

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,
Petitioner

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00015 (Patent 10,036,012 B1)
IPR2025-00016 (Patent 10,876,108 B1)

Record of Oral Hearing
Held: January 22, 2026

Before GEORGIANNA W. BRADEN, ZHENYU YANG, and TIMOTHY
G. MAJORS, *Administrative Patent Judges*.

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The above-entitled matter came on for hearing Thursday, January 22, 2026, commencing at 12:35 p.m. EST, at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

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

12:35 p.m.

THE BAILIFF: All rise.

JUDGE YANG: Good afternoon. This is the consolidation hearing for IPR 2025-00015 and 00016. I am still Judge Yang and with me still are Judges Braden and Majors. I see we have a different lineup for the afternoon, so let's start with counsel introduction starting from Petitioner, please.

MR. HOAGLAND-HANSON: Thank you, Your Honor. Kevin Hoagland-Hanson from Williams & Connolly on behalf of petitioner Integrated DNA Technologies. With me at counsel table and participating in the argument is my colleague, Anna Searle, also from Williams & Connolly. And in the gallery, we have Jessamyn Berniker, Tom Fletcher, Patrick Hynds, and Nicholas Vincent from my firm, as well as Mike Levy (phonetic) from IDT.

JUDGE YANG: Welcome. Patent Owner, please.

MS. CIPRIANO: Good afternoon. I am still Linnea Cipriano from Goodwin, representing Patent Owner Tecan Genomics. With me at counsel table is T.J. Beavers -- Timothy Beavers, also at Goodwin who will be joining me in the argument. In the gallery, we have John Padro, Scott -- and Scott Weingaertner from Goodwin, and from Tecan Genomics, Andreas Shield.

JUDGE YANG: Thank you, and welcome everyone. I understand for the afternoon session, both Petitioner and Patent Owner would each have a LEAP practitioner, correct?

MR. HOAGLAND-HANSON: Yes.

1 JUDGE YANG: All right. In that case, each party would have 75
2 minutes to present your argument. Everything else, in terms of format, how
3 you should conduct yourself, what Judge Braden said this morning still
4 applies. I will only point out one thing. Since this is a consolidated hearing,
5 if there is any argument that only applies to one of the cases, please let us
6 know. Other than that, I don't have anything else.

7 Do either of you have any questions? All right, then Petitioner, how
8 much time would you like to reserve if you want to reserve any time for
9 rebuttal?

10 MR. HOAGLAND-HANSON: We would like to reserve 15 minutes
11 for rebuttal.

12 JUDGE YANG: All right. That gives you 60 at this time. We are
13 ready for you whenever you are.

14 MR. HOAGLAND-HANSON: Thank you, Your Honors. Good
15 afternoon. Kevin Hoagland-Hanson from Williams & Connolly on behalf of
16 Petitioner. I want to start here on Slide 2 with Patent Owner's Responsive
17 Brief. And what this shows is that Patent Owner concedes that most
18 limitations of the Challenge 012 and 108 patents are anticipated by Meyer.
19 The sole dispute, as can be seen here on Slide 2, is the proper construction of
20 the enrichment terms that are found in both -- in the claims of both patents,
21 and whether Meyer discloses those terms as properly construed. In a
22 moment, my colleague Anna Searle will address the claim construction
23 issues, and then I will return to the podium to explain why the record
24 evidence shows that Meyer anticipates or renders obvious all of the
25 limitations of the claims, including the enrichment limitations.

1 Before we get to what's in dispute, though, it's important to focus on
2 what Tecan concedes here. Both of these patents are directed to methods for
3 sequencing an enriched nucleic acid sequence of interest, and both of these
4 patents set out chemical manipulations that must be performed in order to
5 practice the claim. And at this point in the proceeding, Tecan concedes that
6 the 3'-end fragments that are used in the Meyer method undergo every single
7 chemistry step that's recited in the claims of both the 012 patent and the 108
8 patent. There's no dispute that the 3'-end fragments undergo the recited
9 ligation, annealing, extension, amplification, surface annealing, and
10 sequencing steps, and that all of the requisite primers and adapters, they're
11 all found in Meyer. The only dispute is whether or not Meyer does these
12 steps for the right purpose and with the right result, which is to enrich for the
13 nucleic acid sequence of interest.

14 And this enrichment term appears several different places in the claim
15 -- in Claim 1 of both patents, but the parties appear to agree that each of
16 these terms sort of all rise and fall together. Enrichment throughout the
17 claims of both patents means the same thing, and it doesn't matter if it's --
18 you know, if we're talking about to enrich for the nucleic acid sequence of
19 interest here in the 012 Claim 1, or when enriched is recited again in Step
20 1F, or whether we're talking about the thereby enriching term of Step 1C of
21 the 108 patent. The parties agree that all of these issues rise and fall
22 together.

23 And now I'll turn it over to Ms. Searle to first address the proper
24 construction of all of these enrichment terms.

25 MS. SEARLE: Good afternoon, Your Honors. Anna Searle for
26 petitioner IDT, and as my colleague previewed, I'll be addressing the

1 enrichment term -- the proper construction of the enrichment term. So as my
2 colleague previewed, the central claim construction dispute in this case
3 centers on how to properly construe the term "enrich", which appears in
4 Limitation D of Claim 1 of the 012 patent, and also in the analogous
5 limitation C of Claim 1 of the 108 patent.

6 So limitation D is part of a series of chemical manipulations that are
7 recited by the patent that must be performed on a single nucleic acid
8 fragment, which contains the sequence of interest. And the purpose, the
9 claim explains, of these chemical manipulations is to enrich for that
10 sequence of interest that's contained in the initial starting nucleic acid
11 fragment, so that the sequence can be sequenced on a massively parallel
12 sequencer or a next generation sequencer, which sequences millions of
13 fragments at the same time. So in order to generate a signal that can be
14 detected, you can't just have one fragment, you need many, many fragments.

15 So Limitation D -- these steps -- these chemical manipulations sort of
16 culminate here in Limitation D, which is pictured -- which is reproduced on
17 Slide 9, with amplifying, that is, making many, many more copies of that
18 fragment that contains the sequence of interest, as the claim explains, in
19 order to enrich for the nucleic acid sequence of interest. So because the
20 claim sort of sets out what it is that is required for enrichment, in the parties
21 -- in the petition and in Tecan's preliminary response, neither party proposed
22 a special construction for this term "enrich".

23 And the Board in its institution decision similarly agreed, as you'll see
24 from this excerpt from the Board's institution decision on Slide 12, and that's
25 Paper 9 at 15. The Board agreed that it saw no reason to adopt any special
26 meaning for this term "enrich", and it adopted the plain and ordinary

1 meaning, which it defined according to the dictionary definition to mean "to
2 process so as to add or increase the proportion of a desirable ingredient."

3 So as my colleague, Mr. Hoagland-Hanson, will explain in a moment,
4 the record demonstrates that the Meyer method adds or increases the
5 proportion of 3'-end fragments in a number of different ways. Perhaps
6 recognizing this, on Tecan's Patent Owner Response, despite claiming that it
7 does not dispute the Board's construction and it agrees that the plain and
8 ordinary meaning construction should be used, Tecan sought to narrow that
9 construction by introducing a number of unrecited limitations, including
10 limitations that restrict exactly how that increase in proportion has to be
11 measured and specifically what the increase in proportion has to be
12 measured relative to.

13 Now, those limitations aren't present in the claim, but at this point on
14 this record, Your Honors, frankly, it doesn't matter to the outcome of the
15 proceeding whether the Board adopts its original construction of the plain
16 and ordinary meaning or this construction that Tecan puts forward in its
17 Patent Owner Response.

18 Regardless, as my colleague will explain, the record following Dr.
19 Bustamante's deposition, that is, a deposition of Tecan's expert, demonstrates
20 that Meyer increases the proportion of 3'-end fragments in exactly the
21 manner that Tecan says is required by the claim based on its own proposed
22 construction, that is, increases the proportion of nucleic acid fragments
23 containing the sequence of interest relative to other fragments in the sample.

24 So this I've reproduced on Slide 15, and this is a quote from Tecan's
25 Patent Owner Response at Page 21, I believe. So perhaps recognizing this,
26 the factual record puts Tecan in a little bit of a difficult position because

1 Tecan doesn't dispute and cannot dispute that the plain and ordinary
2 meaning should be adopted. Tecan insists that it doesn't dispute the Board's
3 construction of that term, and yet, Tecan needs a way to exclude from the
4 scope of the claim the Meyer method, in which the parties agree each of the
5 required and recited chemical manipulations in the claim occur.

6 So what Tecan does is Tecan insists it has not changed its
7 construction, it stands by its Patent Owner Response construction, and yet,
8 Tecan seeks in various ways throughout its briefing to impose an additional
9 unrecited negative limitation that excludes from the scope of the claim,
10 categorically, any method in which the fragments that don't contain the
11 sequence of interest are amplified at the same time as fragments that do
12 contain the sequence of interest.

13 JUDGE YANG: On claim construction, I have this question, -- when
14 we are talking about the proportion and especially in view of the Meyer
15 reference, which we're talking about the 3' fragment, are we comparing the
16 after amplification with the before amplification, or are we talking about
17 after amplification versus without the Meyer's method?

18 MS. SEARLE: So Your Honor, I think my colleague will get into this
19 more, and this is an important question because I -- this is a source of a lot of
20 confusion if -- Petitioner's position is that it doesn't matter which of those
21 you are comparing to, and the record evidence shows that Meyer shows an
22 increase in the proportion of the 3'-end fragments, whether you're measuring
23 relative to the proportion at which those fragments were present in the
24 original sample, whether you're measuring relative to other fragments that
25 were amplified alongside it in the Meyer method, or whether you're

1 measuring relative to what would happen if you hadn't performed any of the
2 method steps.

3 Petitioner's position is that the record demonstrates that the proportion
4 of 3'-end fragments increases relative to all of those benchmarks. At the
5 same time, Petitioner's position is that any of those benchmarks can be used
6 to measure the increase in proportion because the claim doesn't specify and
7 the patent doesn't specify any specific benchmark or baseline that the
8 increase in proportion has to be measured relative to, although Petitioner's
9 position at this point is that -- sort of more of an academic dispute and
10 Petitioner does not believe that that will impact the outcome of the
11 proceedings. I hope that answers Your Honor's question.

12 JUDGE YANG: Yes. Thank you.

13 MS. SEARLE: And so returning to here to Slide 16, Tecan insists
14 that it's not importing a negative limitation, but regardless of what Tecan
15 wants to call this, Tecan is seeking to exclude from the scope of the claim
16 methods that operate in a certain way, and that negative limitation is
17 nowhere to be found in the claims. It's contrary to the rest of the intrinsic
18 record, and it's also contrary to expert testimony from Tecan's own expert in
19 this proceeding. So Petitioner's position is that the plain and ordinary
20 meaning of enrich, whether it's the Board's construction or Tecan's POR
21 construction, should control, and nothing more is required beyond meeting
22 each chemical manipulation of the -- that's recited in the claim and enriching
23 according to that plain meaning.

24 And this is -- interpreting enriched according to its plain meaning is
25 supported by all of the evidence in the Phillips hierarchy, starting with the
26 claim language.

1 So here on Slide 20, we've reproduced Claim 1 of the 012 patent, or
2 excerpts from Claim 1 of the 012 patent and excerpts from Claim 1 of the
3 108 patent. And as Your Honors will see, both of these claims start with the
4 preamble, which explains this is a method for sequencing an enriched
5 nucleic acid sequence of interest. And then the claim itself lays out exactly
6 what needs to happen for that enrichment to occur. So the claim lays out
7 step by step in Limitations A through D of Claim 1 of the 012 patent what
8 these chemical steps are, and the claim explains that the reason you perform
9 these steps, culminating and amplifying, is in order to enrich for the
10 sequence of interest, which is contained in the nucleic acid fragment that you
11 start with.

12 And this is further confirmed here in the language of Claim 1 of the
13 108 patent, which specifically explains that by annealing, extending, and
14 amplifying, you are -- and I'll direct Your Honors to this direct quote from
15 Claim 1, Limitation C of the 108 patent, You are "thereby enriching the
16 nucleic acid sequence of interest," and the reason you're doing that is
17 because, as the claim states, you are "generating amplified products that
18 comprise that sequence of interest."

19 JUDGE YANG: So the to enrich language as well as the thereby
20 enriching language both appear in step -- the amplifying step. I think Patent
21 Owner's argument is that the enrichment has to be the result of amplification
22 and amplification alone. And I understand Petitioner is arguing that's not the
23 case and the enriching is the end result of all of the above steps.

24 Can we -- can you explain your position here?

25 MS. SEARLE: That's right, Your Honor. So Petitioner's position --
26 and you'll hear Tecan say that Petitioner is seeking to read out this limitation

1 of amplifying to enrich. But Petitioner's position is that each of the steps
2 that's recited in the claim -- all of them -- need to be met, and they need to
3 result in enriching according to the plain meaning of the term. That is, after
4 you've performed all these chemical steps, you do need to show that you've
5 increased the proportion, as Tecan says, perhaps relative to other fragments.

6 But once you've proven that you have met each of the limitations of
7 the claim, and you've shown that you've increased the proportion relative to
8 other fragments, there is nothing else that's required by the claim. The claim
9 doesn't have any limitation, and I'll put up the whole language of the claim
10 in a moment. There's nothing in the claim saying that you have to measure -
11 - you have to take a measurement right before the amplification step and
12 then measure against that.

13 The claim is silent as to any of Tecan's negative limitations it's
14 seeking to import, regardless of how Tecan phrases them, and Tecan does
15 phrase them in a number of different ways. But Petitioner's position is that
16 the claim requires each of the recited chemistry steps and that they must
17 result in enrichment according to its plain meaning, which all parties agree --
18 appear to agree that enrichment should have its plain meaning.

19 JUDGE YANG: Not to dwell on this, but again, the enrich language
20 is in the amplifying step. So why should we read this to -- well, to separate
21 the amplification from the enrichment, meaning why shouldn't it be, you
22 know, you perform whatever manipulation you need to do, A, B, C, and
23 others, given the comprising language, but when you amplify, you enrich the
24 sequence of interest?

25 MS. SEARLE: And so Your Honor, I think I may have
26 misunderstood your question. We agree that the amplification does need to

1 lead to the enrichment and the amplification necessarily leads to enrichment
2 because if you didn't amplify your fragment, if you didn't create
3 exponentially more copies of your fragment, there's no way that that
4 sequence of interest that's contained in that fragment would be increased
5 relative to other sequences in your sample. Because if the sequence isn't
6 amplified, you won't have representation of that sequence at the end of the
7 method.

8 So the amplification step, as Dr. Sims testifies extensively, is
9 absolutely critical to enrichment. There's no possible way that the increase
10 in proportion that's required by the plain and ordinary meaning of the term
11 enrich -- that would not occur in -- without the amplification steps. So the --
12 it does need to result from the amplification step, as well as the proceeding
13 steps that configure the fragment of interest so that it has the correct adapters
14 on it, and so that when you amplify, you are amplifying all the fragments
15 that have the sequence of interest.

16 JUDGE YANG: Okay. In the --sur-reply Patent Owner said
17 Petitioner conflate amplification with enrichment. So here's an example,
18 right? In the starting material, there are three components, A, B, C, that say
19 it's 30 percent, 50 percent and 20 percent. You do PCR and it -- they all get
20 amplified and the end result is still 30 percent, 50 percent, and 20 percent.
21 Anything got enriched?

22 MS. SEARLE: I -- petitioner's position is that in that situation, there
23 is no enrichment.

24 JUDGE YANG: Okay.

25 MS. SEARLE: You do need to show at the end that you have
26 increased relative to the rest of the fragments. So in Your Honor's example,

1 if you had 30 percent -- you're testing my math a lot here, but 30 percent, 50
2 percent, and 20 percent. Say the sequence of interest was the 30 percent
3 one. If at the end of that amplification process where they're all amplified,
4 the sequence of interest has been amplified to a greater degree so that it has
5 then increased to 35 percent of your total sample and the other fragments
6 have been decreased relative to that despite having also been amplified, then
7 that meets the enrichment requirement. But we would agree that if it is truly
8 unbiased amplification, that does not result in an increase in the proportion,
9 and so that does not meet the plain meaning of enrich.

10 JUDGE YANG: Okay. Thank you.

11 MS. SEARLE: And I'd just like to underscore here on Slide 31, that
12 again, ostensibly, there is no dispute that the plain meaning of enrich is all
13 that's required by the claim, and that the Board's construction -- Dr.
14 Bustamante testified here, as we've excerpted on Slide 31, the Board's
15 construction accurately captures what the POSA would understand to be the
16 plain meaning of enrich, and further, Dr. Bustamante testified that the POSA
17 would understand that enrich used in this claim has its plain meaning. It
18 doesn't require anything more than the plain meaning. And this is also
19 consistent with the rest of the intrinsic record. So throughout -- nowhere in
20 the specification or the file history is there any disclaimer or lexicography or
21 language that seeks to restrict the scope of the plain meaning of enrich.

22 And so there's -- I'm now on Slide 33 of the presentation. There is no
23 definition anywhere in the patent of what enrich or enriching means or what
24 enrichment means. There's no language that seeks to narrow the scope of
25 enrichment. There's no explanation for how enrichment should be
26 quantified. There's no minimum threshold amount of enrichment that's

1 required. In fact, there's no sequencing data or enrichment calculations at all
2 anywhere in the patent. There's no data at all in this patent, although it's a
3 patent that claims a method of sequencing.

4 And I'd like to direct Your Honors to excerpts from the 012 patent and
5 the 108 patent here on Slide 34, where this same language, enrich, is used in
6 the specification, and what you'll notice is it's used in the exact same manner
7 that it's used in the claim to describe the result of the immediately preceding
8 chemistry steps, to explain that you are performing these chemical
9 manipulations in order to enrich or thereby enriching the sequence of interest
10 that's contained in your fragment.

11 Now, in Tecan's argument that fragments other -- that do not contain
12 the sequence of interest cannot be amplified alongside fragments containing
13 the sequence of interest, even if the sequence of interest is amplified to a
14 greater degree relative to those other fragments -- in making that argument,
15 Tecan is effectively attempting to impose a minimum threshold amount of
16 enrichment. Tecan's effectively saying that unless you've enriched to an
17 exponential degree relative to the -- these other fragments, that doesn't meet
18 the term enrich. But as Tecan's own expert conceded, the patent itself
19 doesn't set hold -- does not set out any threshold amount by which the
20 fragment has to be enriched at the end of the method. Under the plain
21 meaning of enrich, you simply have to show that there is a higher relative
22 proportion of the sequence of interest relative to other fragments.

23 Now, Tecan's unrecited limitation restricting amplification of other
24 fragments. Tecan introduces this, as I mentioned, in a couple of different
25 ways. Tecan does not acknowledge that this is specifically part of its
26 proposed construction, and Tecan denies that this is a negative limitation,

1 but its statements elsewhere in its briefing are pretty clear. So in Tecan's
2 Patent Owner Response, outside of its claim construction section, Tecan
3 says -- this is Paper 41 at Page 16, "The claims require that the sample
4 include fragments in the solution that do not contain the sequence of interest
5 and that those fragments are not amplified."

6 But that language is nowhere to be found in the claim, and critically,
7 it's nowhere to be found in Tecan's proposed construction. So here, on sur-
8 reply, I'm now on Slide 40 -- and I've included an excerpt from Tecan's sur-
9 reply. That's Paper 53 at Page 9. Tecan appears to double down on this
10 negative limitation, although the language is a little bit difficult to parse.
11 Tecan states, "Petitioner incorrectly alleges that Tecan seeks to import the
12 limitation that only the oligo extension products from Step C undergo the
13 claimed amplification from Figure 1."

14 So Tecan is very vague about what exactly it contends is incorrect
15 about this statement. Is it Tecan's position that there is a requirement -- that
16 there isn't a requirement in the claim that only the extension products
17 undergo amplification, or does Tecan dispute that that requirement is
18 actually a limitation, or does Tecan dispute that that limitation was
19 improperly imported from Figure 1? It's unclear, but what is clear is that at
20 the very end of the same paragraph, Tecan doubles down on its own
21 negative limitation when it states that Limitation 1D is not met by methods
22 in which all fragments undergo amplification. This is confirmation that
23 Tecan is seeking to import this limitation into the claim, and Tecan knows
24 that these words are not present in the claim, so Tecan says -- again on this --
25 from the same excerpt, "This is not an added limitation, but simply how the
26 invention functions."

1 But Your Honors will see that simply how the invention functions is
2 not a basis for importing the limitation into the claim, and the Federal
3 Circuit has rejected this exact argument. So in *Purdue Pharma*, that's 438 F.
4 3rd, 1123 at 1135, the Federal Circuit considered a situation in which the
5 district court construed a term to include an efficacy limitation that was not
6 present in the language of the claim itself, and -- similar to what Tecan seeks
7 to do here.

8 And the trial court justified the importation of this efficacy limitation
9 by stating, "Although there's no claim limitation to that effect, that's how the
10 invention itself operates." The Federal Circuit rejected this reliance on how
11 the invention itself operates by the trial court and the Federal Circuit held
12 that without any specific claim language to interpret, the trial court, in
13 importing this limitation, had impermissibly imported a limitation into the
14 claim. And here, Tecan seeks to do the same thing. There is no limitation in
15 the claim that restricts what does or does not happen to fragments other than
16 the single fragment that tracks each step of the claimed method.

17 So here on Slide 44, I've reproduced the entirety of Claim 1 of the 012
18 patent. It's a lot of -- it's a long claim. There's a lot here, and there's a lot of
19 language here for Tecan to try to find a home for its unrecited limitation, and
20 I hope that Tecan will identify for the Board where it is that it finds a home
21 for any language that restricts amplification of other fragments, because as
22 Your Honors will see, the claim is recited from the perspective of a single
23 nucleic acid fragment and steps and chemical manipulations that happen to
24 that fragment in order to enrich the sequence of interest that's contained in
25 that one fragment. And this is further confirmed by the language of Claim 1
26 of the 108 patent, which I've reproduced here on Slide 45.

1 So similar to the 012 patent Claim 1, again, this claim refers
2 repeatedly to a single nucleic acid fragment and what happens to that
3 fragment. And although the reaction -- the claim acknowledges that the
4 fragment is present in a mixture of multiple fragments, you'll notice that the
5 claim does not go on to say anything about what does or doesn't happen to
6 those other fragments. It only speaks with respect to a single fragment. And
7 Tecan points to several places in the specification to try to find some hook
8 for limiting the meaning of enrich.

9 Tecan cites to portions of the specification that refer to something
10 called targeted enrichment, but again, the claim recites enrichment, not
11 targeted enrichment, and Tecan does not identify any definition anywhere in
12 the patent of either enrichment or targeted enrichment. Neither term is
13 defined. Tecan similarly speaks of selective enrichment, but again, the
14 claim is to enrichment, not selective enrichment, and there is nowhere in the
15 claim -- and nowhere in the patent is selective enrichment defined.

16 Finally, Tecan refers to fold enrichment, and they selectively quote
17 from a passage in Example 1 that describes fold enrichment. They eliminate
18 the word fold, and they state that this is how fold enrichment is calculated.
19 Fold enrichment is a term of art, and notably, Tecan does not include any of
20 the language if it -- to the extent it contends this is definitional, Tecan
21 doesn't include any of this language in its own proposed construction for
22 enrich.

23 Finally, Tecan's proposed negative limitation would require limiting
24 the claim to its preferred embodiment, which is improper. Tecan goes so far
25 as to say that its commercial embodiment is coextensive with the claimed
26 method without any supporting analysis from its expert. All of Tecan's

1 references -- Tecan cites two passages of the specification that state -- in
2 support of its limitation, precluding amplification of other fragments, but
3 both of these excerpts from the specification are referring to the preferred
4 embodiment. They're referring to how Figure 1 operates.

5 And notably, these only further confirmed that if the patentee had
6 wanted to include these negative limitations in their claim, they knew
7 exactly how to draft them because they are there to describe the preferred
8 embodiment. This only further confirms that the patentee intentionally
9 drafted a broader claim to cover more than just the preferred embodiment.
10 But perhaps the best evidence that the scope of the claim is broader than the
11 preferred embodiment is Tecan's positions in district court where Tecan -- as
12 Dr. Bustamante explains at in his declaration, Exhibit 1085, from Paragraphs
13 114 to 120, and as you'll see here on Slide 59, Tecan seeks to claim that
14 IDT's method, which it is undisputed, includes an additional amplification
15 step that Tecan doesn't map onto any limitations of the claim and clearly
16 differs from the preferred embodiment. Tecan claims that that method falls
17 within the scope of this claim. So Tecan can't have it both ways. Either the
18 claim is coextensive with the preferred embodiment or it isn't. Unless Your
19 Honors have any questions, I'll turn it over to my colleague to discuss
20 anticipation.

21 MR. HOAGLAND-HANSON: Thank you, Your Honors. I just want
22 to start very briefly with the chemistry that's actually disclosed in Meyer.
23 And what we have on Slide 61 is Dr. Sims's testimony, our expert, about
24 how the Meyer chemistry works. And specifically, Dr. Sims explains that
25 Meyer used special chemistry to target the 3'-end fragments. And that
26 special chemistry included an extra primer in the reaction that's unique to

1 those fragments and specifically targeted them. And there's no dispute at
2 this point that this is the same chemistry using a unique primer that's recited
3 in the claims of the patent. Tecan doesn't say, oh, there's -- you know,
4 Meyer doesn't have this primer or that primer. And Dr. Sims likewise
5 explained that it's this special chemistry, the same chemistry recited in the
6 claims, that's responsible for enrichment.

7 I just want to go back briefly to what Tecan's proposed construction
8 is. And we think that we win under Tecan's proposed construction.

9 Under Tecan's construction, all that has to happen is there has to be an
10 increase in the 3'-end fragments relative to other fragments in the sample.
11 And under that standard, Meyer enriched in multiple senses. They criticize
12 us for this -- in brief, they say, oh, we have multiple ways that it enriches
13 and say you have to pick one. Not so. And our position on this hasn't
14 changed. There is no comparator recited in the patent for enrichment, and
15 all of the ways that I'm about to talk about meet Tecan's interpretation.
16 There is enrichment of a fragment relative to other fragments in the sample.

17 The first and the simplest is that Meyer only enriched for some
18 mRNAs. Meyer did not amplify or target DNA; it didn't target other kinds
19 of RNA; and it didn't target many, many fragments in the sample that
20 undisputedly either got the wrong adapters or didn't get adapters at all. None
21 of those fragments are amplified.

22 And so in Judge Yang's metaphor from a moment ago, it's not just the
23 case that there are only three fragments in the sample here. There are lots
24 and lots and lots of fragments, and many of them don't undergo
25 amplification. And the method is a method of enrichment of the 3'-end
26 fragments compared to all of those fragments that don't undergo the reaction.

1 JUDGE YANG: In that case, what is your sequence of interest? The
2 entire mRNA group?

3 MR. HOAGLAND-HANSON: Yeah. So another key thing here is
4 that sequence of interest is not defined in the patent. The sequence of
5 interest is just whatever you're trying to enrich, right? And there's no dispute
6 that in Meyer, they were interested in anything at the 3' end of the mRNAs,
7 right? And so all of those mRNAs that are being amplified are sequences of
8 interest compared to, for example, all the ribosomal RNA that's in there, all
9 the genomic DNA. All that stuff is getting left behind. It's only the
10 sequence of interest at the 3' end that's being enriched.

11 And I just want to also be clear that even if the claim required, and
12 this limitation is not there, but even if the claim required enrichment relative
13 to sort of other things that are also being amplified as part of the
14 amplification step, Meyer's data is clear. And this is the math that you're
15 going to hear a lot about today. Meyer found that its method, when
16 sequenced at the end, they observed the 3'-end fragments, right? And they're
17 looking for a specific sequence that's found in those fragments, in 16 percent
18 of the raw reads. That's more than what they said would have been the
19 expectation from unbiased amplification, 10 percent.

20 Meyer's data itself reported an increase in the number of 3'-end
21 fragments proportional to the expected number, and also necessarily
22 proportional to the other pieces of the mRNA, because -- which are sort of
23 necessarily less prevalent here, right? Because if they're expecting 10
24 percent of each piece and instead they see 16 percent of one end, the others
25 have been sort of necessarily decreased. This is in Judge Yang's metaphor, I
26 think, the 35 percent versus the 30 percent in the original sample, right? If

1 you started with 30, 20, 50, and you end up with, and I'm going to try to do
2 this, 35 and then you decrease the others by 2 and a half percent, you know,
3 sort of necessarily, that's sort of exactly what's being reported here in Meyer.

4 Now you're going to hear that no expert testified that this data was
5 evidence of enrichment, but that's not right. Dr. Sims explained that the --
6 that this data was evidence of enrichment multiple times in his declaration,
7 Exhibit 1085; for example, at Paragraphs 145 and 184. And likewise, Dr.
8 Meyer, the first author on the reference, and Tecan's paid expert in this
9 litigation, agrees that this data was appropriate to evaluate whether the issue
10 of under-representation was resolved. And I'll talk about that in a moment.
11 But there's no question that Dr. Meyer testified that you could use this data
12 and that the data was included in the paper for the purpose of explaining the
13 relative proportion of the mRNA fragments.

14 And it's the amplification step, I want to be clear here, that leads to the
15 enrichment that the Meyer authors saw. There -- Tecan says that, oh, this
16 was just because the authors resolved the homopolymer problem. And the
17 homopolymer problem was an issue with these types of 454 sequencers
18 where when you had a sequence with a repeated nucleic acid, as here where
19 you have the poly(A) tail, which has a bunch of adenines or Ts basically in
20 repetition, that you would then somehow blind the sensor and see less of
21 those fragments. In other words, you might see less than the expected 10
22 percent.

23 But resolving the homopolymer problem can only bring you back up
24 to 10 percent. No one has explained how, and the only evidence in the
25 record of how you can get from 10 percent up to 16 percent is Dr. Sims'
26 explanation that that's because of the extra primer that you're using in the

1 amplification step. And that's why the amplification leads to the enrichment.
2 The amplification step is the only thing here that increases the relevant -- the
3 relative prevalence of the 3'-end fragments.

4 And what about Dr. Bustamante? We're going to get in a moment to
5 all of his criticisms of the data and the ways in which he says we should
6 rewrite the reference. None of those are appropriate, but when we asked
7 him, what's the POSA's expectation about the relative prevalence of the 3'-
8 end fragments, taking into account all of the data in the patent and all of his
9 criticisms, and he said it was 13 or 14 percent. 13 or 14 percent is still less
10 than 16 percent, and this is Dr. Bustamante acknowledging that even though
11 he says the 10 percent number is wrong, that the POSA's expectation sort of
12 reading all of the data and taking into account all of his criticisms is that it's
13 13 or 14 percent.

14 Tecan's argument here, as we show on Slide 70, depends on this
15 notion that Meyer was unbiased amplification, and that Meyer, you know,
16 intended for all sequences to be amplified equally. And Tecan created this
17 figure that they -- that we show on Slide 71 that they say is evidence of what
18 happens in Meyer. They say, same relative frequency before and after. One
19 blue, one purple, one green fragment pre amplification. Four blues, four
20 purples, four greens after amplification. So you start with one and you end
21 up with four each. Of course, this ignores in the first box all of the other
22 fragments that don't get amplified, like the other types of nucleic acids, the
23 suppressed fragments. There are huge numbers of fragments here that are
24 not the blue, purples and greens, but regardless, it's also not what Meyer
25 teaches.

1 Meyer expected, as we show here on Slide 72, to see
2 underrepresentation of 3' ends. They said it was -- that the sequencing was
3 expected to result in underrepresentation of the 3' ends of fragments. You're
4 going to hear Tecan argue otherwise, but the alleged overrepresentation
5 concern isn't anywhere in the reference, and their experts couldn't point to
6 any such teaching in the reference suggesting there was a concern about
7 overrepresentation. The only concern actually addressed in the reference is
8 underrepresentation.

9 And what did Meyer do to address that issue? They used special
10 chemistry that applied to the 3'-end fragments. And what did they see at the
11 end? They didn't see unbiased amplification. They saw slightly more 3'-end
12 fragments than the expectation, and their conclusion from that was that 3'
13 ends were well represented. They didn't say equally represented, and they
14 didn't say the same as the expectation. They saw more than the expectation.
15 They expected to see less, and they overshot it when they used the 3'-end
16 chemistry.

17 And so what actually happened, as we show on Slide 74 and 75, it's
18 not what Tecan says, that you get four of each fragment. It's that you got
19 more of the 3'-end fragments. They're the green ones here at the one end of
20 the transcript. You got six, you know? It's not -- the math doesn't exactly
21 match up, but there are more 3'-end fragments here than were actually there.

22 And so that leaves us with Tecan's attempt to sort of ignore what the
23 reference says on its face and to rewrite the reference and substitute Dr.
24 Bustamante's say-so for what's black and white in Meyer. First, there's this
25 issue of what the results were, whether they were from the results in the
26 paper being from Figure 1 and whether you would expect the same thing

1 with Additional file 4. As an initial matter, the reference is very clear.
2 Additional File 4 is an improved version of Figure 1. It has minor
3 modifications and the improved protocol is recommended for researchers,
4 and the experts all seem to agree that the POSA reading this reference would
5 use the Additional file 4 method.

6 And likewise, the relevant chemistry in the two methods is nearly
7 identical. You have the same -- or a similar special primer that targets the 3'
8 ends in both methods. It's the same type of anchored PCR amplification
9 with a tailed primer. And in the institution decision -- and sorry, I'm
10 showing that similar chemistry here on Slide 82. And in the institution
11 decision, the board invited evidence to suggest that this improved method
12 would generate fewer reads of the 3'-end fragments than the 16 percent
13 reported in Meyer. And now today, with the record closed, there is no such
14 evidence. And in fact, Tecan retained Dr. Meyer, the first author on the
15 reference, and what did he say? He says you would get very similar and
16 comparable results between the two methods. That's not evidence that you
17 would get less of the 16 percent argument of the -- of -- than the 16 percent
18 that the authors reported in the paper. And this testimony from Dr. Meyer is
19 on Slide 85.

20 Likewise, we asked Dr. Bustamante for an explanation. We show this
21 testimony on Slide 86. He says, "I can't tell you if one would overrepresent
22 more than the other." That's not evidence the improved method would
23 generate fewer reads of the 3'-end fragments than the 16 percent reported in
24 Meyer, and the Meyer authors report that result as representative of the
25 results of both methods. And of course that's the case because both methods
26 are the same with respect to the relevant 3'-end chemistry.

1 So what does Tecan do next? They try to rewrite what the reference
2 says on its face. The reference is clear, as we show again on Slide 88, that
3 the -- that they saw 16 percent of 3'-end fragments in the sequencing data,
4 but they expected to see 10 percent. And I want to just focus on that 16
5 percent number for a moment. No one says that this is the wrong number to
6 use. Everybody agrees that this is the correct prevalence of 3'-end
7 fragments. It comes from the sequencing data that was actually generated
8 with this chemistry. The only number here that's in any doubt is the 10
9 percent expectation. And before we get to the 10 percent expectation
10 though, I want to talk again about Dr. Meyer.

11 They say that we misconstrue his testimony. They say that he never
12 testified that these numbers are reasonable for assessing enrichment, but let's
13 look at what he actually said. Here on Slide 91, we asked Dr. Meyer
14 whether the calculation was designed to demonstrate that you would resolve
15 the underrepresentation of the 3' ends. He says, "That's correct." In other
16 words, Dr. Meyer agrees that the calculation is appropriate for determining
17 whether they'd resolved what they had expected to see: less 3'-end fragments
18 relative to other fragments. That's the proportional change that Tecan says
19 the claim requires under the plain and ordinary meaning. The statement in
20 the reference was always about the relative proportion of fragments. That's
21 what Tecan says enrichment is, an increase in relative proportion.

22 And then when we asked him if the calculation and the statement were
23 reasonable, he said, "I stand by the statement as written." Now in his
24 declaration, he says, "Oh, you know, whatever I reported in my reference, I
25 didn't mean it to be appropriate for reporting enrichment." Right?
26 Apparently he thinks that means something different than addressing

1 underrepresentation, but I want to be very clear. In Exhibit 1126, Pages 84,
2 Line 19 through 85, Line 8, Dr. Meyer was never provided the patent, never
3 provided with the board's construction, and never provided with Tecan's
4 construction. So it's completely unclear what the single paragraph in Dr.
5 Meyer's declaration was meant to mean, or what he thought enrichment
6 meant, or what construction he thought he was applying. In the actual thing
7 that he wrote at the time, in the reference, he said this was meant to tell you
8 something about whether there were underrepresentation of these fragments,
9 whether he had addressed the expected less relative proportion he expected
10 to see, and he stood by this calculation as evidence of that.

11 So I want to talk very briefly about the criticisms of the 10 percent
12 number itself. I want to say at the beginning that this is not the way this
13 analysis is supposed to work. What the POSA is doing is looking at what
14 the prior art itself teaches. It's not looking under the hood and saying, oh, I
15 would change this, that, or the other thing in the reference. The reference on
16 its face says 16 percent versus 10 percent. That ends the inquiry. And of
17 course, Dr. Meyer, again, he stands by both of these numbers. He stands by
18 the 232 base pair numerator. He stands by the 2,200 base pair denominator.
19 He says that, as we show here on Slide 93, the 232 base pair numerator, that
20 number is not an assumption, and he didn't have any reason to think that you
21 should have used a different number instead. And likewise, as we show on
22 Slide 94, Dr. -- Dr. Meyer agrees the denominator is correct. It was a
23 reasonable number to choose in 2009 when we wrote the paper.

24 So I want to go briefly to the patent owner's specific criticisms of
25 these numbers. I think all -- none of which actually, even if the POSA was
26 going to second guess the reference, lead to where the patent owner wants

1 them to lead. The first is the criticism of the numerator. The issue with the
2 numerator here is that you should have used a different number, this 300 to
3 400 base pairs number from a different part of the reference that's not
4 reported as a fragment length, that's not reported as the numerator. That's
5 not in the reference. Tecan says, because Dr. Sims testified the denominator
6 was based on a gel, that you have to use a gel for the numerator. Notably,
7 Tecan and both of the experts say that Dr. Sims' assumption that this was
8 based on a gel is wrong, but that debate is academic because nobody is
9 proposing a different denominator anyway.

10 But on the numerator, the numbers that Tecan wants to point to are
11 not results. There's no gel result for the numerator for the average fragment
12 length reported anywhere in Meyer. The number that Tecan is citing in its
13 brief here on Slide 98, this 300 to 400 base pair range was reported as the
14 target range from a three-minute sonication. It's not reported as an average
15 fragment length, let alone for this specific experiment. The only thing that
16 the authors report from this experiment that would be appropriate for
17 measuring the fragment length is the read length, which is of course what
18 they used, the 232 base pairs. There's no evidence anywhere that if you --
19 that the Meyer authors when performing this method actually got fragments
20 of 300 to 400 base pairs in length. This is just saying, if you do the
21 sonication for this length of time, this is what you might get.

22 On the denominator, Meyer, again, agrees that this is a -- that this is
23 an appropriate assumption for the total transcript length. Dr. Bustamante is
24 on an island here. He's the only one who says that this number is wrong, but
25 he won't say what it should be other than that it should be smaller than
26 2,200. Notably, none of this is in the reference either. It doesn't say in the

1 reference, we assume an average transcript length of 2,200, but it could be
2 lower. That's not in the reference. Instead, Dr. Bustamante's testimony and
3 Tecan's argument that we show here on Slide 101 from their surreply brief,
4 depends on the notion that the number came from a mammalian transcript,
5 which is allegedly not even in the same file as the choral sequence in Meyer.
6 But this entire mammalian transcript theory rests on a stray piece of
7 testimony from the disqualified Dr. Matz.

8 When we asked Dr. Meyer about this theory that appeared in his
9 declaration to be clear, which was just adopted from Dr. Matz, he wouldn't
10 defend him. We asked him, would the POSA reading the reference think
11 that 2,200 base pairs is based on the average length of a mammalian
12 transcript? And he said, as we show here on Slide 103, "I think your
13 introduction of the term mammalian transcript into that sentence is not
14 necessarily something that we were relying on or that the reader would
15 assume." He says the POSA reading the reference would understand it to be
16 a general average overall transcript length. We didn't mention anything
17 about mammals in this sentence.

18 And so this -- so the primary basis by which Dr. Bustamante criticizes
19 the denominator is something that was recanted by the expert who is the
20 author of the reference. So Dr. Bustamante is on an island. Dr. Sims agrees
21 with the math. Dr. Meyer says the calculation is based on reasonable
22 assumptions. And so we asked Dr. Bustamante, taking into account all of
23 the criticisms of the calculation and taking into account this distribution of
24 sequence reads that he sees in Figure 2, what percentage would be the more
25 appropriate one to use as the expectation? And he said 13 to 14 percent.
26 That's still less than 16 percent.

1 Now, in its surreply brief, as we show here on Slide 104, Patent
2 Owner wants that to be ignored as an estimate. But this was his estimate
3 based on the published distributions, the published distributions in Figure 2
4 that he says are the reason why you would sort of second guess this number.
5 And taking in -- that into account, he still says the expectation is 13 or 14
6 percent.

7 The POSA, of course, would take the reference on its face for what it
8 says and wouldn't rewrite it. But at the end of the day, when he was offered
9 the opportunity to insert his own number into the reference, Dr. Bustamante
10 could only get to a number that still showed enrichment, and because of this,
11 the vast majority of the claims that the parties agree rise and fall with the
12 anticipation of Claim 1 are anticipated.

13 I just want to briefly touch on a handful of unique issues presented by
14 the dependent claims. This is Claim 21 and Claim 22 of the 012 patent.
15 They have unique anticipation issues, and then there are dependent claims in
16 each patent that recite genomic DNA and different kinds of sequencers that
17 we believe the record shows are obvious.

18 So first, Claim 21 of the 012 patent. As we show here on Slide 109,
19 the additional limitation here is just that the source of these fragments is an -
20 - that the source of the fragment that's going through the chemical
21 manipulations and being sequenced is an RNA fragment. And Tecan says,
22 well, in Meyer, what happened, of course, they also started from RNA, but
23 they transcribed to cDNA and then fragmented. And they say, well, that
24 makes it not an RNA fragment anymore. What you have to do is fragment
25 before you reverse transcribe. But in the only example in the patent of RNA
26 sequencing, the cDNA was generated from total RNA first, and then the

1 cDNA was fragmented. This is still an RNA fragment in the sense of the
2 term, even though it's been converted to cDNA and then sequenced.

3 I want to talk briefly about Claim 22 of the 012 patent. This claim, as
4 we show here on Slide 114, adds the limitation that there's ligation of
5 adapters to both ends of the fragment, and there's no dispute that Meyer
6 blocked ligation of one end of the 3'-end fragments as part of generating the
7 cDNAs. So most of the fragments were not ligated. But it's also true that
8 Meyer used random sonication to fragment those cDNAs, and the POSA
9 would know that anytime sonication broke off that last nucleic acid residue
10 that's blocked, or a piece containing that last nucleic acid residue, that that
11 piece would -- that that fragment would then get end repaired and be
12 available for ligation at that position.

13 You're going to hear a lot about inherency. This is not an inherency
14 argument. Dr. Sims explained, as we show here on Slide 117, that this is
15 how the POSA would interpret the disclosure of Meyer. The POSA looks at
16 the process that Meyer has wherein the fragments are -- and if you could
17 give me Slide 115.

18 MS. SEARLE: Yep.

19 MR. HOAGLAND-HANSON: Okay. Maybe I'll have 115 on
20 rebuttal. But in any event, I think what -- if the POSA looking at the method
21 that's disclosed in Meyer, what the POSA sees is that there's a ligation and a
22 blocking step and then a random sonication, and the POSA knows that some
23 of those fragments will be fragmented in the correct region and result in
24 fragments that are ligated at both ends. And of course, the only time the
25 Meyer method was actually performed in the record, there were many
26 fragments that were ligated on both ends. This is what Dr. Sims shows here

1 on Slide 117, that there were fragments that were actually in the sequencing
2 data that were fragmented in this sort of blocked CAP region and got
3 adapters on both ends.

4 And the result of that, of course, is that there were also -- now, so the
5 sequencing data here is of fragments on the other end of the molecule
6 because of the way in which the directionality of the sequencing is
7 happening. These are not 3'-end fragments, they're fragments on the other
8 end. But there's been no evidence to suggest that you wouldn't get the same
9 pattern of fragmentation on the other end of the molecule because this is a
10 random stochastic process and this is happening thousands of times. This is
11 not happening in, you know, some small number of fragments. And Dr.
12 Bustamante conceded, as we show on Slide 118, that the fragments are
13 ligated on both ends of the strands, and he agrees that in the data that Meyer
14 deposited, it did in fact happen. He says it's in about 1 percent or something
15 like that. This is not inherent anticipation. It actually happened. It just
16 didn't happen to every fragment.

17 I want to talk briefly then with the remainder of my time about
18 obviousness.

19 JUDGE YANG: On obviousness, I have an overarching question.

20 MR. HOAGLAND-HANSON: Sure.

21 JUDGE YANG: Does Petitioner still pursue ground 2, which is the
22 single-reference obviousness?

23 MR. HOAGLAND-HANSON: So I think this -- I think there was
24 maybe some lack of clarity on this, but no, in the original petition for most
25 of the claims, we had anticipation as the primary ground, and in the
26 alternative, obviousness, because we didn't really know what they were

1 going to say. I think at this point, it's our position that ground 2 is fully
2 subsumed by ground 1, and that we've shown that the record shows that all
3 the claims are anticipated that are included in ground 1.

4 JUDGE YANG: Okay.

5 MR. HOAGLAND-HANSON: This means that the obviousness
6 issues really only apply to a handful of the dependent claims. The first
7 group of those are Claim 2 of both patents specifies the source of the nucleic
8 acids as genomic DNA. Now, of course, the only thing that's being added
9 here is the source of the DNA, because Meyer also used DNA. It just used
10 cDNA. And any undergraduate biochemistry student will tell you that
11 genomic DNA and cDNA are the same thing, right? They have the same
12 chemistries, the same chemistry can be applied to both. Dr. Bustamante, for
13 his part, didn't contest this basic biochemistry principle, as we show here on
14 Slide 124.

15 JUDGE YANG: Okay.

16 MR. HOAGLAND-HANSON: And there --

17 JUDGE YANG: On that, I actually have a question. Maybe I am not
18 like an undergraduate biochemistry student, but cDNA has the poly(A) tail.

19 MR. HOAGLAND-HANSON: Yes.

20 JUDGE YANG: And the -- the broken chain T primer in Meyer was
21 specifically addressing that. Is the poly(T) or poly(A), the homopolymers
22 also a -- in the genomic DNA?

23 MR. HOAGLAND-HANSON: No. And to be clear, our argument is
24 not that you could sort of take the Meyer method directly and apply it to
25 genomic DNA, but if you were interested in targeting any known sequence,
26 you can use the same chemistry, right? And this is what Dr. Sims explains

1 in his declaration. You can use the same chemistry, right? You might use a
2 different targeted primer, but you can use that same chemistry on something
3 that's in genomic DNA. Of course, that's exactly what the Siebert reference
4 that we talk about in this combination did, right? They were looking at
5 known sequences in genomic DNA and then using the same chemistry steps
6 that are used in Meyer on those sequences.

7 JUDGE YANG: So the broken chain T primer is out of the question
8 for this specific combination, the one with the Siebert reference?

9 MR. HOAGLAND-HANSON: That's right. I mean, the broken chain
10 T is just a synthetic sequence that's getting incorporated earlier on that's
11 basically the same idea as a transposon or anything else that you sort of have
12 inserted somewhere that you're interested in, right, that you know about, --

13 JUDGE YANG: Well, that one is --

14 MR. HOAGLAND-HANSON: -- you're then going to use as a
15 handle.

16 JUDGE YANG: -- it actually is critical because it -- I guess it was
17 targeting 3' ends because if you use anything else, you wouldn't be targeting
18 3' end, correct?

19 MR. HOAGLAND-HANSON: That's right. You wouldn't be
20 targeting the 3' end, but you could target something else that was of interest.
21 And I think one thing that's critical here is Tecan's main argument against
22 this is to say you wouldn't have wanted -- and Siebert undoubtedly, right,
23 was targeting sort of a known genomic position that was adjacent to a known
24 variable region. And they say, oh, you wouldn't have wanted to do that now
25 because Siebert doesn't work on NGS. But Meyer is using the same
26 chemistry, right, in NGS, and they're just using it on a different source

1 material, right, and with a different known sequence of interest. But you
2 could use a sequence of interest like the one in Siebert, right, where you're
3 targeting a known genetic sequence adjacent to a known variable genetic
4 sequence and do that on NGS using the same chemistry that's recited in
5 Meyer.

6 Their big response on this issue is to say, oh, you wouldn't think these
7 Siebert type methods, these anchored PCR methods with a single primer
8 would work, right, on NGS. But Meyer is an example of doing just that.
9 There's only one primer in Meyer that targets the gene of interest. There's
10 no opposing primer. And so their main response on for sort of why it's not
11 obvious to apply this method to genomic DNA is a total non-sequitur. It's to
12 say you wouldn't want to use these anchored PCR methods on NGS.

13 I think that's also consistent with what we have on Slide 128, this is
14 the Leoni reference Exhibit 1052, where they acknowledge that these types
15 of anchored PCR methods, the same type of chemistry disclosed in Siebert
16 and in Meyer are applicable to NGS. They say genome walking strategies
17 will be used and applied to next-generation sequencing. And that's, of
18 course, exactly what Meyer did. It took an anchored PCR method and
19 applied it to NGS.

20 Likewise, the last bucket of claims that are the subject of these
21 obviousness disputes are the ones that recite a particular NGS device. This
22 is Claims 15 and 17 through 19 of the 012 and Claims 11, 12, and 19 of the
23 108. These limitations are basically just take the method of Claim 1 and do
24 it on an Illumina, or take the method of Claim 1 and do it on an Ion Torrent.
25 Of course, there's no suggestion in any briefing or in the patent itself that
26 Tecan somehow discovered the Illumina or discovered the Ion Torrent.

1 These are known machines, and all these limitations require is basically that
2 instead of a 454 in your laboratory, you have an Illumina or an Ion Torrent.

3 And what was happening at the priority date, both experts agree, as
4 we show here from Dr. Bustamante on Slide 130, is that the market had
5 moved on to Illumina or Ion Torrent. And the only thing that you need to do
6 to take Meyer and adapt it to these other methods is change out the adapters.
7 This is not non-obvious. Nobody thinks that you take methods that are
8 anticipated in the prior art and say, do it on an Illumina or do it on the Ion
9 Torrent, the two market leading sequencers, and you thereby render the
10 claims not obvious.

11 Finally, they say that for these two buckets of obviousness claims that
12 the praise and success for their commercial embodiment should overcome
13 all of this. We would submit that the prima facie case here is too strong to
14 be overcome based on some post priority praise and commercial success.
15 Notably, Dr. Bustamante in these proceedings wouldn't even defend their
16 unexpected properties arguments that they advanced in prosecution to get
17 these claims out of the office in the first place. He offered no opinion on
18 unexpected properties. They rested on a declaration from a decade ago from
19 prosecution. But regardless, Dr. Bustamante offered no opinion on whether
20 the two commercial embodiments are commensurate with the full scope of
21 the broad claims as drafted. They, again, here want the claim to be narrow
22 as the preferred embodiment when it suits them, but the claims as drafted are
23 much, much broader.

24 So for these reasons, we would submit that the challenged claims of
25 the 012 and 108 patents are anticipated or obvious. Unless Your Honors
26 have any questions now, I'll see you again on rebuttal.

1 Thank you.

2 JUDGE YANG: You have 75 minutes in total. How much would
3 you like to reserve?

4 MS. CIPRIANO: I'd like to reserve 15 minutes, please.

5 JUDGE YANG: Whenever you're ready.

6 MS. CIPRIANO: Thank you.

7 Good afternoon, Your Honors. Linnea Cipriano again on behalf of
8 patent owner Tecan Genomics.

9 You've just heard from Petitioner about the alleged similarities
10 between the challenged claims and the methods described in the Meyer
11 publication, but Petitioner's arguments suffer from a handful of fatal flaws.
12 First, Petitioner's primary argument relies on a construction of the claims
13 that is not based on the plain meaning of the term "enrich", or at least our
14 understanding from the papers was not based on the plain meaning of enrich,
15 was not anchored by any part of the intrinsic record, and is not supported by
16 expert testimony.

17 Now, if we're truly in agreement that enrich means an increased
18 proportion, then potentially there is no dispute. But based on the papers, that
19 was not our understanding of Petitioner's arguments. So we'll explain that
20 the claims require a step of amplifying extension products to enrich for
21 sequence of interest. And that amplification step must result in sequences
22 targeted by the gene specific primer being present at a higher proportion in
23 the sample relative to other sequences.

24 The specification calls this, as Petitioner points out, targeted
25 enrichment, where one or more sequences are targeted for amplification, and
26 others are inherently or required to be either less amplified or not amplified.

1 So Meyer does not disclose a method where any sequence is targeted
2 with a gene specific primer, and that targeted sequence is enriched in
3 comparison to other sequences in the sample. There is no data in the record
4 that supports that conclusion, and I'll explain that in more detail in a
5 moment.

6 As both Dr. Bustamante and Dr. Meyer testified, the method of Meyer
7 does not provide for such enrichment, and the data does not support that any
8 enrichment occurred. So setting aside that major flaw and looking a little
9 deeper, Petitioner has also failed to show that Meyer anticipates Claims 21
10 and 22, which my colleague and LEAP practitioner, T.J. Beavers, will talk
11 about in more detail in a few moments.

12 And finally, Mr. Beavers will also explain that Petitioner has failed to
13 show any challenge claim is obvious in light of Meyer in combination with
14 the cited references, particularly in light of the secondary considerations.

15 So let's dig into Petitioner's ground 1. As you heard, Petitioner
16 contends that the library preparation -- library preparation -- preparation
17 method of Meyer anticipates the challenge claims. Petitioner's argument,
18 however, is built on three conclusions that are not supported by the record.

19 And these are, first, that the claims are met if all sequences in a
20 sample are amplified without regard to their relevant prevalence. And that
21 was our understanding of Petitioner's arguments on the papers.

22 The second point is that -- the second fallacy here is that the Meyer
23 method on its face provides for enrichment of the 3'-end fragments, and that
24 a person of ordinary skill in the art looking at the method would not expect
25 there to be any enrichment of any particular fragment that Meyer identifies.

1 JUDGE YANG: I understand from underrepresentation to well
2 represented, it increased, right? From -- I understand you challenge the
3 expected 10 percent. But from 10 percent to 16 percent, the proportion was
4 increased, no?

5 MS. CIPRIANO: So I think there are two things I would like to
6 address in your question. First, the underrepresentation issue that Meyer
7 was addressing. And if we can -- let me see what slide it is. Let's go to slide
8 18.

9 The underrepresentation that Meyer is trying to fix is really a
10 sequencing issue. So the -- they wanted to sequence their samples on a 454
11 pyrosequencing device. And in that device, it -- the way that it works, it's an
12 optical sensor that detects which nucleotides are being added to the
13 sequence.

14 And when there are too many of the same nucleotide, a homopolymer,
15 the sensor gets blown out and the data becomes unreadable. So in the data
16 set, the 3' ends were underrepresented because they couldn't see it. There
17 were too many errors in the 3' end of the homopolymer of the poly(A) tail.

18 So the underrepresentation that they're trying to fix, now that was
19 solved through the broken T primer that was introduced in the SMART
20 protocol that I can talk about in more detail in a moment. That
21 underrepresentation is not actually in the sample, that is in the data that
22 comes out. So it's not that the nucleic acids weren't there, it's that they
23 weren't able to see them because they weren't prevalent in the data, because
24 of this homopolymer problem with the 454.

25 Now, the second part of your question that I'd like to address is the
26 difference between the 10 percent and the 16 percent. The 16 percent -- as

1 Petitioner admits, the 16 percent is the only actual data that Meyer reports.
2 The 10 percent is an off-the-cuff, back-of-the-envelope estimate based on a
3 lot of assumptions. The important point there is that it's a qualitative
4 assessment.

5 Is it -- is what they saw for the 3' end is in the ballpark of what they
6 were expecting? Because that's -- that is -- they were trying to fix the
7 homopolymer problem. If they didn't solve the homopolymer problem, the
8 3' end would be orders of magnitude lower than expected, not individual
9 percentage points where we're quibbling over the amounts.

10 The 16 percent that Meyer saw was in one run, one sequencing run of
11 the coral transcriptome they were looking at. It's unclear if the method
12 would consistently report if there is errors in that number. So a person of
13 ordinary skill in the art would not have looked at Meyer's 10 percent based
14 on a lot of assumptions. I think everybody in this case agrees that it's based
15 on a lot of imprecision versus Meyer's 16 percent on this one run. They
16 would not say that that is data of enrichment.

17 And even we saw -- I have testimony from Dr. Meyer. Here, I have it
18 on Slide 31. Dr. Meyer confirms that he didn't -- he doesn't -- he did not
19 think that there was data in the record to support any conclusion regarding
20 whether there was enrichment or not of any particular fragment after the
21 Meyer method was performed.

22 JUDGE YANG: Yeah. But as counsel for Petitioner pointed out, that
23 Dr. Meyer appeared to not have a -- doesn't matter whose definition, a
24 definition of enrichment used in this proceeding. So I guess -- which that
25 goes to my next question. Does it matter, say 1 percent increase, would that
26 be called enrichment?

1 MS. CIPRIANO: Yes. There is no -- as Petitioner pointed out, there
2 is no standard or amount of enrichment that is required --

3 JUDGE YANG: Okay.

4 MS. CIPRIANO: -- here.

5 JUDGE BRADEN: I apologize, Counselor, can we pause for one
6 moment? Can we confirm that Judge Majors is on the line?

7 MS. CIPRIANO: Seems I am unlucky.

8 JUDGE BRADEN: I think this is a preview of what the weather will
9 be bringing us. Do not take it as a personal reflection of any of our
10 presenting counsel. So we're going to take a real quick pause. So hold that
11 thought, and we will get Judge Majors back on and then we will proceed.
12 Thank you for your patience.

13 (Whereupon, the above-entitled matter went off the record at 1:46
14 p.m. and resumed at 1:47 p.m.)

15 JUDGE MAJORS: Yeah, I can hear you.

16 IT TECHNICIAN: Thank you.

17 JUDGE MAJORS: Sorry, Ms. Cipriano. You were just about to say
18 that you had data --

19 JUDGE YANG: All right. Party is over. Let's all come back.

20 JUDGE MAJORS: Ms. Cipriano, did you hear me? I backtracked to
21 where you had left off when I cut out.

22 MS. CIPRIANO: I didn't, Your Honor. If you could repeat that,
23 that'd be helpful?

24 JUDGE MAJORS: Yeah. You were saying that you had either -- I
25 think you were saying some data or some testimony, I think you were going
26 to say from Petitioner's expert.

1 MS. CIPRIANO: I -- if I can just repeat just what I -- the point that I
2 was making is that --

3 JUDGE YANG: So let me help here.

4 MS. CIPRIANO: Yeah. Okay.

5 JUDGE YANG: Did you hear my question, Judge Majors?

6 JUDGE MAJORS: I did not.

7 JUDGE YANG: Okay. I asked the question -- I guess two-pronged.
8 One is the 10 percent versus 16 percent, and despite the patent owner's
9 challenge of the inaccuracy, the alleged inaccuracy of the 10 percent
10 estimated number, wouldn't 16 percent be more than the 10 percent? That's
11 one question.

12 And then I also asked about the 3' and the fragment. From
13 underrepresentation to being well represented, wouldn't that be enrichment?
14 And so we'll start from there. If you could just repeat your answer to those,
15 and I won't start the --

16 MS. CIPRIANO: Okay.

17 JUDGE YANG: -- clock till you are done with that.

18 MS. CIPRIANO: Yes. I'm sure my verbiage will not be put --

19 JUDGE YANG: Yeah, that's fine.

20 MS. CIPRIANO: -- exact, but yes, let me go back over that. So first,
21 I addressed the underrepresentation portion of that -- of Judge Yang's
22 question. And Dr. Meyer was looking to solve the underrepresentation
23 problem seen with the 454 pyrosequencing.

24 So the Dr. Meyer sequence ran his data on a 454 machine, and that
25 machine had an issue with detecting -- accurately detecting long strands of
26 the same nucleotide. And the way that that works is that it's an optical

1 sensor that detects a burst of light, I believe. I'm probably not 100 percent
2 accurate, but it's an optical sensor that detects when a nucleotide is added to
3 the sequence.

4 And when there are too many of the same nucleotide that are added,
5 the machine gets overwhelmed and the data is inaccurate and is unusable,
6 and does not appear in the final data compilation.

7 So the underrepresentation that the Meyer reference is talking about is
8 in that data set. In the -- that the 3' end sequencing reads are not there,
9 because there were issues with gathering the accurate sequence for that. So
10 that is not a question of whether the nucleotides were in the sequencing
11 library, the actual sequences were in the sample. But they couldn't detect
12 them and they couldn't find them, because of this 454 homopolymer
13 problem.

14 So that's the -- how Dr. Meyer -- Dr. Meyer addresses this with the
15 broken T chain that was introduced in the SMART protocol. So that's the
16 under-representation problem.

17 Now, the difference between the 10 percent and the 16 percent, I
18 confirmed that the only data -- actual data point that a person of ordinary
19 skill in the art would see is the 16 percent that Doctor -- that the Meyer
20 reference reports. The 10 percent here, everyone agrees that this is based on
21 a lot of assumptions.

22 There's no -- Dr. Meyer or the -- but Dr. Meyer talks about how he
23 thinks it was calculated. The Meyer publication presents some numbers
24 about how -- what numbers were used, but all of these are -- all of those are
25 assumptions. It is not based on actual data that is reported in the paper about

1 what the amount of these fragments would be before the method or without
2 the specific 3' end primer.

3 So based on that -- based on the 10 percent number is largely
4 inaccurate, the -- or largely ambiguous and it's really unclear where, what,
5 how that actually reflects what was in the sample.

6 A person of ordinary skill in the art would not look to the difference
7 between 10 percent and 16 percent as a hard and fast, absolute evidence of
8 enrichment. They would see that as they're in the same ballpark. And that
9 as Dr. Meyer stated in his -- let's go to Dr. Meyer's conclusion. I have it on a
10 slide 24.

11 Dr. Meyer -- his conclusion is that the comparison suggests that the 3'
12 ends of the fragments were well represented in the dataset. Meaning that
13 they solved -- and this is confirming the effectiveness of this solution for
14 overcoming the homopolymer problem. And that homopolymer problem is
15 what I was talking about, is the difficulty with the 454 pyrosequencing.

16 He did not claim that he was enriching for any sample. He did not
17 claim that this data shows that they hyper -- and hyper amplified the 3' end.
18 His ballpark was -- his assessment was that these numbers were in the same
19 ballpark and they accomplished his goal.

20 So if I could go back just to talk a little bit about the claim
21 construction, because there seems to be a disconnect in the assessment here.
22 So I've put portions of the Claim 1 of the 012 and the 108 patent on slide
23 five. And as Petitioner and the board recognized, the enriching -- the to
24 enrich or thereby enriching portion of the disputed language appears within
25 the amplification step.

1 And it sounds like -- it sounded to me like the parties agree that the
2 amplification step of the method must result in some enrichment. And
3 indeed, Dr. Sims, agreed that if a method -- if a method is performed and
4 just perpetuates enrichment that was existing before the method was
5 performed, that would not meet the claims. And that's at Exhibit 2037 at
6 page 194. So enrichment has to occur as a result of amplification.

7 Now, Tecan's proposed construction is in line with what I've heard is
8 that everybody accepts the plain and ordinary understanding of the term. Oh
9 and let me pause there. I did want to address Judge Yang. You had a
10 question about Dr. Meyer's interpretation of the term enrich in his testimony.

11 And it's Tecan's position that I think everybody understands what
12 enrichment means. It means to change in proportion. And you also -- if you
13 look at his testimony, he's talking about the difference in proportion and the
14 prevalence of the fragment in the sample. So it -- it's clear from the
15 testimony that he does understand what enrichment means and certainly
16 would be in line with the evidence here. So apologies for the non-sequitur
17 there, but --

18 JUDGE BRADEN: So Counsel, just real quick. Clarify for me that
19 when we say enrichment and we're talking about different in proportion, you
20 don't mean just difference in amount?

21 MS. CIPRIANO: We do not mean difference in amount, yes.

22 JUDGE BRADEN: Okay. Thank you.

23 MS. CIPRIANO: Now, Petitioner attempts to construe Tecan's
24 positions as a moving target and pile on language to this construction, but
25 the papers are clear that Tecan's positions have not changed. The "to enrich"

1 portion of the claims should mean to enrich the proportion of the nucleic
2 acid sequence of interest relative to other fragments in the solution.

3 So rather than providing any affirmative explanation of what the term
4 means, IDT has asked the panel to simply ignore the "to enrich" portion of
5 the claims. But such an interpretation is wholly inconsistent with the
6 intrinsic record. And I'd like to take a look just to refer you to a few portions
7 of the patent that highlight the importance and the criticality of the
8 enrichment concept to these claims.

9 So the challenged patents are explicitly directed to methods of
10 targeted nucleic acid enrichment. That's clear from all the language.

11 JUDGE YANG: It's clear in the specification, but it is not in the
12 claim, correct? The targeted enrichment part.

13 MS. CIPRIANO: Yes. And I -- and just in a moment, I want to talk
14 about how the claims -- the sequence of the claims results in targeted
15 enrichment the way that the specification describes it.

16 JUDGE YANG: Okay. I'm sure you will get to it, but just in case I
17 forget about my question later, I'll ask it now. Is it Tecan's position that only
18 the sequence of interest should be amplified? Because I think that may be a
19 point of dispute.

20 MS. CIPRIANO: So it is not Tecan's position that only the target --
21 the -- that there can only be one thing that's amplified in a solution. It is
22 Tecan's position that if we look at the claims, that the way the claims are
23 structured, it is the extension products that result from the gene specific
24 primer that are talk -- that is talked about in the amplification step. And it is
25 those fragments that must be enriched compared to other fragments in the
26 sequence.

1 Now, we acknowledge that it is a comprising claim. So this can
2 happen in parallel -- more than one thing can happen. But ultimately, the --
3 this fragment that's talked about in the claims must get enriched. That's the
4 bottom line.

5 So if we look at -- if we -- if we look at the patent, the patents explain
6 that as of the filing date, next generation systems are becoming more and
7 more accessible. The inventors noted that there lacked a reliable method of
8 focusing resources on only the portion of a sample that was of interest,
9 avoiding gathering sequencing data from the entire sample.

10 And at the time the patents were filed, the existing methods for doing
11 so required complex target specific prime repairs and were rife with
12 problems. The inventors solved this problem with the claimed invention
13 using a single target specific primer coupled with universal primer pair that -
14 - and they were able to preferentially amplify only the portions of the -- only
15 the portions with the sequence of interest.

16 So on Slide 7, I've put up a clip of the abstract that highlights the
17 importance of the enrichment. And the very first sentence of the abstract
18 states that the invention here is a method for targeted sequence enrichment.
19 And this concept is repeated throughout the specification with enrich or
20 enrichment appearing in the patent nearly 70 times. So the board should not
21 ignore the inventor's clear indication that enrichment is central to this
22 invention.

23 So I think we -- we've been over the board's construction in the
24 institution decision, but I think we have to keep our eyes focused on the
25 proportionality requirement, that the base of our understanding of the
26 ordinary meaning of enrichment is based on proportion.

1 And there -- just to illustrate and drive home this idea, I think that
2 answers very clearly Judge Braden's question. At its most basic level,
3 enrichment can happen in two ways. Enrichment is either due to an increase
4 in the amount of a desirable ingredient and no increase or less of an increase
5 in other ingredients, or the opposite. You can purify, you can take out
6 undesirable ingredients, thereby enriching for a desirable ingredient. And
7 this is -- these two options are illustrated on Slide 9.

8 But in both of these scenarios, although the methods are different, the
9 result is enrichment for fragment A, because the proportion of fragment A
10 increased in the mixture. And this is exactly how the term "enrich" is
11 plainly understood, and there's no justification for departing from that
12 change in proportion, the way that we thought that Petitioner was
13 understanding the term.

14 Now, the methods of the claim -- the challenge claims use the
15 preferential increase, as we've talked about, but that necessarily means that
16 there are sequences in the mixture that are either not amplified or amplified
17 to a less extent. There has to be a change in the proportion, and that the only
18 way for that to happen is that for the fragments to be treated differently.
19 And so it's not a negative limitation. That is just a requirement of
20 enrichment, that the fragments -- there must be some differential treatment,
21 or there would be no enrichment. It would just be amplification.

22 Now, I -- I'd like to take a moment to walk through how the claims --
23 and this is what I was saying I was going to get to: how the claims actually
24 do the enrichment, and I think it clarifies what nucleic acid fragment is being
25 referred to in the amplification step that we're talking about.

1 So I've put on Slide 10 a colorized version of the Figure 1 from the
2 patent. And Figure 1 walks through the steps of the method with the -- in a
3 sample that has -- the example has six nucleic acid fragments in the top left
4 of the figure. So in the method, adapters are ligated to those fragments with
5 the first adapter sequence.

6 The method then introduces an oligonucleotide, and this is in the right
7 hand of the figure. And this oligonucleotide has one portion that is
8 complementary to a target sequence of interest, and a second portion that
9 acts as a second adapter sequence. That target specific portion anneals to its
10 complement sequence in the mixture and goes through an extension reaction.

11 Now, in that extension reaction, it is the target-specific
12 oligonucleotides that will generate extension products, and those extension
13 products will contain both the first and second adapter sequence and the
14 target sequence. Following the amplification step where the -- in Figure 1,
15 the only fragments that have both the first and second adapter sequence are
16 going to be those fragments with the target -- or the targeted sequence of
17 interest.

18 And when those are amplified, only those fragments with both the
19 first and second adapters are going to get amplified. And this results in a
20 targeted enrichment, because the other samples in Figure 1, the limited
21 example here, the other samples -- the other fragments in the sample are not
22 amplified because they don't have the proper adapters. And this results in
23 the targeted enrichment that is claimed.

24 So Petitioner alleges that Tecan is improperly importing limitations
25 from Figure 1 into its construction, and that's certainly not Tecan's intention
26 here. Figure 1 provides an illustration of how the targeted amplification and

1 the claim leads to enrichment, but we appreciate that other things could be
2 going on in this mixture.

3 For example, there could be more than one target-specific
4 oligonucleotide that are targeting more than one sequence of interest in the
5 same reaction, but that doesn't avoid the requirement that the oligonucleotide
6 directed to the target sequence, that fragment must be enriched in order to
7 meet the claims.

8 It was certainly Dr. Sims' understanding that enrichment must result in
9 a difference in proportion relative to other fragments in the sample. Dr.
10 Sims testified throughout his deposition, defining enrichment in relation to
11 others in sample -- other fragments in the sample. We don't -- I don't think
12 that there is a dispute after hearing Petitioner's argument today.

13 JUDGE YANG: I -- I'm sorry. What you just said, you don't think
14 there is a dispute after hearing Petitioner's argument?

15 MS. CIPRIANO: I believe Ms. Searle repeatedly said that enrichment
16 must result in an increased proportion in the sample. If that --

17 JUDGE YANG: Okay.

18 MS. CIPRIANO: -- is the case, then I -- then we agree on the term
19 "enrichment".

20 JUDGE YANG: Okay.

21 MS. CIPRIANO: And I think that we -- my colleague had a version
22 of this, but -- and I just wanted to highlight. We believe that the slide that
23 we have on -- the figure we have on Slide 12, this is what happens in
24 Meyer's reference.

1 Each of the pre-amplification fragments are treated the same way.
2 And if they're treated the same way, then they -- you result in the same
3 proportion before and after amplification and no enrichment occurs.

4 JUDGE YANG: I think Petitioner points out on the left side, there are
5 unshown -- other materials that didn't get amplified. Tecan's response to
6 that? Doesn't count or --

7 MS. CIPRIANO: So I believe -- I'm not -- I didn't exactly follow that
8 line of argument. But I believe in the papers, Petitioner has taken the
9 position that potentially there are other RNAs. I -- is that what the --

10
11 JUDGE YANG: Correct.

12 MS. CIPRIANO: Other RNA. Now, if there are other pieces in the
13 method and in the sample before the amplification step, there -- in Meyer,
14 let's just anchor it in Meyer. That Petitioner alleges that there were other
15 RNAs that were not amplified in the method. But those other RNAs were
16 purified and excluded in the SMART protocol. And that happened before
17 fragmentation, before any of the amplification steps that are the subject of
18 the challenge claims.

19 So that falls into the case of when Dr. Sims admitted and then agreed
20 that if that amplification does not happen in -- or that that enrichment doesn't
21 happen in the amplification step, then it doesn't meet the claims. That would
22 -- that enrichment of -- for the mRNAs, that happens before any of the steps
23 that occur in the challenge claims.

24 JUDGE YANG: So the enrichment has to be the -- well, let me
25 rephrase. So amplification has to be the sole reason for the enrichment is
26 Tecan's position?

1 MS. CIPRIANO: No, Your Honor. But it has to enrich. It has to
2 result in either -- if there is some enrichment already present, it has to
3 contribute to the enrichment. There has to be some part of the amplification
4 step that enriches that actually does that step.

5 JUDGE YANG: The claim uses the language "comprising" and then
6 A, B, C, D. Let's say prior to step A, Meyer does something else and
7 somehow enriched the sequence of interest. And then it goes through the A,
8 B, C, D and after amplifying, it results in the enrichment. Well, the
9 proportion is there. You're saying that's -- that doesn't fall under this
10 enrichment language or --

11 MS. CIPRIANO: That's correct. So I -- let's separate out. While that
12 -- the fragment may be enriched, as you're talking about, it wouldn't fall
13 under the claimed methods, because the amplification didn't result in
14 enrichment of anything. That that enrichment -- the amplification just
15 perpetuated the enrichment that was already there.

16 JUDGE YANG: Okay. Now I think I may understand you better. So
17 the enrichment could be because of other things, but amplification itself has
18 to enrich?

19 MS. CIPRIANO: Yes.

20 JUDGE YANG: Okay. Got it.

21 MS. CIPRIANO: Yes, Your Honor.

22 JUDGE YANG: Thank you.

23 MS. CIPRIANO: And so very briefly, I just want to talk about a few
24 reasons why the board really shouldn't overlook the enrichment element of
25 these claims. You know, patent -- or Petitioner claims that the -- that there --

1 the "to enrich" or "thereby enriching" terms should be viewed like whereby
2 clauses. That would be improper here.

3 Just looking at the structure of the claims, the "to enrich" or "thereby
4 enriching" the nucleic acid sequence of interest, is the antecedent basis of
5 the language that appears in 1F of the 012 patent and 1D of the 108 patent.
6 Clearly the enriched nucleic acid sequence of interest must come from
7 somewhere, and that is from the amplification step in the preceding steps.

8 Additionally, the Federal Circuit confirmed that where the patent
9 specification makes clear that a concept is material to patentability, it
10 shouldn't be ignored and can't be written out of the claims. And this is
11 discussed in more detail in our papers. Happy to answer questions, but I
12 think I'll move on to Meyer.

13 So based on the claim construction, we know that the enrichment
14 language should not be ignored and that the inventors were using the plain
15 and ordinary meaning of enrich, that is, to increase the proportion of a
16 fragment. And Petitioner's -- moving to Petitioner's anticipation arguments.

17 Here, as you heard, and as you know, the board heard from the first
18 author of the Meyer reference, Dr. Eli Meyer. Dr. Meyer was the scientist
19 doing the hands-on experiments that were reported in the publication. And
20 as I've put up on Slide 16, Dr. Meyer testified under oath and penalty of
21 perjury that the method was not designed to enrich, the experiment did not
22 involve enrichment, and the data doesn't reflect enrichment of specific
23 fragments.

24 Petitioner -- so let's talk about the specific library method discussed in
25 Meyer. Meyer's goal was -- and I put the Figure 1 on Slide 17 which
26 appears in the body of the Meyer paper. Meyer's goal was to sequence the

1 full transcriptome of the coral species they were studying. So they were not
2 simply isolating all the genetic material and sequencing that. They were
3 looking to study the genes the coral was actively using and those that were
4 being transcribed and processed into DNA -- into RNA.

5 Now, Petitioner takes the position that the goal of the Meyer method
6 is irrelevant, that you shouldn't look at it. Now, there is no dispute that the
7 stated goal cannot overcome the disclosure of a contrary outcome, but that's
8 not the case here. We don't have data that shows enrichment. We have
9 estimates and speculation about potential changes in numbers, but we don't
10 have data that shows enrichment.

11 So the goal of Meyer is important to consider because it informs how
12 a person of ordinary skill in the art would understand the method described.
13 And a person of ordinary skill would be able to look at the method described
14 in figure one, and anticipate how the fragments would behave.

15 And so the assessment here is whether the -- a person of ordinary skill
16 in the art would have looked at the method of Meyer and conclude that
17 amplification -- that the amplification step would result in enrichment. Here,
18 because all fragments were amplified with the same universal adapters and
19 they all end up with a universal Adapter A and a universal Adapter B, a
20 person of ordinary skill in the art would have understood the method to
21 achieve Meyer's goal of sufficient representation across the entire
22 transcriptome.

23 Now, I'd like to walk through a few portions of Meyer that we haven't
24 talked about yet. So we talked a little bit about the SMART protocol, but
25 just to highlight, the SMART protocol is what happens first. And that's what
26 Meyer used to convert the cDNA, or the RNA to cDNA. And as part of that

1 SMART method, nucleic acid sequence are added to the ends of the cDNA,
2 and Meyer refers to those as the CAP primers. That's in the orange and blue,
3 and green and blue.

4 Meyer explained that they used a modified CAP primer, as I've
5 discussed, and that was specifically used to address the homopolymer
6 problem in the 454. They call this the broken T chain. It introduced another
7 nucleotide to disrupt the homopolymer that you would see and, quote,
8 unquote, "broke" the chain that would have disrupted the sequencing
9 analysis.

10 Now, there were several kits available at the time that could have been
11 used to convert RNA into cDNA. And as Dr. Bustamante explained and
12 how, as we've put in the -- this excerpt from the SMART protocol at the
13 bottom of slide 18, a person of ordinary skill in the art would have
14 appreciated that one of the benefits of the SMART protocol, not of Meyer's
15 method, but of the SMART protocol, was its ability to preferentially
16 generate or enrich for cDNA from full length transcripts.

17 And this is what I was talking about, that they solved the other RNA
18 problem at the SMART protocol level before they got to fragments or any of
19 the fragments that we're talking about for the claimed methods.

20 Now Meyer took those full length cDNAs and processed them for
21 sequencing, as shown on the slide 19. Meyer fragmented the cDNAs and
22 generated what they described as three types of fragments: 5'-end fragment,
23 a 3'-end fragment, and internal fragment. Now --

24 UNIDENTIFIED SPEAKER: (inaudible)

25 MS. CIPRIANO: I'm sorry, I'm hearing --

1 JUDGE BRADEN: We're working to make sure that feedback is
2 muted. We apologize for the technical issue.

3 MS. CIPRIANO: I really am bad luck.

4 JUDGE YANG: No. Sorry about that.

5 MS. CIPRIANO: It's okay. Okay. I -- I'm going to -- can I continue?

6 JUDGE YANG: Yes.

7 MS. CIPRIANO: Okay. Now, the Meyer's Figure 1 only shows one
8 internal fragment, but in reality, there were several internal fragments for
9 each transcript. Meyer ligated A and B Adapters shown in yellow and red to
10 all available end fragments, and that those available end fragments would be
11 those without the CAP-ed ends.

12 And Meyer then used a set of three primers to amplify: a primer
13 specific to Adapter A, a primer specific to Adapter B, and a primer specific
14 to the CAP sequences that incorporated the Adapter A sequence. So the
15 result at the right of the figure, you see the results of the amplification step
16 would be 5'-end fragments with an A and a B Adapter on both sides, 3'-end
17 fragments with an A and a B on both sides, and internal fragments with an A
18 and a B on both sides.

19 Now, for completeness at the bottom of Meyer's Figure 1 method, and
20 I put on Slide 20, is Meyer's depiction of the PCR suppression mechanism
21 that was commonly used to ensure that all fragments had the proper adapters
22 for sequencing.

23 So on Slide 21, I've put a comparison between Figure 1, an Additional
24 file 4, the two protocols that are presented in Meyer. And as Petitioner
25 discussed, the Meyer publication provided a modified version of their
26 method in Additional file 4 that included suggested modifications after

1 conducting their experiments. The petition focused specifically on the red
2 box there, the 3'-end fragments from Additional file 4, and argue that this
3 was the fragment that was enriched.

4 So here, we can see that, you know, Petitioner has made a couple of
5 arguments about what exactly the 3'-end fragment is enriched over. But a
6 person of ordinary skill in the art would have looked at the fragments here
7 and would have understood that they were all treated the same. That they
8 were all amplified, that there is no -- the 3'-end fragments that Petitioner
9 claims are enriched -- are amplified with the same primers, ultimately, as the
10 internal fragments and the 5'-end fragments.

11 So you were going to end up with a consistent proportionality of all of
12 these fragments resulting from the Meyer method.

13 JUDGE YANG: If I understand petitioner's argument correctly, I
14 think their comparator is without the Meyer method. Meaning, you know,
15 the so-called underrepresented -- the dataset with the underrepresented 3'
16 fragment. Can you explain why that is improper?

17 MS. CIPRIANO: So if I understand your question, the question is
18 whether there is enrichment over not using the --

19 JUDGE YANG: So the 16 percent versus 10 percent, right, the 16
20 percent is the data here, and the 10 percent, if I understand it correctly, is
21 without this improved method. I don't mean the Additional file 4, without
22 the Meyer's method.

23 So without Meyer's method, there is the potentially
24 underrepresentation, and that's the 10 percent. And with Meyer's method,
25 now it is 16 percent. I think that's the comparison, unless I misunderstood
26 what 10 percent is about.

1 MS. CIPRIANO: That is Petitioner's claim. But I think let's talk
2 about how that 10 percent is calculated, because I think that informs what is
3 really the comparison. The comparison is what is actually in the sample.

4 So they're making the 10 percent is an estimate of what they would
5 see conceptually if you broke -- if you just could -- you could see and
6 measure the actual fragments, how many of those fragments in the original
7 sample were 3' ends? Based on our expectation of the transcripts are a
8 certain length and we're breaking them up randomly, but we take an average
9 and we're estimating how many of those, and this is maybe slide 25 is -- just
10 focuses on this.

11 They -- they're trying to understand, you know, if this is -- if this was
12 accurate, if the transcript was actually broken into only three pieces, then
13 you would expect 33 percent 3'-end fragment, 33 percent internal fragment,
14 33 percent 5' fragment if all of the fragments were broken up in that.

15 Meyer appreciated that it wasn't that simple, so he was trying to
16 understand what the proportionality based on what they thought the length
17 would be. And that is really what the 10 percent is without his solving the
18 454. Really he's looking at making sure that it accurately represents what is
19 a -- what is in the sample. He's looking at a genome or a transcriptome that
20 had never been sequenced before. So he's trying to make sure he has an
21 accurate representation, and that's his estimation of the 10 percent.

22 JUDGE YANG: Right. That is Petitioner's position, I believe, that's
23 the comparison. Which sounds like Patent Owner disagrees. I guess
24 ultimately, we are disputing what the comparator should be, right?

25 MS. CIPRIANO: Yes.
26

1 JUDGE YANG: So what is the comparator in Tecan's view?

2 MS. CIPRIANO: Well, I think that it's Tecan's view that there isn't
3 enough information to understand what the comparator should be. There is
4 no data.

5 JUDGE YANG: What about for the claim? What is -- when you say
6 enriched, what is -- what are you comparing to?

7 MS. CIPRIANO: Oh, I think in theory, Dr. Meyer is making an okay
8 assessment that he -- his calculation is not off base in the conceptual basis of
9 the calculation. But the claims contemplate before and after amplification
10 that a starting material -- you have a sample that has certain proportions of a
11 mixture. And after the method, you have a different proportion of the
12 method that increases your target sequence of interest. That is what the
13 claims before and after the method.

14 JUDGE YANG: All right.

15 MS. CIPRIANO: So let's talk about this calculation a little bit more.
16 And I think what I -- what I'd like to come away with, I have a calculation
17 summary based on Slide 24. And really the critical takeaway is first of all
18 that the Meyer method does not mechanistically support a conclusion that
19 enrichment would occur.

20 So we're looking -- what Petitioner is asking the board to conclude is
21 that a person of ordinary skill in the art would have questioned the way the
22 method worked based on the imprecise back-of-the-envelope calculation that
23 we're talking about in the Meyer paper.

24 And really we're talking about a single, you know, a single part of the
25 discussion section when Meyer is talking about his paper, and we look at
26 what he actually said. His ultimate conclusion is they were, as I said, they

1 were able to overcome the homopolymer problem, and he never claims that
2 they were able to overrepresent the 3' ends.

3 He doesn't make any comment about the difference between 16 and
4 10 percent other than it's slightly more than we expected. It's a -- he doesn't
5 say that that is an actual increase in the data, and for good reasons.

6 The estimations that allowed Meyer to reach this were imprecise.
7 And so far in this case, we have three -- well, we have four different ways to
8 question the data, and I'll go through them quickly as I know Mr. Beavers
9 wants to speak to you all.

10 First, we have questions about the numerator in Dr. Meyer's
11 assessment. And Dr. Bustamante pointed out that Meyer used an average
12 read length of 232 base pairs for his estimation. But if we look at the -- at
13 figure 2A from Meyer that's reproduced on slide 26, this is Meyer's report of
14 the distribution of the read lengths. And these data suggest that most reads
15 were actually higher than the 232 base pair used for the Meyer's estimation.

16 So a person of ordinary skill in the art would look at that immediately
17 and say, well, there is some variability in what we're estimating here. And
18 certainly a higher numerator used in that equation would push Meyer's
19 estimate a little higher.

20 If we look at the denominator, there are also a number of questions of
21 three different theories on where the denominator of the two -- 2,200 base
22 pair came from. The figure on Slide 27 is from Dr. Bustamante's -- well, it's
23 originally from Meyer, but annotated by Dr. Bustamante. And Dr.
24 Bustamante's understanding was that the 2,200 number could have come
25 from this Figure 2(b), which is the reassembled transcript lengths. Now,
26 Meyer's estimate falls in the red box, but as you can see, the majority of

1 transcripts are much shorter, with most of the prevalent lengths being around
2 500 base pairs.

3 So taking this to a -- in -- into account, again, a person of ordinary still
4 -- skill in the art would appreciated that a smaller denominator in Meyer's
5 estimation would have more accurately represented the reported data, and it
6 would be closer to the 16 percent that he observed.

7 We talked a little bit about -- petitioner talked a little bit about Dr.
8 Meyer's testimony about the 2,200 number. And I -- so I put his declaration
9 testimony on Slide 28, but really on Slide 29, there's no -- Dr. Meyer didn't
10 recant his testimony. He simply confirmed that he thought it was reasonable
11 at the time. But it also underscores that this is an -- there is a lot of
12 imprecision in these estimates. They didn't know what the average transcript
13 length would be.

14 This was the first time this transcriptome was being sequenced. They
15 had to make a lot of guesses in this. And even the data that's talked about in
16 Dr. Meyer's in the Meyer publication indicates that it -- that much of the gels
17 and things like that, that would directly observe the fragment lengths and the
18 read lengths would be smears. So any estimation of that is really a guess
19 and a best guess here.

20 So Petitioner also referenced Patent Owner's points about Dr. Sims'
21 analysis of the number. And I'd like to point out Petitioner claims that Dr.
22 Sims did an analysis of this data. Really, Dr. Sims has one paragraph and
23 just merely repeats what is in Dr. Meyer's paper, and that's at Exhibit 1085,
24 at Paragraph 184. He just accepts the numbers at face value.

25 And that -- the board is not required to accept a statement in a prior
26 reference that a prior -- that a person of ordinary skill in the art would doubt

1 or call into question. So here, we have an issue where a person of ordinary
2 skill in the art would understand that this was a qualitative assessment of the
3 difference and the expectation of what Meyer was looking for, and not a
4 quantitative assessment of an enrichment of a target fragment.

5 And that's exactly what Dr. Meyer confirmed at his deposition. He
6 confirmed that he just -- he didn't have enough information and the data
7 didn't exist either in the Meyer publication or what we have today. It doesn't
8 exist that Meyer resulted in enrichment. They solved the homopolymer
9 problem, but that does not mean that they enriched for the 3'-end fragment.

10 So unless the panel has questions for me on these issues, I'm going to
11 turn it over to my colleague, Mr. Beavers.

12 MR. BEAVERS: Good afternoon, Your Honors. My name is T.J.
13 Beavers, and I'll be continuing the arguments on behalf of Tecan Genomics.
14 And as my colleague mentioned earlier, I'll be covering why the petition
15 fails to show anticipation with respect to Claims 21 and 22, as well as why
16 the obviousness grounds fail, and what the evidence of secondary
17 considerations shows us.

18 Now, with respect to Claim 21, it's directed to the method of Claim 1,
19 wherein, as my opposing counsel mentioned earlier, the nucleic acid
20 fragment is obtained to the reverse transcription of an RNA fragment.

21 JUDGE YANG: So let me help you cut this short a little bit.

22 MR. BEAVERS: Yes, Your Honor.

23 JUDGE YANG: Petitioner's counsel pointed out that in the
24 challenged patent itself you showed that the mRNA was transcribed first and
25 then fragmented. What's the difference between that and Meyer's --

1 MR. BEAVERS: Certainly, Your Honor. So -- okay. So first off,
2 what they point to is one embodiment in the specification, and that
3 embodiment talks about reverse transcription, and then proceeds from there
4 to talk about how DNA could be fragmented, right. The problem though, is
5 that the specification does not limit, as they suggest, to just embodiments
6 where the reverse transcription occurs before fragmentation, right.

7 For example, so the specification notes that in one embodiment, the
8 input can be RNA, right. And as it discusses what that RNA can be, it
9 mentions, for example, mRNA, and then it explains in fragments thereof.
10 The specification then continues by discussing that the input could instead
11 be cDNA, which is obtained through reverse transcription of RNA.

12 At that point, the specification does not specify and does not require
13 one way or the other whether the reverse transcription occurs before or after
14 fragmentation. And that's actually consistent with Dr. Bustamante's
15 testimony when considering Example 3 of the patent, where he explained
16 that the example, again, does not specify one way or the other the order
17 between the reverse transcription and the fragmentation.

18 However, I do want to direct the panel to a couple of points in the
19 patent that do distinguish the terms. And so first, just to put this in context,
20 right. The Petitioner's construction is that RNA fragment means any RNA
21 polynucleotide. That construction conflates both RNA and RNA fragment.
22 However, both the intrinsic record and the extrinsic record make clear that
23 those terms could be understood to mean two different things.

24 As the Federal Circuit has explained in Phillips, for example, patent
25 terms are to be construed consistently across claims in a patent. And in fact,
26 when construing terms, it's helpful to see how other claims use them. And

1 so I'd like to direct the panel's attention to Claims 16 and 20 of the 012
2 patent. In both of those claims, it requires fragmenting a nucleic acid, so
3 like an RNA, thereby generating a nucleic acid fragment, an RNA fragment.

4 These two limitations make clear that in a nucleic acid and a nucleic
5 acid fragment are two distinct concepts, and that the fragment is obtained
6 through fragmentation. And I will note in the petition, and this is at Pages
7 61 and 62 of the petition, the petitioner actually maps the cDNA
8 fragmentation of Meyer to both of these claims. They do not map RNA
9 fragmentation.

10 And so to note one other point: The Petitioner mentions and claims
11 that Tecan is excluding all embodiments. As I've noted, that's not correct.
12 But secondly, even more, so the Federal Circuit has explained where you
13 have multiple embodiments, such as the case here. Not every claim needs to
14 map onto or be construed to cover every embodiment. And that makes sense
15 because sometimes the claims, especially dependent claims, cover different,
16 sometimes mutually exclusive embodiments.

17 For example, the nucleic acid fragment comprising DNA, comprising
18 RNA. Those can be mutually exclusive. And so the Federal Circuit has
19 made clear that in such instances, the claims are not required to cover every
20 embodiment.

21 And so turning to Meyer, and this does not necessarily seem to be as
22 much of a dispute, it seems more the claim construction is the issue. But
23 when looking at Meyer, and Petitioner concedes this as well, that Meyer
24 uses the SMART protocol to enrich for full length mRNA that is reverse
25 transcribed to cDNA. And so after that enrichment process, the cDNA
26 transcript is fragmented into the fragments that we see here.

1 And so Petitioner fails to point to any evidence to show that the
2 fragments that they have mapped to the 3'-end fragment, for example, was
3 reversed -- was obtained through the reverse transcription of an RNA
4 fragment as opposed to a full length mRNA. And so for that reason,
5 Petitioner fails to demonstrate that Meyer anticipates Claim 21.

6 Now, I'd like to turn to Claim 22 unless there are any questions with
7 respect to it. Perfect. So Claim 22 is directed to a method wherein the
8 nucleic acid fragment, which contains the nucleic acid sequence of interest,
9 it contains or is ligated to a partial duplex adapter at each end. And Meyer
10 expressly discloses that the opposite happens in the Meyer methods. Both
11 figures of Meyer show that the CAP primers, the blue primer on the ends of
12 the 5' and 3' fragments, blocks the ligation of the partial duplex adapter.

13 And in fact, that's the reason why Meyer then follows up with an
14 oligonucleotide that targets either the CAP primer or in the example of the
15 modified method, the broken T chain to actually include that Adapter A
16 sequence, so the yellow sequence, so that those fragments can be amplified
17 and sequenced with the 454 sequencer.

18 But even more so, rather than just the figure, Meyer tells us explicitly,
19 and this is on Page 19 of the Meyer reference, that the CAP primers lack a 5'
20 phosphate, and because of that, ligation cannot occur. And so the POSA
21 reading this reference is reading multiple disclosures telling us that ligation
22 of the partial duplex adapter is not going to occur on one of the two ends of
23 the end fragments.

24 And so instead, what Petitioner has asked, as you heard earlier,
25 they've asked you to take sequencing data from one sequencing run that they
26 have admitted, both they and their expert have admitted, are not to the

1 fragments that actually underwent the entire claim method. And they're
2 asking you to assume though, to infer that that data is going to be
3 representative of the fragments that do undergo that whole method. And that
4 is exactly asking you to find inherency. They cannot point to an express
5 disclosure, so instead they are asking you to infer that that disclosure exists
6 within the reference.

7 And as the Federal Circuit has made clear, in such instances, the
8 challenger has to show that by practicing the prior method, you are
9 inevitably going to essentially achieve the claim limitation, that it has to
10 necessarily occur. And the Federal Circuit has explained that it cannot be
11 based on possibilities or probabilities; you have to show inevitability, and
12 that is something the petitioner has failed to do so here.

13 JUDGE YANG: Right. So we understand Petitioner has said no
14 inherency argument, that they are not relying on it. Instead, they rely on this
15 SmithKline case. Do you know which one I'm talking about or --

16 MR. BEAVERS: Yes, Your Honor.

17 JUDGE YANG: Could you address that?

18 MR. BEAVERS: Yes, Your Honor. So what they're -- so there's two
19 parts here, right. So as you'll recall in the papers, they had pointed to the
20 cases considering the fact of accidental anticipation, right. To claim that in
21 this instance, because there are sequences that they're pointing to, that it's --
22 it falls outside the scope of the Federal Circuit's discussion of inherent
23 anticipation.

24 And there's two problems with that, right. So the first is, in those
25 Federal Circuit decisions, the Federal Circuit never said that accidental
26 anticipation is not a thing, right. The decision was focused on whether or

1 not a POSA needed to appreciate the accident, or they needed to know that it
2 was occurring before it occurring for it to actually anticipate.

3 And in that case, the Federal Circuit said, no. They don't need to
4 know that the accident is occurring if it's inevitably occurring, right? And
5 that's the problem here, is that in these instances, we don't have an express
6 disclosure that shows you that the mapped fragments are actually being --
7 are having partial duplex adapters ligated to each end.

8 Instead, what we have is this disclosure of other fragments where
9 Petitioner has pointed to accidents, unintentional results that conflict with
10 the express disclosures in Meyer. And the petitioner is asking you to infer
11 from those fragments that anticipation has occurred. And in that instance,
12 even Petitioner's own case law makes clear that they have to show
13 inevitability. This is not a case where they had pointed to an express
14 disclosure.

15 So I hope that answers your question. And I just put up on Slide 43,
16 this is a portion of Petitioner's expert declaration, where he even notes that
17 the observed sequences do not belong to the fragments that actually
18 underwent the full method. And so just to show you real quick, and I do
19 apologize, this is kind of simplistic and I made this slide in the picture. So
20 I'm a little not that artistic, so -- but if you look at this here, right, it
21 emphasizes the variability, right?

22 Dr. Bustamante told us that the Meyer method has a lot of different
23 variables at play; for example, there are different ways you can fragment.
24 You can fragment for different time variables. In fact, Opposing Counsel
25 earlier mentioned that they had -- that Meyer fragmented for three minutes,
26 right, but there are other variables you could have done.

1 And so this figure is meant to show that during fragmentation's
2 allocation, the break could have occurred anywhere, right? These lightning
3 bolts could have struck anywhere along the transcript, right? And what
4 we're looking at is essentially a sequence, the CAP primer, that is about 1
5 percent of the transcript, right, and so it could have struck anywhere.

6 And the petitioner is asking you to infer that every time you practice
7 the Meyer method, inevitably that fracture is going to occur at least once at
8 the CAP primer, and then from there, ligation of the partial duplex adapter is
9 going to occur. The problem though is that the petitioner has not presented
10 any evidence to establish that that will occur.

11 In fact, as Dr. Meyer told us, there were no replicates of this
12 experiment, right? It was a single run through. The data we have is all we
13 have. There were no other replicates. There have been no attempts by
14 Petitioner's expert to, you know, redo the experiment under other conditions
15 that are taught in the Meyer method to be able to establish that this will
16 happen inevitably each time. And so for that reason, the petition fails to
17 establish by its burden, that Meyer anticipates Claim 22 of the 012 patent.

18 Now briefly, I want to talk a little bit about some of the obviousness
19 claims. It's my understanding I'll be stealing five minutes of the time we
20 were going to do for rebuttal. So as we talked about earlier, it sounds like at
21 this point, Petitioner has conceded that their ground to obviousness by just
22 Meyer alone rises or falls with their anticipation arguments. So I won't
23 spend any more time on that. We do discuss in our papers why the ground,
24 as it is in the petition, is legally insufficient.

25 Now turning to ground 3. Ground 3 concerns Claim 2, right, for both
26 patents, and this is directed to the use of genomic DNA. And so Petitioner's

1 main argument here is that Meyer, with the combination of Siebert, teaches
2 or essentially renders obvious the claimed invention, right? And then
3 ultimately what petitioners we see in the papers uses Siebert for is to say,
4 hey, people were interested in characterizing genomic DNA, right? Because
5 Siebert doesn't sequence it. Siebert is using electrophoresis. But they were
6 interested in genomic DNA, and so automatically the POSA would be
7 interested in taking Meyer and adapting it for use with genomic DNA.
8 However, as Dr. Bustamante has explained to us, there are a number of
9 issues with that.

10 And so first off, Dr. Bustamante explained that the petitioner made no
11 effort to actually tell us how you would do that, right? And, Your Honor,
12 you mentioned earlier the fact that with genomic DNA, you're not going to
13 be targeting the poly(A) tail, and so you're not going to have this broken
14 chain, right? And that's important, if I could -- actually, I'll flip to the next
15 slide to show. It's important because of that, there's no reason to use the
16 SMART protocol, right? Which is one of the reasons that Meyer uses it, but
17 that is an important downstream issue, right? And as Dr. Bustamante
18 explains to us, Meyer leverages the CAP primers from the SMART protocol
19 to promote directionality, right? And that's because Meyer cares about
20 where the red box is; so the primer B sequences are placed on each
21 fragment.

22 And so Meyer tells us that because of these CAP primers, they can
23 control which side of the fragment ends up with the yellow and which side
24 ends up with the red. Problem is, without the SMART protocol, you don't
25 have the CAP primer. Petitioner made no effort to explain how the POSA
26 practicing Meyer for genomic DNA would modify the method to be able to

1 still incorporate this same concept from Meyer. And as Dr. Bustamante
2 testified in his deposition, he couldn't think of a way to do it. And so as Dr.
3 Bustamante explained, this is a big issue that would have discouraged a
4 POSA from trying to figure out how to adapt Meyer for use of genomic
5 DNA.

6 Now, I put four -- Dr. Bustamante provided four main reasons why
7 there's a lack of motivation, and I put all four up on Slide 50. The point I
8 want to also make here is that Petitioner only attempted to rebut the last one,
9 the fourth. They did not rebut the other three. They provided no expert
10 testimony in rebuttal to Dr. Bustamante's explanations as to why a POSA for
11 1 through 3 would have lacked a motivation. So I want to turn briefly to 4.

12 Now, as Dr. Bustamante explained, Siebert and similar prior genome
13 walking prior methods would have taught away and discouraged the POSA
14 from practicing the claim method. And so as you'll see here, Siebert
15 describes how prior PCR methods were inefficient. They were complicated,
16 and even in their own hands, they struggled with them. And so ultimately,
17 Siebert came up with this method that uses a special type of adapter that
18 relies on PCR suppression, and that uses a specific type of nested PCR in an
19 effort to fix these problems. However, a decade later, the prior art paper still
20 talked about how these issues persisted, and so people tried to come up with
21 new ways to solve these problems. And months before the priority date for
22 the patents, Sohn published a patent publication where Sohn talked about the
23 most serious problems the PCR-based genome walking methods are low
24 amplification efficiency and non-specific amplification. Sohn noted to
25 improve this problem, complicated multistep methods were developed, but
26 satisfactory performance has not yet been achieved.

1 Noting this, Sohn mentioned that, you know, they wanted to propose a
2 new method that was simpler in nature, and Sohn ultimately proposed a
3 method that is different from the claim dimensions, which as the Federal
4 Circuit has explained, especially in a moment like this, where the prior art
5 recognizes the problems and goes in a different direction, it speaks to the
6 non-obviousness of the claims.

7 Now, the petitioner relies on Leoni, and I want to make two points
8 with Leoni. Their own art shows the complexity of the genome walking
9 papers. Siebert is one of 53 methods identified in Leoni, and in fact, when
10 Leoni talks about Siebert later on in the publication, Leoni talks about the
11 fact that it's used for PCR suppression. That was the point that the art took
12 away from it, not the suggestion of combining Meyer with Siebert so that
13 you could practice the claim dimensions for genomic DNA.

14 Now, briefly, I just want to mention ground 5. The petition has failed
15 to explain why a POSA would look specifically towards Meyer, a method
16 designed to fix a 454 sequencing issue -- or sensor issue and apply that to
17 other sequencing instruments that do not suffer from the same sensor issue.
18 This is a problem that Petitioner has never addressed. Instead, what they've
19 told us is, well, there were other sequencers more popular at the time, so you
20 would just do it. A POSA would just know. But that is not establishing the
21 motivation necessary.

22 And then finally, Petitioner has claimed that Dr. Bustamante failed to
23 actually apply the right nexus analysis. As we note in our papers, Petitioner
24 is citing to a discussion of unexpected results within the In re: Kao paper.
25 That is not the standard across the board for all secondary considerations.
26 And on Slide 58, as we've referred the board to, the Janssen decision, which

1 is a District of New Jersey decision that was affirmed on other grounds by
2 the Federal Circuit, has explained that all you need to show for the
3 secondary considerations at issue here is that there is a connection between
4 the actual evidence and the novel aspects of the claimed invention, which
5 Dr. Bustamante did show, and I will note the petitioner has provided no
6 factual evidence rebutting any of the secondary considerations identified by
7 Tecan.

8 And so it's for these reasons that the petitioner has failed to establish
9 prima facie obviousness and has also failed to rebut the evidence of
10 secondary considerations presented by Tecan. Thank you.

11
12 JUDGE YANG: Actually, before you go into any of your thoughts, I
13 have a question, I need some help. So Patent Owner's counsel explained that
14 this homopolymer issue is -- it exists in the dataset and not in the physical --
15 the library. And this morning, counsel for Petitioner, you know, well, for
16 both parties, discussed the physical limitations and the computer assisted
17 limitations. In -- so here, we're talking about the physical aspect of the
18 limitation, right? So if the 3'-end fragments were there, and it's just the
19 machine that didn't -- couldn't see it or couldn't read it properly, could you
20 elaborate on that part how this actually, when we talk about enrichment, is it
21 enriching the sequence in the library or just enriching the read?

22 MR. HOAGLAND-HANSON: Sure. So I think the parties agree, and
23 I think this is what Ms. Cipriano just testified, that the patent is speaking to
24 something happening with the physical fragments, right? And I think the
25 comparator everybody agrees is also to what was in the sample at the
26 beginning physically and what was in the sample at the end, right? But of

1 course, what you observe at the end, you don't, like, take a microscope and
2 see the fragments. You can only look at the sequencing data to see what
3 happened at the end.

4 And I think on the homopolymer data processing problem, there are
5 two -- there are -- well, there are more than two. There are multiple different
6 ways that the authors tried to address that issue, right? One way was by
7 inserting the broken chain T that breaks up the homopolymer problem, but
8 the other was there's an extra primer in here, right? There's an extra primer
9 that's specific to those fragments. And I think we heard Ms. Cipriano say
10 there's been somehow no mechanistic explanation for how there could have
11 been biased amplification in the -- in addition to, right, but resolving the data
12 observation problem from the homopolymer problem, but that's not right.
13 There's a whole extra primer in there.

14 And what Dr. Sims says in Exhibit 1085 at Paragraphs 183 and 184 of
15 his declaration is that extra primer is selectively targeting and enriching
16 those fragments and they -- it's entirely possible. And in fact, this is what
17 the reference reports that they got more than they expected, and that can't
18 have just been the data processing problem because then they would have
19 gotten just back to 10 percent.

20 And I think where we stand now is that all the chemistry is there, and
21 there's a report in the reference that there was an increase in proportion,
22 right? They -- that they got more than the expectation, right? And, you
23 know, at this point, we're at the point of, as the saying goes, who are you
24 going to believe, Tecan or your lying eyes, right? The reference has all the
25 limitations in it, and we're now going back to sort of second guess the math
26 that's reported in the reference. And I think Ms. Cipriano said a few times

1 that this was somehow a qualitative assessment, and that was sort of
2 categorically different. I think first of all, it's a quantitative assessment. It's
3 reporting two numbers. It's not just saying they're well represented. It's
4 saying, we observed 16 percent and we compared that to 10 percent.

5 But regardless, even if it was a qualitative assessment and they just
6 said, we saw more than we expected, that would be enough. There's no
7 threshold in the claims. There's nothing in the claims that says what's
8 required is basically what Dr. Meyer was talking about in the slides we just
9 saw that somehow enrichment required a microscope on the fragments
10 beforehand and a microscope on the fragments after. The data that they
11 observed from the sequencing data versus what they expected to see in the
12 sequencing data is enough. And it's what they reported and it's what he
13 thought was sufficient to show not just that they'd overcome the
14 homopolymer problem, but also the result of this chemistry. And of course,
15 that's what scientists do all the time, right, is make inferences from data
16 about what's happening in the sample without directly observing each
17 fragment. And likewise, you know, what -- I think what Patent Owner is
18 suggesting is not what we need to do to show by a preponderance of the
19 evidence that there was enrichment here. All the chemistries in the reference
20 and it reports that there's an increase in proportion.

21 I think I already touched on this, but I just want to emphasize too, it's
22 not the case that there's no differential treatment of these other fragments or
23 that somehow all the fragments in Meyer are treated the same. There's an
24 extra primer that targets only the 3'-end fragments. That primer doesn't
25 target any of the other fragments, and that's what Dr. Sims explained is the
26 result of the results in the preferential enrichment of the 3'-end fragments.

1 Now, I think we also heard, and this is one point that I want to clarify,
2 that pre-enrichment doesn't meet the claims, but that's not so. For these
3 other fragments that are sort of in the sample, but then not caught up in the
4 process, they are further -- they're enriched at one step, right, where they are
5 no -- not subject to the SMART protocol, and then they're enriched again as
6 every -- as the mRNA is further amplified, leaving those fragments behind.
7 So they go from, you know, a 1 percent relative prevalence to a 0.1 percent
8 relative prevalence after that extra amplification step. And what I'm still
9 unclear on is whether they're saying that all of the enrichment has to be the
10 result of the amplification step. I'm not sure that was clear. I think there's
11 no -- there's nothing in the claim to suggest that all of the enrichment must
12 be the result of the amplification step. And that if as here, there are some
13 fragments that are sort of left behind during other unrecited steps and then
14 not subject to the amplification, that the amplification can't be contributing
15 to the enrichment.

16 And I'll just direct the panel to the section of Dr. Sims' testimony that
17 she's discussing in Exhibit 2037 at Pages 190 to 192 of the transcript. What
18 Dr. Sims says is that all the amplification step has to do is to further
19 contribute to enrichment. And he used this metaphor of like taking the train
20 to work. That's part of going to work and it gets him closer to his office, but
21 it's not the only thing that he needs to do on his commute to get to work.
22 And so if enrichment is sort of already under way and then furthered, of
23 course, by the amplification step, that's enough for the claims. And I don't
24 think we've seen anything to suggest that the claims somehow require all of
25 the amplification to be the result of -- all of the enrichment rather to be the
26 result of the amplification step.

1 JUDGE YANG: Okay. On the amplification step leading to further
2 enrichment, could you walk through -- I am looking at the figure for -- in
3 Meyer for the Additional file 4. You mentioned an extra primer. Just walk
4 me through this amplification step and explain to me, did the proportion of
5 the 3'-end fragments increase after the amplification versus prior to
6 amplification?

7 MR. HOAGLAND-HANSON: Right. So I think the fragments that
8 we're talking about, and this is Figure 1, not Additional file 4, but it's the
9 same chemistry --

10 JUDGE YANG: Yeah, it's the same as that.

11 MR. HOAGLAND-HANSON: -- as the 3'-end fragments, right? So
12 two things have happened here. First of all, the fragments that are shown
13 here in the amplification step are not the only fragments.

14 JUDGE YANG: Right. I understand.

15 MR. HOAGLAND-HANSON: There's also the non-RNA. And then
16 in the -- for the remaining fragments, the mRNA fragments that were the
17 subject of the SMART protocol that are now being amplified in this step,
18 what Meyer -- what Dr. Sims explains and what the Meyer reference shows
19 is that extra blue primer, right, that comes in first and adds the tail to those
20 fragments is unique to the 3'-end fragments, right? And so while there's a
21 PCR going on here with three different primers, right? Red, yellow, and
22 blue, right? The blue ones only apply to the 3'-end fragments. Now it's a
23 little bit different in Figure 1 because here it also applies to the 5'-end
24 fragments, but the report at the end is that because of the inclusion of that
25 blue primer, they saw more of the fragments with that in it.

1 And so that amplification step and every -- there's -- it's true that
2 Meyer just says we observed at the end more than we expected. And it's true
3 that they don't attribute causality to anything in particular. But what Dr.
4 Sims explains is there's nothing else here other than that extra blue primer
5 that could be resulting in this increase in the relative prevalence because the
6 homopolymer problem would have just resulted in a decrease. They couldn't
7 have gone above the 10 percent expectation unless something else was
8 happening to increase the fragments.

9 I just want to address one other point on this is that obviously this
10 amplification step did continue the enrichment, and this is what Dr. Sims --
11 oh, I think I already covered that point.

12 We heard a bit about then just one issue on the skewing, right? And
13 there's the figure that Dr. Bustamante has with the red figure where he says,
14 oh, this is why the 10 percent number should have been skewed. That was
15 the data that he was referring to in his answer where he told me that the
16 revised expectation would be 13 or 14 percent. He says, "I only have the
17 published distributions, but taking those into account, I would say 13 or 14
18 percent." That's why -- that's still less than the 16 percent. I want to talk
19 briefly about Claim 22 and the issue of the ligation of the adapters.

20 Anna, could you give me Slide 160? Yeah, this is it. Thank you.

21 I -- to be very clear, what Dr. Sims explained is that the POSA reading
22 this reference sees that there's this cDNA fragment that's created, and then
23 sees that it's fragmented by sonication and knows that because of the way
24 sonication works and because it's a stochastic process, that some of these
25 blue fragments will be cut off in that CAP region, right? That's what the
26 POSA understands from reading the reference, and that is then what happens

1 in the actual data, is that the data shows that some of these blue fragments
2 were fragmented in this region.

3 And Anna, could I have Slide 185, please?

4 And this is Mr. Beavers' figure where he shows this and says, oh, this
5 is somehow in doubt. But this lightning bolt struck thousands of times on
6 the other end. That's what's not in dispute. And so the -- there's just no
7 question that the POSA reading the reference understands that random
8 sonication can cleave in these regions, and that that did in fact happen in the
9 exact blue CAP on the other side, thousands of times, and that's why Dr.
10 Bustamante -- if I can have Slide 118, Anna -- conceded, as we show here on
11 Slide 118, that in -- that it did in fact happen. He just said it didn't happen
12 very often, but that doesn't take us into the land of inherency. This is still an
13 actual anticipation.

14 And then so just very briefly, one final point on obviousness of Claim
15 2. I think we just heard Mr. Beavers say that there was no explanation from
16 Dr. Sims of how to adapt the Meyer reference to the -- to genomic DNA.
17 And of course, there was also no argument that there's something special
18 about this method as applied to genomic DNA, but Dr. Sims, in Exhibit
19 1085 at Paragraphs 322 to 324, did explain how to adapt it. And what he
20 said was, this is the same chemistry that's known in the art for targeting a
21 known sequence and reading into an unknown region, right? That's what
22 Siebert was trying to do with genome walking where they knew about one
23 gene with a variable region adjacent and they're trying to read from the
24 known gene into the variable region. That's the same thing Meyer is trying
25 to do. It knows it has a -- it has a poly(A) tale at one end and it's trying to
26 read into the unknown portion of the transcript. This is a known technique

1 and there's nothing non-obvious about saying, oh, the source of the DNA is
2 now different or the sequence that you're targeting is different.

3 And in fact, Anna, if I could have Slide 57.

4 Just to avoid any doubt here that somehow the patent is shooting at,
5 like, some specific sequence or somehow that it's directed to targeting a
6 single gene or anything like that, what we show here on Slide 57 is that the
7 patent is expressly not limited in terms of the sequence you're targeting.
8 Any sequence known in the art to be something that you want to amplify can
9 be used. There's an embodiment of the patent of using random sequences to
10 target it. The patent says you can use this to enrich the whole transcriptome.
11 There's just nothing here that demonstrates that there's something non-
12 obvious about what you're choosing to do. You're using known chemistry
13 steps that are used to target a variable region based on a fixed sequence, and
14 you're applying them to NGS. That's exactly what Meyer did. There's just
15 nothing here to suggest the genomic DNA is somehow interesting or special
16 or takes it out of the anticipated claim. So unless Your Honors have any
17 further questions, I'll turn it back over to Ms. Cipriano. Thank you.

18 MS. CIPRIANO: Yeah. I don't think we need it. Thank you.

19 You're being very generous with the ten minutes, I'll try not to take all
20 of it. So I'd like to address three points and hopefully I'll be quick about it
21 and then Mr. Beavers is going to address a couple.

22 First of all, you heard counsel for Petitioner talk about the presence of
23 these mysterious other nucleic acids that might have been present in the
24 mixture at the amplification step in Meyer, and that those are -- the
25 fragments are being enriched over that. But this is directly contrary to what
26 Dr. Sims testified at deposition where he confirmed that he would not have

1 expected any other nucleic acids to be present at the amplification step in
2 Meyer. And that's at Exhibit 2037, Lines -- sorry, Page 214 to 216. So I
3 direct your attention to that testimony to say really there -- we're talking
4 about the fragments that Meyer is looking at and that -- the -- my -- are in
5 Meyer's figures.

6 The second point that I wanted to address, Counsels -- and Judge
7 Yang, you asked a question about the -- how the method could result in
8 enrichment. And really the -- that would require a lot of assumptions and
9 Petitioner makes a lot of assumptions there. At Dr. Meyer's deposition,
10 counsel for Petitioner and Dr. Meyer had a conversation about the potential
11 for different efficiencies in primers. And counsel for Petitioner was asking
12 Dr. Meyer whether that could result in enrichment if one primer was more
13 efficient than the other and produced more extension products and
14 amplification products, couldn't that result in enrichment? In Dr. Meyer's
15 testimony, and this is at Pages 172 and 173 of -- the exhibit number? Of his
16 deposition transcript.

17 MR. BEAVERS: 1126.

18 MS. CIPRIANO: 1026?

19 MR. BEAVERS: 1126.

20 MS. CIPRIANO: 1126. Thank you.

21 MR. BEAVERS: Does that help?

22 MS. CIPRIANO: He actually testified that he understood that the
23 primers A and primer B were more efficient than the primer directed to the
24 target-specific primer, to the poly(A) tail -- or the CAP primer, excuse me.
25 So just, I direct your attention to that testimony on that point.

1 And finally, there -- there's been a lot of talk about Dr. Bustamante's
2 testimony about the 13 to 14 percent and his off-the-cuff there. And again
3 the testimony that's cited is excerpted from a long answer from Dr.
4 Bustamante where he explains he has no data. He is just making it off the
5 cuff just the same way that Dr. Meyer did. And his testimony is that there is
6 no enrichment; this data is not accurate enough to determine whether there
7 would actually be that 10 percent, 13 percent, 14 percent, 16 percent. In the
8 original sample, it's purely a guess. It's a speculation. So it's not sufficient
9 here to support that finding that Meyer anticipates the enrichment method
10 described in the claims. So with that, I'll turn it over to Mr. Beavers.

11 MR. BEAVERS: Hi, Your Honors, two points real quick. So
12 Petitioner a minute ago suggested that Dr. Sims had provided an explanation
13 as to how the POSA would modify the Meyer method to practice Claim 2.
14 And the petitioner said to Paragraphs 322 through 324 of Dr. Sims'
15 declaration -- I encourage you to look at those paragraphs. You'll see that
16 Dr. Sims said, just like Petitioner, because cDNA is like genomic DNA, the
17 POSA would just know. That does not address the issue with trying to
18 install the CAP primer, which is specifically installed through the reverse
19 transcription of RNA leveraging the cDNA synthesis process.

20 Secondly, Petitioner a moment ago at Slide 57 pointed to a portion of
21 the specification discussing a transcriptome, and Petitioner has offered this
22 argument that the patent allows you to just amplify the entire transcript of its
23 sequence that -- but there's a little imprecision there, right? The patent
24 specification makes clear that it is the target-specific primers as a group can
25 comprise a whole transcriptome. When you map that to the Meyer method,
26 Petitioner only points to two target-specific primers. In the primary, they

1 point to the broken T-chain primer, which is at the 3' end. In the secondary,
2 they point to the CAP primers, and that is it, right? The end fragments.
3 They never point to any primers throughout the entire -- sorry, throughout
4 the entire internal fragments because there are no target-specific primers.

5 And so that disclosure is not applicable to Meyer where -- because
6 Meyer has incorporated the second adapter sequence onto each of the
7 fragments across the entire transcript that are being exponentially amplified.
8 There is no specificity in terms of the target-specific primers that actually
9 fits the claimed invention. And so unless you have any questions, I'll yield
10 the remaining time. Thank you so much.

11 JUDGE YANG: All right. Great job, both sides, and especially our
12 LEAP practitioners, welcome to PTAB practice. Thank you both for your
13 time. I learned a lot from you today and we will issue the final decisions in
14 these cases, and we are adjourned.

15 But please, Ms. Court Reporter, if you need anything from the parties,
16 they will be here to help out.

17 (Whereupon, the above-entitled matter went off the record at 3:05
18 p.m.)

IPR2025-00015 (Patent 10,036,012 B1)
IPR2025-00016 (Patent 10,876,108 B1)

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