has said -- Dr. Spellman hasn't said that
6 he's applying the plain and ordinary meaning of cross-over error, which is
7 blank. He has agreed with our expert that this isn't a known term of art.
8 There's not a plain and ordinary meaning known to a POSA. Therefore, you
9 have to dive into the intrinsic evidence and figure out what it is.

10 JUDGE REIMERS: Thank you.

11 MR. MATTY: So turning to Patent Owner's Slide 22, next, we'll
12 address the lack of motivation to combine Parameswaran and Gloor. And
13 again, as Your Honors are aware, this is an issue that raises a number of
14 points stretching across both grounds of the 964 IPR and also some of the
15 965 because there's a lot of overlapping motivations to combine here.

16 So jumping to Patent Owner Slide 24, we highlight a major
17 shortcoming in the obviousness analysis here. There's a consistent theme
18 here where the petition and Dr. Spellman repeatedly stretch their references
19 to assert that the publications in the record contain disclosures and concepts
20 that just are not there. And it starts with the prior art asserted in this ground,
21 Parameswaran and Gloor. The notion that cross-over error arising in NGS
22 machines was widely known prior to the invention in this Molecular Loop
23 Patent was a fundamental point for their motivation to combine analysis in
24 the petition.

25 Petitioner said in the petition, for example, at page 38, as of

1 December 2010, a POSA would have known that chimeric sequences,
2 including those resulting from cross-over errors, were problematic for next-
3 generation sequencing platforms, including Illumina sequencing. But Dr.
4 Adalsteinsson went through the evidence that was submitted in the petition
5 in support of that assertion. In painstaking detail, he went through one by
6 one and addressed the evidence and explained why it failed to show a real
7 awareness of that problem on NGS platforms, particularly on Illumina
8 machines. That analysis spans paragraphs 105 through 130 of his
9 declaration, and we'll walk through some of that now.

10 First for Parameswaran, it did not appreciate this problem. When
11 Parameswaran saw what it called its, "mismatched barcode motifs," it
12 guessed at three causes that those could have come from, and none of those
13 show any appreciation of the cross-over error problem. The first cause
14 Parameswaran guessed at was, "errors during barcode synthesis or
15 sequencing." Those are errors that would exist sort of within the barcodes
16 themselves, for example, as they're synthesized or created. That's not an
17 issue created by problems with amplification of template nucleic acid, and it
18 doesn't get at the cross-over error problem.

19 The second cause Parameswaran guessed at was, "contamination in
20 the PCR primer stock." That's sort of an issue with your starting reagents.
21 It's not an issue created by problems again with amplification of template
22 nucleic acids. So again, it doesn't get at the cross-over error problem. And
23 the third cause that Parameswaran guessed a was, "general cross-
24 contamination in the second round of PCR. What that refers to is a step in
25 Parameswaran where it ran each individual sample through two independent

1 rounds of PCR while they're all still separate before it pulled them together.
2 So if this is around of a PCR, each sample on its own is part of the,
3 essentially, the initial prep. Then at some point later, the samples were
4 eventually pooled together for sequencing. So even for this one, because
5 that round of PCR was performed before samples were even combined
6 together, it wasn't showing any appreciation of the cross-over error
7 happening between samples during your cluster amplification. The samples
8 would have to be combined to really give rise to that sort of issue.

9 Then for Gloor, on the key issue of the cross-over error that is
10 created here, there really isn't much of a dispute that Gloor used
11 combinatorial indexing. And that approach simply can't detect when one
12 sample index hops from one nucleic acid to the other because the new
13 chimeric sequence that would be formed in that scenario, it'll match another
14 sample that's in the set. And Gloor couldn't detect this cross-over error
15 problem.

16 JUDGE YANG: Counsel, so Petitioner points out that before the
17 priority date, one skilled in the art has been talking about this concept of
18 jumping PCR. Wouldn't jumping PCR result in cross-over error?

19 MR. MATTY: No, Your Honor. And this is important. So I'll go
20 to Patent Owner Slide 25, which is the evidence where they talk about
21 jumping PCR. Jumping PCR refers to the phenomenon where chimeras are
22 formed during the initial PCR amplification of a single sample. And it is
23 talking about everything within one sample. And chimera is forming from
24 cross-over nucleic acid within that one sample. They're not looking at
25 anything to do with cluster amplification. They're not looking at cross-over

1 in sample barcodes. And these references are not looking at even pooled
2 samples that could create a situation where chimeras are formed between
3 two different samples.

4 Essentially, what Petitioner has shown with jumping PCR was a
5 phenomenon that was known for DNA recombination in standard PCR in a
6 test tube, not anything related to NGS. And it wasn't appreciated until after
7 the Molecular Loop Patent that there could be additional problems when
8 you're doing multiplexing and amplifying in an NGS machine. And if we
9 look at the references that they've submitted, both in the petition and in the
10 reply in support of this notion that jumping PCR shows some widespread
11 appreciation of cross-over error -- if we look at what those references
12 actually say, it highlights this point.

13 So we heard a little bit about some of these references that we have
14 on Slide 25 in Petitioner's opening, and I want to address some of them in a
15 little more detail. And I'll start with the Creer reference. That's Exhibit
16 1034. Creer is one that has been cited a number of times. Petitioner referred
17 to it on their Slide 9. And we've heard this characterized as describing NGS
18 as the ideal breeding ground for chimeric sequences. That's how Petitioner
19 characterized this reference in their papers. In this case, it was the title of
20 their Slide 9. It says, "NGS was an ideal breeding ground for chimeras."

21 But the implication here, obviously, is that the resulting problems
22 from cross-over errors were well known for NGS platforms, including
23 Illumina sequencers. If we look at what Creer is actually talking about,
24 including in that key quote about being a breeding ground, it simply doesn't
25 say what Petitioner and Dr. Spellman say that it stands for. If we look at

1 page 10 of the Creer reference -- I was told the document camera here is not
2 working today.

3 So I'll just read from my hard copy and direct Your Honor's
4 attention to where I'm reading in the reference. Page 10 of Creer is where
5 this breeding ground quote arises, and it's what Petitioner has focused on.
6 It's in a section that's talking about PCR recombination and chimera
7 formation. And what it says is, this is from Creer, in many ways -- I'm
8 sorry. This is on page 10, the first full paragraph on the right hand column.
9 Creer says, "In many ways, metagenetic ultra sequencing experiments are
10 the ideal breeding ground for recombinant DNA molecules.

11 They are based on the amplification of homologous regions from a
12 large number of potentially highly related organisms, and the actual species
13 richness and taxonomic composition of the samples may contribute to the
14 level of chimera formation." There's nothing in there about Illumina
15 sequencers. There's nothing in there about NGS platforms. What this is
16 talking about is a specific type of experiment, a metagenetic ultra
17 sequencing experiment that Creer says can give rise to chimera formation.

18 And what Creer explains is, in those specific types of experiments,
19 this is sort of a problem of the input to the experiment, not the platform that
20 the experiment itself is run on. It talks about these experiments being based
21 on the amplification of homologous regions from a large number of highly
22 related organisms. It's the DNA input to this specific type of organisms that
23 Creer says creates this breeding ground for chimeras. And we know this
24 can't be anything about NGS because it cites a number of papers to say this
25 has been known for these experiments for a little while. It's citing papers

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1 from 1997 and 2001, which obviously predate the emergence of NGS
2 systems.

3 Dr. Adalsteinsson explained that in his declaration at paragraph
4 112. And essentially, at the end of the day, Petitioner's broad statements
5 here equating this with cross-over error simply are not what the Creer paper
6 says.

7 JUDGE REIMERS: And can I just ask for clarification? When
8 you're saying page 10, it's Illumina's exhibit numbers, right? Their page
9 numbers.

10 MR. MATTY: That's correct. It's stamped at the bottom Illumina
11 page 10 of 17.

12 JUDGE REIMERS: Gotcha.

13 MR. MATTY: Yeah. It's the first full paragraph in the right hand
14 column of that page. Starts with, "in many ways." And then turning to the
15 other four set of exhibits, Exhibits 1017 through 1020, Petitioner mentioned
16 those in their opening argument. The bottom line for this group of exhibits
17 is that they show at most knowledge of recombination of DNA during
18 standard PCR of single samples. These do not address any issue with NGS.
19 They do not address any issue in multiplexed sequencing. They do not
20 address any issues arising during cluster amplification.

21 JUDGE YANG: So if I hear you correctly, Counsel, you're saying
22 a problem in the regular PCR, one skilled in the art wouldn't expect that to
23 happen in the NGS. Is that what you're saying?

24 MR. MATTY: That's right. There was not an appreciation that a
25 similar phenomenon was happening during the cluster amplification in an

1 NGS machine.

2 JUDGE YANG: Forgive me for asking this, but does the
3 amplification step -- isn't it also a PCR step?

4 MR. MATTY: It is. There are particular types of PCRs. They
5 aren't kind of the standard PCRs that you would do in a tube in library prep.
6 They were things like PCR that's formed on the sequence of a bead or on the
7 sequence of a flow cell. So it's sometimes called bridge PCR or B-based
8 PCR. But the way it actually is carried out is different than just your
9 standard reagents in a tube (CROSSTALK) --

10 JUDGE YANG: I understand the vessel might be different, but the
11 steps are still the same. You denature. You amplify. The basic mechanisms
12 of PCR is still the same. So a problem that could happen in a regular PCR,
13 would it not carry over to -- okay, you use the bead or the flow cell, but you
14 still need to denature and rehybridize and all that?

15 MR. MATTY: Yes, Your Honor. Except in the standard PCR,
16 you're not really doing it the same way. There's denaturing steps. There's
17 cycle steps. There's heat cycles and things like that. But in a test tube where
18 you have things floating around, you're not anchoring your nucleic acids to a
19 bead or to a flow cell where things are supposed to be hybridized and
20 clustered in place. That's the main focus of creating the cluster.

21 With that sort of fixing to the flow cell, there wasn't an
22 appreciation at the time of you might have two things that when they bridge
23 over, go to the wrong primer, that are fixed on the surface of the flow cell or
24 on a bead. You weren't using those kind of primers fixed to the, whatever
25 the substrate is, depending on your NGS platform, when you were doing

1 your sort of free-floating PCR in a tube.

2 So briefly for the Lahr paper, which is Exhibit 1017, Dr.

3 Adalsteinsson explained at paragraph 107 of his declaration, talks about
4 potential issues with the diversity of nucleic acids within a single sample.

5 Similarly, Meyerhans' Exhibit 1018 talks about the same issue. Dr.

6 Adalsteinsson explained that at paragraph 108 of his declaration. And as we
7 know from that one, it's dated 1990, which is years before NGS was even
8 developed. It's a similar story for Paabo Exhibit 1019 and Odelberg Exhibit
9 1020. That's discussed by Dr. Adalsteinsson at paragraphs 109 and 110 of
10 his declaration.

11 So I'll skip ahead. Petitioner submitted a host of new references in
12 reply that we think should be disregarded because they should have been
13 submitted with the petition. We made that point in our sur-reply, but I'll
14 jump right to the substance. Even if you look at these references that were
15 submitted in reply, they still do not show the wide awareness of the cross-
16 over error that Petitioner continues to argue was known.

17 There's a lot of focus in the reply on this Campbell reference,
18 Exhibit 1057. It was addressed in Petitioner's opening. So I want to take a
19 minute and address the details of the Campbell reference. Campbell
20 discusses 1.2 million rearrangements. That's in Campbell at page 2. And it
21 identifies examples of what its rearrangements are. It has things like
22 deletions, duplications, and inversions. Those are listed in its table 1 at page
23 3 of Campbell. Campbell doesn't mention chimeras. It doesn't talk about
24 chimeric sequences, and it doesn't talk about chimeric sequences forming
25 between two different samples. Those characterizations appear only in the

1 reply by Petitioner.

2 The rearrangements that are actually identified in Campbell are not
3 chimeras. They're not chimeras formed between two different nucleic acid
4 molecules like the chimeras we're talking about here today. Campbell also
5 does not show rearrangements between different samples. And if we look at
6 the actual type of rearrangements that are discussed in Campbell, we drill
7 down on those a little bit and ask Dr. Spellman what those refer to. And his
8 answers highlight that these are not talking about chimeras made from
9 nucleic acids from different templates.

10 The first type of rearrangements Campbell talks about are
11 deletions. Dr. Spellman said what a deletion is referring to is basically
12 dropping bases out of a sequence. He talked about that at page 50 and 51 of
13 his second deposition, Exhibit 2015, talks about things like dropping a G out
14 of a sequence as a point mutation. That would be an example of a deletion.
15 So an example where you have a sequence and some bases are just dropping
16 out of that sequence cannot be a chimera that's formed from two different
17 nucleic acids. It's not what that rearrangement is referring to.

18 Second, for duplications, which Campbell lists is another example
19 of its rearrangements, Dr. Spellman said those are about repeating sequences
20 of bases within a single nucleic acid. He was asked about this at page 52 of
21 his deposition. He gave the example of a sequence of ATGC having that G
22 repeated and becoming ATGGC, again, within that single nucleic acid. It's
23 not referring to any chimeras formed between two different nucleic acids,
24 and it's not the types of chimeras that we're talking about here today.

25 The third example in Campbell was inversions. That one is when a

1 sequence within a nucleic acid essentially gets flipped. Dr. Campbell at
2 page 55 of his second deposition, Exhibit 2015, likened it to a one-way street
3 where you take that sequence within the nucleic acid and flip it the other
4 way. Again, that's something that's formed within a single nucleic acid. It's
5 not talking about a chimera where you have two different template nucleic
6 acids coming together. So none of those rearrangements have anything to do
7 with chimeras formed from multiple nucleic acid molecules. And again, we
8 just have Dr. Spellman and his conclusory testimony saying that these
9 rearrangements have something to do with chimeras. If you dig into the
10 details like we did with Dr. Spellman in his deposition, that simply is not the
11 case.

12 For the remaining new references that Petitioners submitted with
13 their reply, they don't fare any better with those. The Varela paper, Exhibit
14 1066, that has the same problems as the Campbell reference. Actually, it's
15 from the same group. It has a lot of overlap in the authors. And in Varela at
16 page 10, they explicitly call them "intramolecular rearrangements," which is
17 exactly the point we just made and the point we made with Dr. Spellman at
18 his deposition. These are intramolecular phenomena. They're not chimeras
19 of two different tempered nucleic acids coming together. It's not what the
20 rearrangements are talking about.

21 The Maher paper, Exhibit 1061, that was one that talks about
22 detecting biological chimeras. Those are chimeras that occurred in the
23 genomic samples that were collected. They were naturally existing. They
24 can be used for things like cancer detection. And in Maher, Petitioner
25 focuses on discussions of identical mate pairs. Those are not actually

1 chimeras formed between multiple template nucleic acids. There are issues
2 in the detection pipeline when the sequencing machine basically mistakes
3 one cluster of a sequence for two different clusters, kind of counts them
4 twice. And that's what Dr. Spellman testified about in his deposition. We
5 have the citations on our Slide 27 where he discussed that PCR duplicate
6 phenomenon.

7 And for the last few, the Whiteford paper, Exhibit 1067, that was
8 also mischaracterized in the reply. That one is not about chimeric sequences
9 formed during sequencing, but it's a different detection error known as
10 mixed clusters. That's when two different clusters are detected as one on the
11 flow cell. It reads the color as one cluster instead of two each time it adds a
12 base. It's not a problem of chimera formation.

13 And again, that's what Dr. Spellman described when we asked him
14 about what mixed clusters refer to in his deposition at pages 26 to 27, 30 to
15 31, and 46 to 48. So again, even if we take all these new papers into
16 account, Petitioner and Dr. Spellman are again pitching these as references
17 that teach a lot more than they actually say. The widespread disclosure of
18 chimeras and cross-over error simply is not supported by the references
19 themselves.

20 Turning to Patent Owner Slide 28, this is an important point. And
21 I think it's telling in view of the assertions Illumina is making here in view
22 of some of the issues and questions that we've discussed already today. The
23 earliest evidence in the record here of anyone other than the inventors on
24 these Molecular Loop Patents actually acknowledging and discussing the
25 problem of cross-over error on Illumina sequencers is the paper from

1 Kircher from late 2011, which is Exhibit 2004. Dr. Adalsteinsson addressed
2 this later-emerging awareness of the problems that the inventors here had
3 been on to earlier. And he explained in paragraph 43 of his declaration how
4 this was not a known issue among those in the field until after the '852
5 Patent, when the Kircher paper came out and made some headlines. And
6 there's some important discussions in Kircher of this notion of jumping PCR
7 that we talked about, and I want to make sure to highlight some of those.

8 So again, this is from Kircher Exhibit 2004. It's the publication
9 that came after the '852 Patent, and it's the first evidence of others in the
10 field actually recognizing cross-over errors on NGS machines, specifically
11 Illumina machines. It's what the title of the paper referred to as inaccuracies.
12 And they acknowledged again, in the title after the '852 Patent, that double
13 indexing, like is described in the '852 Patent, could address this. The quote
14 on page 2 of Kircher, this one's on the left hand column towards the bottom.
15 This is the reference to jumping PCR that Petitioner referred to.

16 Kircher acknowledged that, "jumping PCR during initial PCR prep
17 stages was known previously." It cited Exhibits 1017 to 1020, which talked
18 about that jumping PCR issue happening in your standard initial library prep
19 PCR. So they said we knew about jumping PCR. We knew about that
20 before. But what they're describing in this paper they say is something new.
21 This isn't jumping PCR. There's something else going on here that we didn't
22 know about before. And to see that, we can look at page 3 of the Kircher
23 paper.

24 In the right-hand column on the top there's the section that starts
25 with results. And in that section they talk about the sort of mixed-up sample

1 indexes that they saw in the sequences that they had looked at in their
2 experiment. And they noted that they knew about jumping PCR. But when
3 they looked at what was coming out of the Illumina machine, they saw a lot
4 more false index pairs than you would expect just from jumping PCR. And
5 at the end of that first paragraph in their results section, they say,
6 "Interestingly, we observed extremely high fractions of false index pairs,
7 irrespective of whether libraries were only sequenced together or also
8 amplified together, indicating that factors other than jumping PCR must
9 contribute substantially to the fraction of false pairs."

10 The end of that sentence is the key to why this paper matters. It's
11 the first acknowledgement that when we're running Illumina machines, we're
12 seeing problems with mismatched indexes, and there must be something
13 other than jumping PCR that contributes substantially to this fraction of false
14 pairings. So this isn't just the known issues of jumping PCR coming to roost
15 again. This is Kircher and his co-author saying there's something new here.
16 And it's the first publication after the '852 Patent to acknowledge that
17 something else must be going on in the sequencer. It's the first group to
18 actually pick up on the cross-over trail that the '852 Patent inventors had
19 discovered earlier.

20 And it was even later when Illumina themselves finally came
21 around and acknowledged the problem of cross-over error, what became
22 known as index hopping occurring on its machines. Illumina all along had
23 continued to instruct users to just use single indexes when multiplexing on
24 their machines, not showing an awareness of the cross-over problem. Dr.
25 Adalsteinsson explained that in paragraph 128 of his declaration. He cited

IPR2024-00964 (Patent 11,041,852 B2)

IPR2024-00965 (Patent 11,768,200 B2)

1 Exhibits 2006 and 2007 as examples of Illumina continuing to instruct the
2 use of single indexes.

3 Then finally later, Illumina released a white paper that addressed
4 the problem of cross-over error for the first time and what Illumina called
5 hopped reads. That's in Exhibit 2003, specifically at page 3. And Illumina
6 finally switched from single indexes and instructed the use of unique dual
7 indexes to address the problem. And I think it's important. Again,
8 Illumina's release said this problem had been known since multiplexing
9 began. But what they cited for that notion was the Kircher 2011 paper,
10 specifically in Exhibit 2003 at page 1, Illumina's release cited to its reference
11 number 2. If we look at the list of references in the paper, that's the 2011
12 Kircher paper that we've highlighted as sort of the first emergence of
13 someone publishing about this phenomenon. So that actually further
14 highlights that Kircher was really the first announcement of this problem
15 after the '852 Patent and I think highlights the point that it was not known
16 prior to that.

17 So I'll turn ahead to Patent Owner Slide 30 to close the loop on the
18 motivation to combine. Petitioner's motivation to combine here sought to
19 apply Parameswaran's unique dual indexing and Gloor's flow cell
20 sequencing. But if you read both of those references, both are actually
21 urging away from that approach. Both of these papers teach that
22 combinatorial dual indexing is the way to go, not unique dual indexing.
23 Parameswaran found that the potential for incorrect barcoding was so
24 minimal that it would be far better to use combinatorial dual indexing. It
25 highlighted that in its conclusion. And of course Gloor appreciated the same

1 thing. They explained that's why they used combinatorial dual indexing in
2 their approach.

3 So I'll turn to Patent Owner Slide 32 and go to the issue of
4 reasonable expectation of success. We can start just by setting the context
5 on what's required for a reasonable expectation of success. It's the
6 limitations recited in the challenged claims that dictate this analysis. And
7 Petitioner here has to show a reasonable expectation of success in combining
8 the prior art to meet the limitations of the claimed invention. It's not just a
9 question of whether the prior art references could be mixed together or
10 whether they might be compatible. It's a question of whether a person of
11 ordinary skill would have had a reasonable expectation of meeting the
12 limitations of the claims with their combination. And the important
13 limitation for issue -- the important limitation for the issues, in this case for
14 the '852 Patent, is the step of discarding sequence reads.

15 The claims require that you do the discarding thereby to reduce
16 cross-over error. So here, this analysis requires that a person of ordinary
17 skill would have had a reasonable expectation of success in reducing cross-
18 over error by discarding certain sequences. That's the same understanding
19 Dr. Spellman had. He confirmed that pages 132 to 133 of Exhibit 2015.
20 And in view of this claim limitation, Petitioner here fails to show a
21 reasonable expectation of success.

22 Turning to Patent Owner Slide 33, the petition here made three
23 points that allegedly showed a reasonable expectation of success. The first
24 was that Parameswaran's method could be adapted to Gloor sequencers by
25 swapping certain adapters. The second was at the read length on Illumina

1 sequencers were long enough for the reads in Parameswaran. Those two
2 reasons don't get at the heart of the issue here. They address questions of
3 whether or not the two systems in the combination are compatible or
4 whether they would work together. But even if those arguments are true,
5 they don't show any reason why a person of ordinary skill would have
6 expected to reduce cross-over error as claimed.

7 Petitioner's third point was that unique dual indexing would
8 generally reduce errors on Illumina sequencers. But again, as we've talked
9 about, the petition does not show that a person of ordinary skill would have
10 expected to reduce the particular type of error claimed, which is cross-over
11 error.

12 JUDGE YANG: So on that issue, if the -- well, not if. Cross-over
13 error is one type of the errors. So if you generally reduce errors, wouldn't
14 you also reduce cross-over error?

15 MR. MATTY: The question looks at the claim limitation, I think
16 backwards. I think that's essentially what Illumina is arguing. But the
17 question is for reasonable expectation of success in reducing errors
18 generally. If you expected to do that, could you have a reasonable
19 expectation of success in doing what's claimed, which is reducing cross-over
20 error? Essentially it's asking if you thought you were going to reduce errors
21 generally, what errors would you reasonably expect you were reducing?
22 And one of those errors has to be cross-over error. So even if a person of
23 ordinary skill at the time would have thought there might be some errors in
24 the system that I might reduce, if they're not aware of the cross-over error in
25 the first place, they can't be aware that that's one of the things that they're

1 going to be reducing. So it's sort of taken this high-level view of -- what you
2 need to do here is show more than a reasonable expectation of success in
3 making the system more accurate. You need to show a reasonable
4 expectation of success in doing what the claim limitation says, which is
5 thereby reducing cross-over. And that's the key question.

6 I'll go to the next issue, which is the discarding step, and I'll turn to
7 Patent Owner's Slide 35. Petitioner's assertions for the discarding step, they,
8 I think, go back and forth a bit between whether this is disclosed or just
9 obvious in the combination. But either way you look at it, they haven't met
10 their burden here. Petitioner's arguments for Parameswaran focused on the
11 mismatched barcode motif sequences that it detected. Parameswaran did not
12 discard those sequences. It explicitly kept them. Dr. Adalsteinsson
13 explained that in his declaration at paragraph 140, noting that Parameswaran
14 kept these sequences because Parameswaran included any sequence having a
15 match to at least one barcode motif. That's what Parameswaran says at page
16 8 of the reference, "All sequences with a match to one of the two expected
17 motifs" were included in its analysis set. Beyond that, Parameswaran was
18 actually explicit about which sequences it did discard. It says on that same
19 page 8 that only the sequences with no perfect matches to any barcode motif
20 were discarded. So Parameswaran sort of confirms in two different ways
21 that it did not have this discarding step. It explicitly says it kept sequences
22 having only one perfect match, and it explicitly says the only thing it
23 discarded was sequences having zero barcode matches.

24 I'll turn to Patent Owner Slide 36. And this is addressing a couple
25 of the main arguments that we heard today for Parameswaran that came up

1 in Petitioner's reply. First, Petitioner argued that Parameswaran calls the
2 mismatched barcodes unexpected motifs and that somehow means that they
3 were discarded. That interpretation isn't given anywhere in Parameswaran,
4 which instead distinguishes these unexpected motifs from sequences that
5 actually have zero barcode matches. And it's only those zero match
6 sequences that are actually discarded. But actually in the petition here,
7 before this issue really arose, Petitioner acknowledged that sequence having
8 perfect unexpected barcode motifs were considered to have one matching
9 barcode in Parameswaran. In the last sentence on page 24 of the petition
10 here, Petitioner said that 5 to 6 percent of the sequences in Parameswaran
11 had perfect barcode motifs only at one end. Then on the next page, page 25
12 in the first sentence, Petitioner says a subset of these 5 to 6 percent of
13 sequences, meaning a subset of the sequences having a perfect barcode at
14 only one end contained a pair of mismatched barcode motifs. So in the
15 petition, Petitioner actually agreed that the mismatch barcode motifs were
16 considered to have a barcode at only one end. That's also exactly what
17 Parameswaran says on page 7 of Parameswaran. It's a quote that was
18 actually excerpted on Petitioner slides on slide 19. On page 7,
19 Parameswaran says -- it talks about splitting up sequences that have a perfect
20 match to only one of the expected motifs into three classes, and it lists those
21 three classes. The first class that it lists is perfect unexpected motifs. So
22 that confirms that Parameswaran considered these unexpected motifs as
23 having a barcode at only one end and thus confirms that they were kept in
24 the analysis, not discarded in Parameswaran.

25 Now the second argument that we have about Parameswaran now

1 was about these gray cells in Parameswaran's data tables. Nothing in
2 Parameswaran says why those cells are gray. Nothing in Parameswaran says
3 that those sequences were discarded. Really it's just Dr. Spellman's
4 conclusory testimony and reply addressing those gray cells and saying that
5 those mean they were discarded. Dr. Spellman did agree, though, that for
6 the cells that actually correspond to the sequences having zero matches to
7 any barcodes, those are four cells in those data tables down in the bottom
8 right corner. Those cells in all Parameswaran's data tables are blank because
9 Parameswaran actually discarded those sequences. That's why they're blank.
10 They're not just grayed out. There's no number there because those are the
11 sequences that were actually discarded. In contrast, the gray cells that
12 Petitioner argues about now are not blank. They actually have numbers in
13 them because those sequences were kept and used in the analysis. So that
14 steps through each argument that Petitioner made for this claim step. And at
15 the end of the day there's just no showing that this step is disclosed or
16 obvious in the combination. That's another independent reason why the
17 invalidity challenge here fails.

18 I'll turn then to Patent Owners Slide 39 and get to the issue of
19 Gloor and its alleged prior art status. Gloor is a paper that was allegedly
20 submitted to A-R-X-I-V, arXiv.org. I think it's important to point out that
21 this is not a standard sort of publication. This is a basically a digital archive
22 of papers that anyone can submit and apparently will be stored in a database
23 that arXiv maintains. This isn't a question of a journal that takes
24 submissions and puts out regular issues, regular publications, regular
25 editions with your usual sort of journal article that might have a copyright

1 date or something on it. This is something different. And I think that's
2 important because the nature of the publication, as we all know, can change
3 the nature of the inquiry into its prior art status. Something like a newspaper
4 article that's sent out into the world daily or weekly might be a little easier to
5 prove up than a digital archive that's just dumped into a database somewhere
6 or a thesis that might be in the back shelves of some college library
7 somewhere that someone would have to go dig out. This is one of those
8 types of publications, allegedly, that someone would have to go looking for.
9 Now, arXiv.org can support prior art publications that's been found by the
10 Board in the past. The Board has highlighted in the past some of the
11 evidence that can help to establish the public availability of an article from
12 arXiv.org. Some of those were highlighted in some of the earlier papers in
13 these IPRs. They include things like testimony from an actual custodian of
14 the documents, testimony from arXiv.org, metadata produced from the
15 database where these things are stored. The Board noted in one of its earlier
16 decisions, the alleged email that was sent to archive subscribers here could
17 have helped show public availability and prior art status here. We don't have
18 any of that in this case. And importantly, Your Honor asked the question of
19 whether this was searchable or cataloged. There is no evidence in the record
20 regarding how this article or even arXiv.org generally was cataloged or
21 searchable in 2010 in such a way that a person of ordinary skill would have
22 found this paper. For example, you might see often in cases of theses that
23 are cataloged in library shelves. There's no evidence like that here.

24 Turning to Patent Owner's Slide 40, we highlight some of the
25 things that could have helped here but are missing from the record. There's

1 no archived webpage of the actual article that was allegedly published here.
2 There's no metadata for the article that was in arXiv.org in the record here.
3 There's no declaration from anyone at arXiv.org who would have had
4 firsthand knowledge as an actual custodian of this document. Instead, what
5 Petitioners leaned on is Dr. Gloor himself. He has no firsthand knowledge
6 of arXiv.org. He didn't work there. He was a user there. I think he signed
7 up the day before he allegedly submitted this article. And what Dr. Gloor
8 has provided is a number of emails that he had with arXiv.org. But it's
9 interesting and telling, I think, that there is no actual email announcement of
10 this publication that anyone has provided. Not from arXiv, not from Dr.
11 Gloor, not from anybody in the record. We know Dr. Gloor has access to
12 his email account that he used with arXiv.org. He submitted some of those
13 emails, including when he submitted the paper. He has emails from that
14 account before the alleged announcement, right after the alleged
15 announcement. But we know he searched his emails at least twice. He put
16 in a declaration with the petition. He put in a declaration in reply. He
17 doesn't have the email actually publicly announcing this page paper. I think
18 it's an important piece of missing evidence here.

19 JUDGE YANG: For the sake of time, I'd like you to address
20 Exhibit 1052, which is a printout from a forum discussion. According to
21 Petitioner, somebody on that forum actually referred to the Gloor paper and
22 provided the link to access it. How do you respond to that?

23 MR. MATTY: Yes. Your Honor, we still, even with this article,
24 we don't have anything showing what was actually at that link. This is why
25 in Exhibit 2008 that Your Honor asked about, we went and looked to see

1 what was that link. Back in 2010, when they were allegedly talking about
2 this, this looks like in October, what was at the link? There are papers in the
3 past where people have gone to arXiv.org and shown that in 2010, if you
4 went to this link, here's what would come up. It's a copy of the Gloor paper.
5 It matches the Gloor paper that I'm putting into evidence now. Therefore, it
6 was publicly available. We don't have that evidence here. And I think,
7 because this is an important case where this is a digital archive, where it's
8 not your traditional publication, we just don't have any direct evidence what
9 was actually in that link. And importantly, I think, even looking at their
10 Exhibit 1052, we're getting into October, November 2010, January 2013.
11 We're getting closer and closer to the priority date when the Molecular Loop
12 Patent is at issue here. The assertion that was in the petition that they've
13 argued all along is that July 28, 2010, is when this paper was published. If it
14 was October, if it was November of that year, there might be potential for
15 swearing behind that date. That hasn't come up because that assertion has
16 never been made here. But it doesn't show what was available in July 2010,
17 and it still doesn't show what actually was available at that link in October
18 2010. We know arXiv.org doesn't have that because we went and tried to
19 look for it, and the earliest we could find was a link that went back to
20 December 2020. So in the interest of time, for the remaining issues that we
21 know are in these cases, we'll rest on the arguments in our papers. Unless
22 Your Honors have further questions, I'll save my remaining time for rebuttal.

23 JUDGE YANG: Whenever you're ready.

24 MR. RAICH: Thank you, Your Honor. I'd like to start with the
25 issue of claim construction. And if we could have Slide 14, please. So I

1 think it's very important just to start with the words of the claims. And I
2 think Counsel is working hard to move away from what the claim actually
3 says, which is that the cross-over error is "introduced during the sequencing
4 workflow." The workflow includes the entire step of the process. The claim
5 is not limited to just things that occur on the flow cell. So I think that's
6 fundamental point one. You have to look at what the language of the claims
7 say. And the Molecular Loop Patent includes a hypothesis. That's really
8 what it is. There are two drawings that are guesses as to where cross-over
9 events may occur on the flow cell. That's not actually data or an
10 embodiment. Figures 1 and 2 are just guesses. Then there's Figure 3. But
11 even as Counsel acknowledged, the experiment in Figure 3 is also just a
12 hypothesis. It's comparing one barcode versus two barcodes. And even if
13 that weren't the case, and even if it definitively established that in fact cross-
14 over events were occurring on the flow cell, you still don't read limitations
15 from embodiments in the specification into the claims to override what the
16 claim language is actually directed to. Even if every embodiment in their
17 patent says the same thing, you don't override the plain language of the
18 claim. So that's first one. That is the Hill-Rom case and Thorner versus
19 Sony.

20 JUDGE REIMERS: So can I ask you a question? So if I'm
21 looking at it --, okay. I'm trying to figure out what this claim term means.
22 Everybody agrees there's no ordinary meaning to it. It's a new term. So it's
23 not something that somebody of skill in the art would just know what the
24 claim term means. So if I'm looking at the specification, and it's telling me
25 what the term means, is that really importing a limitation from the spec into

1 the claim? Or am I just doing what I should do in claim construction, and
2 I'm looking at the spec to inform me what that term means?

3 MR. RAICH: Yeah. I think that this is a term that is used in the
4 art. They did not invent the term cross-over error. You asked Counsel are
5 you just acting as your lexicographer? There's no definition in the
6 Molecular Loop Patent in terms of what this term means. Cross-over error
7 was used in the prior art to refer just to a mixture of signals. Generally,
8 when you have templates crossing over, that is in fact a term. It doesn't all
9 of a sudden imply that the cross-over errors were created at a particular stage
10 of the sequencing workflow. And that's where they're really reading into the
11 claim from the embodiments. And we respectfully think that's improper.

12 JUDGE REIMERS: And forgive me. I should know this, but do
13 both parties agree that the preamble is limiting?

14 MR. RAICH: There's been no dispute because we think the
15 preamble is obvious. We did not separately argue that the preamble is not
16 limiting.

17 JUDGE REIMERS: Okay.

18 MR. RAICH: Okay. I'd like to talk a little bit about jumping PCR
19 and Exhibit 1015 and maybe we could bring up Slide -- our Slide 10. And
20 so first of all, jumping PCR is a known phenomenon. I think I heard
21 Counsel say -- I believe he said it wasn't known in the context of multiplex
22 sequencing on Illumina sequencers. Exhibit 1015 is a prior art article
23 discussing multiplex sequencing on Illumina sequencers and talks
24 specifically about jumping PCRs. So this concept of jumping PCR was in
25 fact known. Counsel also mentioned a reference called Creer, which is

1 Exhibit 1034. And in fact, on their Slide number 25 referred to the fact that
2 it's discussing PCR of single samples. Creer is actually a multiplex
3 sequencing experiment. It was using 454 sequencing. So that that statement
4 is incorrect. And it identified chimeric sequences that were formed in that
5 multiplex experiment. That's reported in the Creer reference, and that is the
6 same paper that talked about the sequencing being the ideal breeding ground
7 for chimera formation. Of course, that was understood in the context of
8 multiplex sequencing machines where you're sequencing lots and lots of
9 templates that are very similar to one another all at the same time. And
10 that's what Dr. Spellman explained.

11 Now, on the issues of chimera formation, several things about this.
12 So their argument generally is that it's unknown that chimeras formed on the
13 flow cell. They again did not address the quote in Gloor that we put in front
14 of you and that I talked about at some length. Your Honor is absolutely
15 right. You asked Counsel is there a distinction in terms of why PCR on the
16 flow cell would be different than PCR that occurs anywhere else, PCR in
17 solution or PCR in prep steps. And our expert testified that there would be
18 understood to be no difference. And Counsel referenced the fact that this
19 occurring on -- that the difference is that on the flow cell that you have
20 spots. But as Gloor mentioned and other reference talks about, it was known
21 that those spots actually form adjacent to one another and can even overlap.
22 And as Gloor says, that's how chimeric sequences can form. In a way,
23 you're taking these similar sequences, and you're anchoring them together
24 near one another on the flow cell. And so just consistently, just like the fact
25 that it was well known that PCR could form -- could lead to recombination

1 and lead to chimera formation, that was certainly also true on a flow cell.

2 Now, Counsel spent a fair amount of time talking about the
3 Campbell reference. If we could have a Illumina Slide 31. And they said,
4 well, there's a distinction between the rearrangements reported in Campbell
5 and chimeras. And that's both incorrect and unsupported. Dr. Spellman
6 explained that Campbell described these sequences as chimeras. And
7 Counsel said, no. Actually, Campbell is talking about things like -- things
8 that are unrelated like deletions and duplications and pointed to table 1 in
9 Campbell. Table 1 in Campbell is talking about the biologic chimeras that
10 -- the naturally occurring chimeras. It's not talking about the artificial
11 chimeras that resulted as a consequence of the sequencing workflow. And
12 all of the testimony that Counsel elicited from our expert was just explaining
13 what these things are. It wasn't an admission about anything, about what the
14 Campbell reference act actually discloses. So yes, deletion or a point
15 mutation may be a different type of mutation, but Dr. Spellman certainly
16 never testified that the rearrangements in Campbell are not actually
17 chimeras, including chimeras created on the flow cell. The opposite is true.

18 Counsel also referenced the Maher paper, which I believe is
19 Exhibit 1061, and said that our expert admitted that that was somehow
20 irrelevant because it's talking about optical duplicates. The quote from the
21 -- and this is at Exhibit 1061 at page 8. What Maher says is quote, "Next,
22 we observed that some candidates had identical mate pair reads that were in
23 close proximity on the flow cell. These duplicates were likely an artifact of
24 the analysis pipeline and resulted in overrepresentation of a subset of
25 chimeras." Again, it was specifically talking about chimeras. That's what

1 the paper says.

2 If we could have a -- our Slide 33, please. And I want to return
3 briefly to the Kircher paper that they talked about. If you look at that paper,
4 it's Exhibit 2004 and Counsel read from this paper. At page 7, it talks about
5 false assignments being formed from -- this is Exhibit 2004, page 7 -- from
6 mixed clusters, i.e. clusters originating from two templates. Again, this is
7 consistent with what Gloor explained at page 8, that this is one of the causes
8 that can form chimeric sequences. Furthermore, the Kircher paper does cite
9 the earlier paper that discusses the problem of, for example, jumping PCR
10 and cites all of the other PCR references that talk about chimera formation.
11 So there's a direct line across -- into the prior art. And as Dr. Spellman
12 explained and as Your Honor commented, there's no scientific basis for
13 asserting that chimeric molecules would not form during clustering.

14 JUDGE YANG: So on this jumping PCR and Kircher paper,
15 Counsel for Patent Owner also pointed out on page 3 of the paper where
16 Kircher actually said what they observed there indicated that factors other
17 than jumping PCR was contributing to the fraction of false pairings. And I
18 believe Counsel for Patent Owner would -- argued that that shows that
19 jumping PCR wasn't the -- wasn't recognized as leading to cross-over errors
20 before. And this Kircher paper published after the priority date was the first
21 recognition. So what do you say about page 3, where it mentioned factors
22 other than jumping PCR?

23 MR. RAICH: I think Kircher acknowledges that there are multiple
24 different types of cross-overs that can lead to chimeric sequences, some of
25 which can occur during the prep stages and some of which can occur on the

1 flow cell. And as I just mentioned, that same Exhibit 2004 goes on and talks
2 about mixed clusters being issue -- the issue of these overlapping spots,
3 which was the same issue that was previously identified in the Gloor paper.

4 I want to talk about motivation. So they argued that Parameswaran
5 somehow teaches towards combinatorial indexing instead of unique dual
6 indexing. This is what Parameswaran says about its unique dual-indexing
7 approach. This is Exhibit 1004 at page 8. We have described a, quote,
8 "barcoding approach that allows for the unambiguous assignment of nucleic
9 acid sequences from a mixture of libraries from 48 samples." It then states
10 that there may be additional utility from combining barcodes. That is not a
11 teaching away from the unique dual-indexing approach. I think,
12 respectfully, Counsel is massively overstating what Parameswaran says and
13 the relevance of Parameswaran, which is why papers like Pfreder and Wu
14 and Fuller talk about Parameswaran and its barcoding technique and its
15 applicability to Illumina sequencing.

16 I'd like to talk about reasonable expectation of success. And
17 they've made the argument that a person couldn't have a reasonable
18 expectation of success if they weren't aware of cross-over error occurring on
19 the flow cell. And respectfully, that is absolutely wrong. I mean first of all,
20 it assumes that their claim construction is correct. But Your Honor was
21 absolutely right. There is no dispute in this case that the combination of
22 Parameswaran and Gloor, that that method would in fact reduce cross-over
23 errors regardless of whether they occurred on the flow cell or elsewhere
24 during the sequencing process.

25 And it's holding the prior art to a much higher standard than the

1 patent itself to say that the prior art somehow needed to specifically call out
2 cross-over error when occurring on the flow cell when the method would fix
3 these cross-overs regardless of where they occurred. And just to draw an
4 analogy, for example, this happens in polymorph cases where the polymorph
5 might cite a particular X-ray diffraction pattern. You don't have to have a
6 reasonable expectation of success of specifically what that pattern is in order
7 to have a reasonable expectation of success. Here, a person of skill in the art
8 would have a reasonable expectation of success that the references could be
9 combined to reduce all of these chimeric sequences, including ones that
10 arose on the flow cell. And respectfully, that should be enough.

11 With Your Honor's permission, just two additional quick topics
12 that I'd like to hit. And if we could have Slide 66, please. So this relates to
13 the discarding step. And Parameswaran specifically identifies these
14 sequences as false discoveries. A person of skill in the art would understand
15 that those sequences either were discarded or could be discarded. Why
16 would you want to include false discoveries ultimately if what you cared
17 about was sample assignment? Furthermore, this sentence, one of the
18 sentences that they're relying on, is referring to expected sequence motifs.
19 But we're talking about the perfect unexpected sequences which can't be
20 assigned because the two barcodes don't correspond to any particular sample
21 as originally assigned.

22 Finally, on the public availability of the Gloor reference, just a
23 couple things. I mean, first of all, that Exhibit 1052 that you cited, it really
24 is like a Wayback crawl. I mean, it is a date-stamped article, a date-stamped
25 document that specifically describes the paper, includes the link, the same

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1 link that's printed on the paper, the same link that's available today. It has a
2 description of the paper, and it shows that it was in fact available, which is
3 consistent with, for example, Dr. Gloor's declaration. Dr. Gloor is not an
4 interested party. Dr. Gloor testified about when he submitted the paper,
5 when it was publicly available. And they had the opportunity to depose him.
6 They asked him for his deposition. We made him available, and then they
7 chose not to depose him. But there's no reason to doubt any of the
8 statements in his sworn declarations. I see that I'm over time. Does anyone
9 have any further questions? Otherwise, we will stand at our briefing and
10 respectfully request that all of the challenge claims are held
11 (INDISCERNIBLE).

12 JUDGE YANG: Judge Reimers, any questions?

13 JUDGE REIMERS: Nothing for me. Thank you.

14 MR. RAICH: Thank you, Your Honors.

15 JUDGE YANG: So Patent Owner, you had about three minutes
16 left. We gave Petitioner a few extra minutes. So we'll put in six and a half,
17 something like that. So go with that (CROSSTALK) --

18 MR. MATTY: I appreciate it. Thank you, Your Honor. I'll just
19 walk through a couple of the issues that we just heard about in order to. So,
20 first, on claim construction, I think it's confirmed there is no dispute that
21 every figure, every embodiment in this patent is consistent with Patent
22 Owner's construction. We haven't heard any example coming from the
23 figures or the embodiments that conflicts with the requirements that these
24 chimeras were talking about be formed during cluster amplification.

25 And so Petitioner hasn't provided any reason for including the one

1 limitation from every example that they like, which is that these are
2 chimeras formed from template nucleic acids derived from different samples
3 but excluding the second feature that's also true of every example, which is
4 that those chimeras are formed during cluster amplification. It's not
5 improperly reading in an embodiment. It's staying true to the specification.

6 And we also heard, I think for the first time, that the term cross-
7 over error is used all over the prior art. If Your Honor looks through the
8 claim construction sections of the briefing, the supporting sections of Dr.
9 Spellman's declaration, you won't find any of that. There wasn't any
10 evidence of prior art actually using cross-over error. That's why both
11 experts and both parties were addressing the disclosures and the
12 specification.

13 Second, for Exhibit 1015, which is the Maher paper, this is the
14 paper that Counsel highlighted as using Illumina machines and talking about
15 jumping PCR. It talks about jumping PCR at page 9 of that exhibit, and it
16 cites the Meyerhans paper, which is another exhibit in this proceeding. This
17 is just another example of awareness that jumping PCR can happen during
18 initial PCR steps. There is no awareness of chimeras being formed on the
19 NGS platform, even in the Maher paper. And we know that because at page
20 9 of Maher, when they talk about jumping PCR, they suggest ways to deal
21 with it are to limit the initial PCR to do the sequencing without amplifying.

22 In other words, getting rid of just that initial PCR step where
23 jumping PCR was thought to happen. You'd still go through the sequencing.
24 You'd still go through the Illumina machine. It didn't say anything about
25 concerns of jumping PCR happening at those stages. This highlights that

1 they thought this was limited to an initial PCR steps issue, not something
2 that's happening on the sequencer.

3 I think it's important in the paper because of that they still use the
4 single barcoding that couldn't detect this problem. And maybe an important
5 additional point here to keep in mind. The authors on Exhibit 1015 are
6 Maher and Kircher. And those are the same authors that are on Exhibit
7 2004. On the Kircher paper, you see Kircher and Maher. And we know in
8 that paper they themselves, despite what they had said in 2008, 2009 in
9 Exhibit 1015, in 2011, when they published about this happening on
10 Illumina machines, they said, you know what? This is our first realization
11 there's something other than jumping PCR going on here. So I think it's
12 important that it was those very same authors on that later paper in Exhibit
13 2004.

14 A point on the Campbell reference, there was a distinction made
15 between the biological rearrangements and the artificial rearrangements that
16 Campbell discusses. There is nothing in the record here, nothing in
17 Campbell, nothing in Dr. Spellman's declaration, nothing in his testimony to
18 explain how the artificial rearrangements would somehow be referring to
19 different types of rearrangements than the biological rearrangements that are
20 discussed in Campbell. It uses the term rearrangement interchangeably.
21 And we know from the Varela paper published by the same group, they're
22 talking about intramolecular rearrangements throughout their discussions of
23 rearrangements in their studies.

24 Then on the Kircher paper, again, as we've noted, the Kircher
25 paper was key for identifying some surprise by that group that there was

1 something different going on other than just jumping PCR in the studies that
2 they ran in the Illumina machine. If this was just an issue of jumping PCR,
3 there would have been no surprise. There would have been no reason for
4 them to get a much higher fraction of incorrect indexes than they expected
5 from simply jumping PCR. That's exactly what they noted in their paper in
6 2011. There's something different going on here. It was an issue that wasn't
7 appreciated previously.

8 Then finally, I'll close on Parameswaran and Parameswaran urging
9 the use of combinatorial dual indexing after running its studies. The
10 important point here is that Parameswaran saw its unexpected mismatches as
11 such a small error that it urged going to an approach that couldn't even detect
12 those sequences in the first place, combinatorial dual indexing. What
13 Parameswaran teaches is that there's nothing wrong here. We can go use
14 CDIs and sequence up to, I think it was 2300 samples with the same number
15 of barcodes that we used to sample 48 barcodes. It's pushing efficiency. It's
16 pushing higher throughput. It's pushing greater multiplexing through the use
17 of CDI after determining that these unexpected mismatches aren't going to
18 affect your analysis.

19 And I want to be clear. Counsel mentioned teaching away. We
20 know that evidence like this does not need to rise to the level of teaching
21 away to be relevant. You have to consider reasons to combine, reasons to
22 modify in balance with reasons not to combine and reasons not to modify.
23 That's discussed in detail in the (INDISCERNIBLE) case that's cited
24 throughout the briefing. So with that, unless Your Honors have further
25 questions, we'll rest on our papers for any remaining (INDISCERNIBLE).

1 JUDGE YANG: I actually do have a question. So I'd like you to
2 address Petitioner's argument about the Fuller paper. That is authored by
3 one of the co-inventors, Exhibit 1059, where it specifically discussed the
4 Parameswaran reference in the context of Illumina's platform.

5 MR. MATTY: Yeah. Yes, Your Honor. So Fuller is sort of an
6 overview paper. It's talking about pyrosequencing, talking about Illumina
7 sequencing. It's talking about various NGS approaches and sample
8 preparation methods. It's a general overview of NGS methods. And it says,
9 this is from page 1, they're presenting views of some of the investigators
10 who received grants on underlying limitations and challenges of next-
11 generation sequencing with the goal of informing and engaging the broader
12 community.

13 And the focus of Fuller was how to address costs with these
14 machines. This is again going back to 2008, 2009. These are machines that
15 are in sort of research labs. People are trying to figure out how to make
16 them efficient, how to make them commercially applicable. And Fuller
17 explains that the cost of NGS was prohibitive and highlighted the need to
18 reduce costs in order to make NGS more accessible to genomic researchers.
19 It talks about that in its abstract. And Fuller does not mention the use of
20 unique dual indexes or using Parameswaran's specific UDIs.

21 Instead, Fuller cites Parameswaran merely as one example of
22 multiplexing with tagging in order to sequence multiple samples together as
23 a cost-saving mechanism. That's what they say at page 3. One option would
24 be an effective technology to judiciously add sequence tags. You can start
25 using tagging to try to multiplex and get at this cost issue that is the focus of

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1 Fuller. And that's really the import of the paper. It's the focus, and it's what
2 they're talking about in the one sentence that Petitioner has quoted because it
3 cites Parameswaran.

4 JUDGE YANG: I don't have anything else. Judge Reimers?

5 JUDGE REIMERS: Nothing for me. Thank you.

6 JUDGE YANG: We would like to thank the parties. Both sides
7 did a great job, and I actually enjoyed today's argument. I learned a lot from
8 both of you, so thank you for that. This case is submitted, and we will issue
9 -- actually, these two cases. Let's not forget about the '200 patent. These
10 two cases are submitted, and we will issue the final decisions in due course.
11 We are adjourned. But I would like to ask Counsel to stay for Ms. Reporter
12 in case she needs some help.

13 (Whereupon, the above-entitled matter went off the record at
14 approximately 3:24 p.m.)

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