

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN SCIENCES, LLC,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00028 (Patent 10,036,012 B2)
IPR2025-00029 (Patent 10,876,108 B2)

Record of Oral Hearing
Held: February 11, 2026

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

IPR2025-00028 (Patent 10,036,012 B2)
IPR2025-00029 (Patent 10,876,108 B2)

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The above-entitled matter came on for hearing on
Wednesday, February 11, 2026, commencing at 10:00 a.m.

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

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3 JUDGE YANG: Good morning. This is a consolidated
4 hearing for IPR2025-0028 and 29. I'm Judge Yang. And joining
5 us via video are Judges Braden and Majors.

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

8 MR. BILSKER: Good morning, Your Honor. David
9 Bilsker for Petitioner. At my side is Mr. Landon Smith. In the
10 gallery is Jürgen Schneider, the head of IP at Qiagen. And next to
11 him is Matthew Traupman, who will be arguing on the UMI, Your
12 Honor.

13 JUDGE YANG: All right. Thank you. Patent Owner.

14 MS. CIPRIANO: Good morning. Linnea Cipriano for
15 Patent Owner. With me is Timothy Beavers at counsel table. Also
16 with me are Scott Weingaertner and John Padro from Goodwin
17 and Andrea Schultz (PHONETIC) from Tecan Genomics.

18 JUDGE YANG: Well, thank you. And welcome,
19 everyone. As set in the trial order, each party has 60 minutes to
20 present its argument. Do I understand it correctly that both parties
21 would have a LEAP practitioner?

22 MS. CIPRIANO: Yes.

23 JUDGE YANG: Okay.

24 MR. BILSKER: Yes.

25 JUDGE YANG: All right. Given that's the case, each

1 party would have 75 minutes. We'll start with Petitioner and
2 followed by the Patent Owner. Each party may, if you want to,
3 reserve up to 20 minutes for rebuttal. Because it's a consolidated
4 hearing, if there is any argument that is only -- that only applies to
5 one case, please let us know.

6 The court reporter will provide a transcript for the
7 hearing, and that will serve as the official record. And to make
8 sure that the transcript is clear later when we come back to review
9 it, please clearly identify the record, and that would include the
10 slide number of the demonstratives.

11 On that topic, thank you both for filing the
12 demonstratives. And we see both parties promptly objected to the
13 other side's demonstratives. I just want to remind you that
14 demonstratives are not evidence. They are here to help us and
15 probably to help you organize your thoughts, too. We will not
16 consider any new argument in the final decision.

17 I recognize that we actually have an outstanding motion
18 to strike. But for today's argument, you are free to proceed
19 however you want. Just remember, time is yours, use it wisely.
20 You don't want to waste time on things we will later not consider.

21 If you believe the opposing consul is making that
22 mistake, you can object. But we ask you to hold your objection to
23 when it is your time to argue. And if Patent Owner makes that
24 mistake in -- during sur-rebuttal, Petitioner, you can let us know
25 afterwards.

1 I don't think I have anything else. Any questions?

2 MR. BILSKER: No, Your Honor.

3 JUDGE YANG: Okay. Very good. Petitioner, would
4 you like to reserve any time for rebuttal?

5 MR. BILSKER: Fifteen minutes and I guess more in the
6 unlikely event that we don't go up to that.

7 JUDGE YANG: Okay. I'll set the timer while you can
8 get ready.

9 MR. BILSKER: So just one question. Am I correct if I
10 use the pointer to point to a particular language and then the judges
11 on the videos will not be able to see it?

12 JUDGE YANG: They will not. That's the reason, if you
13 can just explain which slide you're on, what language you are, you
14 know --

15 MR. BILSKER: Okay.

16 JUDGE YANG: -- referring to, they will be able to
17 follow you.

18 MR. BILSKER: All right.

19 JUDGE YANG: All right. You may start.

20 MR. BILSKER: Good morning, Your Honors. So it is a
21 consolidated hearing, we're talking about the claims of the '012 and
22 the '108 Patent. There are no arguments that are different for
23 either patent. And really, the only argument is on the Independent
24 Claim 1. There have been no separate arguments made by Patent
25 Owner as to the unpatentability of the dependent claims.

1 I have Claim 1 of the '012 up on the slide, which is Slide
2 3. And as you can see, there are a number of elements, but almost
3 all of the elements go to the method for enriching a library. It's
4 only the very last step that relates to sequencing and that's the
5 analysis part. So there are two parts to the claim, there's an
6 enrichment part, which is a method for enriching, and then there's
7 the last step, which is how you analyze that enriched library.

8 Now, the major argument here, the -- almost really the
9 only argument, even when you consider secondary considerations
10 is: Was there a motivation to combine? And the reason for that is
11 because the enrichment steps that are claimed in the patent are
12 identical to the Shapero enrichment method. There's really no
13 dispute about that.

14 But just to focus the argument, if you see what the Patent
15 Owner said in their sur-reply, they said that the Petitioner assumes
16 there's a motivation to combine where none exists. And not once
17 their claim is -- not once does Shapero suggest that MARA, which
18 is the name that Shapero gave to his enrichment methodology, not
19 once does he suggest that it should be used with anything other
20 than arrays. And that's really not supportable by the facts.

21 When you look at the Shapero reference -- and we're on
22 Slide 7 right now. So in the abstract, what it's telling you right
23 from the start, that he's developed a method or his group has
24 developed a method that prepares a target-specific DNA for
25 analysis, and he calls that MARA. And actually, you know, right

1 in the abstract there is a later part where he tells you how he does
2 the analysis. But the main part, the thrust of it, is the enrichment
3 method. And that's also really the main thrust of even the title of
4 the article.

5 Now, Shapero then goes on in many, many places, and
6 we can't go through all of them, we'll go through some of them.
7 But he introduces this by saying there's a lot of methods of
8 analysis of genotyping that have been done in the past. And they
9 all share some common goal. And that common goal in many of
10 them is that you need to enrich the library for the portion -- or you
11 need to enrich the sample for the part of the DNA that you're
12 interested in.

13 And that is the common feature of all of these different
14 methods of analysis. Regardless of whether they're done on
15 arrays, whether done by extension polymerases, they all share this
16 common feature.

17 And what he says is, you know, there's a problem in the
18 sense that when you want to analyze a lot of different loci, a lot of
19 different target sections, it's hard to multiplex with PCR -- with
20 traditional PCR. And the reason for that is because you use two
21 primers, you use a primer for the top strand of the DNA and a
22 primer for the bottom strand.

23 And when you use those target-specific primers for top
24 and bottom strands, what has been happening in traditional PCR,
25 once you get above a number and there's -- some of the articles say

1 10, some say a dozen, some say two dozen. But it's definitely not
2 more than two dozen. You can't get above that; that's the upper
3 limit. When you have a certain number -- and again, the lower
4 number was 10 -- those primers -- those target-specific primers
5 start interfering with each other, they start hybridizing to each
6 other and extending. And that causes spurious results.

7 So what Shapero has said is we figured out a way to
8 actually create the enriched library which avoids that multiplexing
9 problem. And that methodology is we use one target specific
10 primer, we have adapters ligated on. And just without one target
11 specific primer, we avoid the problem of multiplexing. And we've
12 done these experiments and we showed you what the results are.

13 Now, again, there's many places in Shapero that we cite
14 in the briefs, but we couldn't go through them all in this hearing.
15 But what Shapero says is he has a number of results presented.
16 And what he says is, hey, our results look pretty good. We've
17 compared them to other things. We've done multiplex reactions.
18 So we've done -- the lowest number that they did was a 250-plex.
19 So 250-plex means they were looking at 250 separate loci. They
20 did a 750-plex. I think they did 1,000-plex and then they did a
21 4,500-plex.

22 Now, compared to what the patent did, the patent put in
23 prophetic examples and their highest number, I believe, was 17
24 loci. And there's no evidence that they actually even did it in the
25 patent. But in any event, what Shapero tells you is that MARA

1 can serve as an enrichment method for multiplexing to generate
2 very locus-specific sections. And he doesn't limit the analysis to
3 hybrid arrays. He said that is their preferred method because that's
4 how they do it.

5 But, you know, at that previous slide we saw, he said all
6 these other methods have in common, this need for multiplexing
7 and they're all going to benefit from this. So Shapero really is two
8 separate things, there is an enrichment portion and then there's an
9 analysis portion. And he does not say this MARA method of
10 enrichment is limited to only hybrid arrays.

11 And how do we know that? We don't have to just look at
12 Shapero. The Jones reference, which is Exhibit 1011, which is on
13 -- I have to put my glasses on to see that -- Slide 10. That was the
14 reference the examiner cited during prosecution. And it's the same
15 method, it's MARA.

16 But the Jones reference didn't actually present data. He
17 didn't present data, you know, showing how good his enrichment
18 method was, and Shapero did. And we'll get to that a little bit later
19 in the presentation.

20 But what Jones actually says, it drives it home even
21 further, you know. He again says, the invention relates to
22 enrichment methods and amplification. But then there's a portion
23 where he's talking, like, about some of their results and how you
24 do things. He always point the Jones group -- which is also
25 Shapero, they always point to hybrid arrays as an example of a

1 way that you can do the analysis.

2 And it's very, very clear when you read Jones, which any
3 person of ordinary skill in the art has to have knowledge of when
4 considering Shapero. He tells you -- and I'm looking at the right
5 box in paragraph 80; it's the highlighted portion. There's also
6 something that's underlined in red. He actually says, the amplified
7 sample -- so that's the enriched sample that he's done by the same
8 exact enrichment steps that are claimed in the '012 and the '108
9 Patents.

10 He actually says, hey, you don't have to just analyze
11 these by the array, which is the method our company uses. You
12 can analyze them and genotype. Actually, the Affymetrix array is
13 a genotyping array. It's looking for something called SNPs, single
14 nucleotide polymorphisms. He actually says you can analyze them
15 by all these other methods.

16 Now, at least two or three of those are specifically
17 sequencing methods. So MALDI time-of-flight, that's the
18 MALDI-TOP (sic), which is discussed in the Syvänen reference.
19 That's a mass spec way to determine what nucleotides are in there.
20 You're actually sequencing. It's kind of cumbersome.

21 But he goes through a whole list of things and then he
22 says, for a complete list of things that exist at this time, of ways to
23 genotype, see the Syvänen reference. And that's actually telling
24 you, it's not limited -- our enrichment method is not just limited to
25 analyzing by hybridization. Look at this reference that's

1 specifically identified there, and it will tell you a lot of other ways
2 which are identified.

3 Now, just to take a step back for a second, the goals that
4 Shapero is driving toward and the goal that the '102 (sic) Patent
5 and '108 Patents are driving - are identical. They're both basically
6 telling you -- and we're on Slide 14 now. And Shapero is telling
7 you, hey, we've got to -- what we're looking for is a way to
8 multiplex in a better fashion. And the '012 Patent is actually
9 saying the same thing. They actually mentioned kind of the same
10 things. There's a limit to how many loci you can multiplex for
11 when you use traditional primer pairs.

12 Shapero says, I think -- I don't remember exactly, but I
13 think he says a couple of dozen. I think the '012 says a few less.
14 And I can just skip through this one.

15 So another thing that's kind of interesting about the '012
16 Patent is when you look at the '012 Patent and it's disclosing the
17 things that the enriched library the way the analysis can occur, it
18 not only mentions sequencing, it actually tells you that you can do
19 the analysis by hybrid arrays or hybridization. So it's actually
20 agreeing with what Shapero has told you many years before. It's
21 saying this enriched library can be analyzed not only by
22 sequencing, but you can do it by hybridization platforms. And it
23 says it in a couple of places.

24 But at Slide 16, there's a discussion of downstream
25 applications. And in this, again, the underline tells you, you can

1 do it by next generation sequencing the analysis or by
2 hybridization platforms. That's at the very beginning of the
3 column that starts with downstream applications.

4 When you go to the next column, it actually specifically
5 even mentions Affy chips. And that's pointed out at highlight to
6 the '468 Patent, that's a patent to Affymetrix on hybridization
7 arrays. So he's actually telling you the same exact thing that
8 Shapero is telling you.

9 Now, if we look at the Syvänen reference, which is what
10 Shapero referenced in his article when he said, hey, there's many
11 forms of analysis and they all share this common thing. It was in a
12 parenthetical with a cite to references and Syvänen was referenced.

13 And then in the Jones patent, which is also the Shapero
14 group, Syvänen is actually called out by name instead of just as a
15 reference. Again, it's 2001, so this is years before next generation
16 sequencing actually has come out. But Syvänen actually lists all
17 these methods that you can use for genotyping.

18 And before you get to that, it actually tells you that for
19 genotyping, virtually all of the genotyping methods that exist at
20 that time require amplification of the thing that you're looking for.
21 And the reason you need amplification is because if you just have
22 one molecule with some kind of fluorescent marker on it, your
23 signal a lot of times isn't strong enough. So really, like even in the
24 old days when you were looking for stuff, people running gels and
25 they were labeled, you put a lot of the thing that you want to light

1 up to indicate that something's there. And --

2 JUDGE YANG: So Counsel, on the amplification side, I
3 think Patent Owner has been emphasizing the teaching in -- did
4 you call it Syvänen?

5 MR. BILSKER: Yeah. It's hard to pronounce that name.
6 There's a lot of --

7 JUDGE YANG: Yeah. Okay. This reference, Syvänen
8 -- so in that reference, it actually said avoid PCR amplification,
9 several places. I'm sure you know where they are. But for the
10 record, I'll point out page 11 of -- page 940 of the reference. It
11 says, the next generation technology for SNP analysis should avoid
12 the PCR amplification step.

13 And earlier when it were -- it was discussing the
14 advantages and special features of different methods, it also
15 highlighted which ones actually avoids PCR amplification. So
16 could you just elaborate a bit on that?

17 MR. BILSKER: Sure. And I can get to that specific
18 thing. So on Slide 25 I have the thing that you were referring to, I
19 believe -- or actually, it's on Slide 26. But if I can just go back for
20 a second. So Syvänen -- it's S-Y-V-A-N-E-N, Exhibit 1012
21 -- actually lists all the ways that people do genotyping at the time.

22 And you can see there that two of the ways, one of them
23 is identified as mini sequencing. It's actually sequencing, you just
24 don't identify a lot of nucleotides. But another way that's
25 identified there is pyrosequencing, which identifies up to 50 bases.

1 So that's actually literal sequencing of up to 50 bases.

2 And there's a description of what, you know, of -- in
3 Syvänen of what pyrosequencing is and how it works on Slide 24.
4 And then there's a section called future trends. And in that section
5 on Slide 25, it's actually identifying again things for the future.
6 And one of the things that identifies is it's telling you, you know,
7 in these situations where you are going to amplify, one of the
8 limitations is multiplexing.

9 And it identifies, for example, ways to potentially
10 multiplex isolating things on an array, like individual fragments on
11 an array so that you don't have to worry about the primers
12 interacting with each other. So you're almost doing like multiple
13 separate PCR reactions in their own tube or in their own space.

14 But when she gets to the part that you were talking about,
15 which is the thing about the future, it's actually not referring -- it's
16 the analysis portion that she's referring to there. And it actually
17 says that the next generation technology for SNP analysis. That's
18 after the library is created. The SNP analysis which would be, say,
19 the sequencing or the hybridization. She's telling you it might be
20 best to avoid PCR because that can cause bias.

21 And you know that because the example that she gives is
22 an atomic force microscope, so identify SNPs using an atomic
23 force microscope, which, you know, what the future proved is her
24 prophetic looking into the future just did not prove correct as to
25 like how people were going to analyze things in the future. Now,

1 there are single molecule tools of analysis. And actually, all the
2 next generation sequencing articles that we cited -- that we've
3 referred to go through them all.

4 And for example, there is a sequencing method called
5 helicase, which was you only used a single molecule to do the
6 analysis, so you didn't have to amplify. But what all of those
7 references actually say is that they're limited -- like each method of
8 analysis or each method of sequencing has its advantages and its
9 disadvantages.

10 And for example, the helicase methodology that only
11 used a single molecule and -- it actually petered out. It never
12 really went anywhere. It's not a commercial product anymore.
13 But it's good for RNA analysis where you have to convert the
14 RNA to cDNA, which is where you get a lot of the problems with
15 the amplification stuff.

16 But they also say, you know, the next generation
17 sequencing methods, like 454 and Illumina, which by 2007 or
18 2008 well before the priority date was really the dominant -- you
19 know, the 800-pound gorilla in the sequencing world. And it
20 relied on amplification.

21 So Syvänen's like prophetic, like what happens in the
22 future? How are people going to do the analysis in the future?
23 When she says an atomic force microscope might be the best, it
24 just never proved to be the case, you know, a few years forward.
25 And you have to take what exists at the time of priority. And the

1 way that people were at -- the majority of the way people were
2 sequencing was through methodologies that required
3 amplification.

4 And I know from other cases, people have said and
5 there's investigations, Illumina sequencers which rely on
6 amplification have 80 percent of the market. So almost everyone
7 was using amplification. There are a couple of other
8 methodologies like PacBio, which is discussed in all of these
9 references. It's a single molecule form, and so it's Oxford
10 Nanopore, which -- actually, nanopore sequencing existed at the
11 time Syvänen wrote this article. I don't know why she didn't
12 mention it.

13 But in any event, it's not -- this would not tell a person of
14 ordinary skill in the prior -- in the art in, say, 2009, 2010, 2011, oh,
15 you can't use sequencing because this person predicted in 2001
16 that the best way to analyze would be not to do any amplification.

17 So the reference that we're using to combine the Shapero
18 method of enrichment with the next generation sequencing, we're
19 relying on the Delseny reference, which is Exhibit 1007. And
20 throughout this reference, it's actually telling you that next
21 generation sequencing is really going to be the way that people are
22 going to do the analysis portion of genotyping.

23 And again, we have two separate things. You have kind
24 of like the methodology to prepare something that you then put on
25 an analysis platform. The methodology here, there's no argument

1 that the enrichment methodology is any different between Shapero
2 and what's claimed in the '102 and -- '012 and '108.

3 The only thing that we have an argument over is: Is there
4 any indication in Shapero to do -- to use something other than the
5 hybridization array? And there is by that reference to Syvänen,
6 which tells you, you can genotype by pyrosequencing. So if you're
7 going to genotype by pyrosequencing, why would you not then
8 genotype by the next iteration of sequencing technology that
9 comes around?

10 And there really just is no -- there really is no reason.
11 And in fact, the Delseny reference gives you some advantages of
12 using, say, sequencing over an array. So for example, it tells you
13 -- and I'm on Slide 28 here. When you use an array, you miss
14 things. You miss things that are called indels, insertions and
15 deletions. You miss repeats. Hybridization arrays can't give you
16 that level of information. And Delseny is actually telling you
17 that's one reason that genotyping by NGS is actually better. Now,
18 Patent Owner -- and that's in section 4.3, it's on Slide 28.

19 Patent Owner tells you that you have to disregard
20 Delseny because Delseny is telling you a couple of things, you can
21 only genotype when the loci that you're attempting to identify have
22 already been sequenced. Well, I don't believe that Delseny says
23 that, but who cares? I mean, that's not -- that doesn't exclude you
24 from the claim.

25 And in fact, the examples -- the prophetic examples in

1 the patent, they never did it. But the examples are all on loci that
2 have already been characterized. They've already been sequenced
3 as well. So that argument doesn't really make any sense.

4 The second argument they tell you is that the only
5 genotyping that is done in Delseny, the only genotyping that is
6 mentioned, is whole genome sequencing genotyping. So, you
7 know, you take some genome and you sequence the entire genome,
8 no targeted, anything. And then once you sequence the entire
9 thing, you compare it to, like, reference genomes and determine if
10 there are SNPs present.

11 Well, I don't see how anyone can make that argument
12 when section 4.4 -- we're on Slide 29. It's a whole section that
13 says targeted sequencing. So Delseny is actually telling you, one
14 of the important things that's going to be coming around in
15 medicine -- I mean, Delseny is mostly a plant person and he's
16 speaking mostly about plant genotypes. And I mean, those are
17 important.

18 But he's telling you that even in medicine, for clinical
19 applications, targeted sequencing has become very, very important.
20 And he has a whole section on targeted sequencing and even
21 identifies some of the methods of targeted sequencing that have
22 occurred, and one of them is a reference that you'll hear about later
23 today, it's Porreca.

24 So Porreca, in the UMI cases, he had a method for doing
25 enrichment, it was called MIPS. So he mentions that one. It

1 doesn't go into a lot of detail. But he definitely identifies that you
2 don't have to sequence the entire genome, that targeted sequencing
3 is going to be relevant.

4 Now, the same thing shows up in Tucker, which Tucker
5 was the next generation sequencing reference that the examiner
6 identified during prosecution. And again, you know, we have
7 -- I'm going to present to you, like, three references on the next
8 generation sequencing, this is Tucker. And we'll also talk about
9 Dr. Metzker's paper and he was our expert.

10 But Tucker basically says the same thing. He's saying
11 that for genotyping, massively parallel sequencing or next
12 generation sequencing has become so -- such a good tool that it's
13 actually going to replace -- I mean, he says that right at the very
14 beginning, it's going to potentially replace, like, genotyping based
15 on arrays. And he, too, goes through multiple places in his article
16 explaining that.

17 He explains -- I think it's Figure 6A to 6D. He actually
18 goes through a number of enrichment techniques for creating the
19 enriched loci. Some of them are quite similar to the Shapero
20 methodology, which is the methodology that the '012 essentially
21 copied.

22 But he's saying that using those methodologies, you can
23 create the libraries which then can be analyzed on next generation
24 sequencers. And just like Delseny said, Tucker also says that there
25 are advantages to genotyping using next generation sequencing

1 over arrays. And he actually identifies the same advantages as
2 Delseny did. I'm actually on Slide 32 right now. But these are
3 some of the places where he identifies the methods for doing the
4 targeted library enrichment, which will then be analyzed on next
5 generation sequencers.

6 Again, Slide 33, he's identifying how this is going to be
7 genotyped using next generation sequencing once you've created
8 your enriched libraries. And in here -- I just want to -- in here, he
9 starts that -- at 33, he starts a discussion as to why those might be
10 better than the array.

11 But in Slide 34, he goes into more detail as to why
12 genotyping in next generation sequencing may be better than doing
13 it on an array. And that's not to say arrays are bad, you know.
14 These arrays have millions and millions of spots on them that can
15 identify millions and millions of SNPs. So it's very robust. But
16 there are things that it misses. And this is actually telling you that
17 these are the arrays and he's telling you in other places that the
18 next generation sequencing method of genotyping may actually
19 take over for everything else.

20 And this is kind of the conclusion. So this is, essentially,
21 his conclusion there, which is this next generation sequencing
22 methodology of genotyping really maybe -- it's essentially going to
23 be the future, even in clinical applications.

24 I'm going to skip this one for a moment because I'm
25 going to get back to it when we talk about Dr. Metzker. So, you

1 know, I just kind of want to highlight what Petitioner -- or what
2 Patent Owner said in its reply. They say that Petitioner is making
3 these arguments just based on conclusory statements. So one of
4 the statements that -- so this is from Patent Owner's sur-reply on
5 the left. It says Petitioner's arguments are almost entirely based on
6 conclusory statements.

7 Well, what we actually said in our reply was that even
8 Dr. Bustamante, their expert, admits that by 2010 genotyping was
9 being done on next generation sequencers. And we've put that
10 testimony there on the right-hand slide. So we're not just pulling
11 out of the air these conclusory statements. This is just driving
12 home the fact that, like, it's not backward looking. This is not
13 hindsight.

14 You had Shapero telling you there's multiple ways that
15 our methodology can be utilized for analyzing SNPs or mutations.
16 They point you to a reference, Syvänen, that identifies multiple
17 ways of sequencing. Again, those are pre NGS because NGS
18 didn't even exist for five or six years after -- until after Syvänen
19 was published. And, you know, Dr. Bustamante is just confirming
20 that, yeah, people of ordinary skill in the art, by 2010, two years
21 before the priority date, they are genotyping using next generation
22 sequencing.

23 Now, Dr. Metzker's article is another one that, you know,
24 we cited and we relied on heavily in the -- in our briefs. And in
25 that article, they actually are saying that Dr. Metzker teaches away

1 from using -- doing genotyping on a next generation sequencer by
2 multiplexing. And that's not what he says.

3 So at Slide 38, he's saying that he's going to go through
4 all the next generation sequencing technologies that currently exist
5 and what they've been used for. And he's going to highlight how
6 those can be used for genotyping and in the sense of targeted
7 sequencing, not just whole genome sequencing.

8 And so we're now on Slide 40. And this is the portion
9 that Patent Owner claims Dr. Metzker is actually telling you, oh,
10 stay away from something like Shapero. What Dr. Metzker is
11 actually saying -- and this is in the left-hand box -- is he's saying,
12 you know, the capacity of a next generation sequencer is huge.

13 And if you're going to try to use the entire capacity of a
14 next generation sequencer and for targeted genotyping using
15 traditional paired primer multiplexing, you're never going to be
16 able to use the entire capacity of the machine. Remember, you
17 can't get above maybe 10 primer pairs or 15 primer pairs. And
18 there's no way that you're going to be able to use the entire
19 capacity in the machine.

20 That's not actually telling you, oh, stay away from
21 multiplex PCR like Shapero uses or stay away from targeted
22 multiplexing. And how do we know that? Because as you go on
23 in that paragraph, Dr. Metzker is actually identifying methods in
24 which people were multiplexing to put on next generation
25 sequencers.

1 And the state of the art at that time was from a company
2 called RainDance. They had a RainStorm product. And that
3 product is kind of complicated. It would actually do separate PCR
4 reactions in little oil droplets. And he explains that it's at about -- I
5 think it was 3,900 -- you could do 3,900 reactions. Actually, he's
6 not saying don't do multiplexing. He's just saying if you use
7 traditional primer pairs, there's no way that you can use the entire
8 capacity of a next generation sequencer.

9 And, you know, since we're here, I'm also going to go
10 through those middle two columns, too. Dr. Metzker is actually
11 mentioning the levels of enrichment people got when they put their
12 enriched libraries on a next generation sequencer and they
13 compared them -- you know, they identified what the enrichment
14 levels were.

15 And the reason this is relevant is because Patent Owner,
16 throughout their arguments, both in the patent office and here
17 -- and it's been changing a little bit. But they have this argument
18 that, oh, a person of ordinary skill in the art would run away if you
19 thought that, you know, the on-target rates were low. And low, at
20 least in the Brooks declaration, he considered 50 percent to be
21 something that would make a Patent Owner run away.

22 But what Dr. Metzker is actually identifying here is that
23 people were doing next generation sequencing with their kind of
24 state-of-the-art enrichment methodologies at the time. And they
25 were getting, you know, 50 percent -- I think it's 53 percent. And

1 Dr. Bustamante -- and we cited those in our briefs -- agreed that
2 Dr. Metzker's reporting on work other people have done.

3 And this is work by 2009 because that's when this was
4 actually first published online. By 2009, people were only
5 enriching at 50 percent, yet they were getting useful results on next
6 generation sequencers.

7 And if we come back to the Tucker that I told you we're
8 going to come back, you know, when Dr. Metzker says, if you use
9 traditional primer pairs, you can't use the entire capacity of a next
10 generation sequencer. Well, would that make a person of ordinary
11 skill in the art run away and say, well, wow, I mean, I'm using like,
12 you know, a tank to kill a butterfly here or a mosquito?

13 Well, no, because it's well-known -- it was well-known
14 by the time that Tucker published and -- even earlier because
15 Tucker cites other people, that because the capacities of next
16 generation sequencers were so huge, what people would do is they
17 would pool their samples or what they wanted to put on. So now,
18 you and I and the other judges could all have our own samples.
19 We could put them all on the same sequencer.

20 And by barcoding, we actually would be able at the end
21 of the day to tell whose results were for whom. But that was the
22 way to allow people to use the entire capacity of a next generation
23 sequencer, even if you didn't have enough material on your own to
24 do it. And Tucker -- so this is Slide 41, and this is that page 6 of
25 Tucker -- or sorry, page 8 of Tucker, which is Exhibit 1013, tells

1 you, oh, you know, one way to deal with the capacity issue is to
2 pool.

3 And in our briefs, we also cite to Dr. Bustamante, who
4 tells you, you know, at universities they have these things called
5 core facilities, which is not every researcher has, like, a million
6 and a half dollar Illumina sequencer in their lab. There's a core
7 facility. You deposit your -- you know, you drop your stuff off at
8 the core facilities and they do the sequencing for you.

9 And it's very common at core facilities, unless you want
10 to -- well, unless you want to pay for the whole capacity of the
11 sequencer. You wait until there's been other scientists who have
12 given their samples, and they get all pulled together and barcoded.
13 And Dr. Bustamante admitted that that was very common.

14 So again, there are now all these reasons why a -- Patent
15 Owner comes up with all these reasons why a person would be
16 -- there'd be a teaching a way to use the Shapero methodology for
17 enrichment on a next generation sequencer. One of the arguments
18 they make is of the enrichment levels, you know, they just have to
19 be so high. And a person of ordinary skill in the art would know
20 that, and they would be scared away from Shapero.

21 Well, you know, what we've got is a lot of Dr.
22 Bustamante's testimony that will highlight some of it. He actually
23 says the claims don't require any specific level of enrichment. The
24 claims don't require -- and there's actually not a single discussion
25 anywhere in the patent that says, hey, this is only beneficial if you

1 have certain levels of enrichment, or we've enriched to certain
2 levels. There's no mention of any enrichment level. So that's one
3 point.

4 And then with respect to -- we actually went through a
5 bunch of different percentages, you know, asked Dr. Bustamante,
6 could you do it if you only enriched at 25 percent? And it kind of
7 phrased it in the negative that it would be garbage and someone
8 would run away. And he said, no, that's not what I said.

9 So we're at Slide 48 and 46, and we don't have to read
10 through all the testimony. But he actually said, even with high
11 -- he would consider, like, 75 percent off target and 25 percent on
12 target to be a high rate of off. But you could still get useful
13 information on the next generation sequencer with that.

14 And I think the thing that actually drove that home the
15 most was Dr. Bustamante actually admitted -- or he brought it up
16 on his own at the deposition that, oh, well, I know of all these
17 papers, there's very famous papers where they sequence
18 Neanderthal DNA. And, you know, we looked at those papers,
19 and they only enriched between at the lower end, 5 percent; and at
20 the upper end, 30 percent.

21 But they got useful data. So there's no, you know -- and
22 that was like -- I think that was in 2008 or 2009. And there's
23 actually a couple of the Neanderthal papers. The one that we have
24 up here is -- well, I guess this is Exhibit 1120. This is one of the
25 ones that we raised at his deposition or when he mentioned that we

1 happened to have it.

2 There was also a later one that I think was Briggs that is
3 also identified in our briefs where the enrichment method Dr.
4 Metzker actually says, the enrichment methodology, again, they're
5 not very high, they're in the high 20s maybe. But the enrichment
6 methodology is very similar to what Shapero does. So these are
7 published papers where people are enriching at relatively low
8 levels. They're publishing the results and they're saying they're
9 good.

10 Now, in their responses, what Patent Owner says is, well,
11 that's a special case because Neanderthal DNA is really important
12 and, you know, so people would be willing to do it. I'm sorry, but,
13 like, Neanderthal DNA, I mean, looking for cancer or mutations
14 that are, you know, linked to cancer, that's also important.

15 And especially when people are developing their assays,
16 they're not going to run away because they think that the
17 enrichment level is only 5, 10, 15 percent and they're just not
18 going to do it, given all the advantages that the sequencing -- the
19 targeted sequencing has over other methodologies. And this is Dr.
20 Bustamante's testimony, just confirming that what Dr. Metzker had
21 in his article was correct.

22 Now, one thing that's kind of interesting is, you know,
23 we asked Dr. Bustamante, you've looked at the Brooks declaration,
24 which was the whole reason the patent got allowed in the first
25 place, where Dr. Brooks said, you know, I expected running the

1 product of the Patent Owner that I'd only get 50 percent
2 enrichment. So we asked Dr. Bustamante, well, do you agree with
3 that? What he said is, I'm not sure. I mean, he tried to wiggle
4 around it a bunch of different ways.

5 But in multiple ways, he said, I wouldn't agree with that.
6 And then he actually said in later testimony, there's really no way
7 to absolutely predict what level of enrichment you're going to get
8 just by looking at what you're putting in. It all depends on the loci
9 that you're targeting, the conditions. You actually would just run
10 it. And you're not going to know what your level of enrichment is
11 until you sequence it.

12 And when you look at the claims in the patent, the claims
13 in the patent say it's enriched. Well, you have no idea what the
14 level of enrichment is and then it says sequence it. So you don't
15 know what the enrichment is until the process is finished. The
16 enrichment on the enrichment steps, you're -- you just don't have
17 any information about that.

18 One other thing that's interesting is, you know, this
19 drives home the point again, which is this is a reference that Patent
20 Owner cited, and it's from Garber, and it's actually telling you that,
21 look, old -- or next generation sequencing, the prices are coming
22 down. Like, in the semiconductor world, there used to be this
23 thing called Moore's law where you would double the amount of
24 transistors on a chip, like, every couple of years.

25 Now, in next generation sequencing, it's every couple of

1 years. Like, the price of sequencing an entire genome keeps
2 dropping. It was, you know, when they did the genome project
3 and sequenced the first thing, it was like billions of dollars. We're
4 now talking about, like, sequencing an entire genome and next
5 generation sequencing like hundreds of dollars.

6 But even in this time, in 2009, which is still at the early
7 stages, they're saying, it's getting to the point where it's cheap
8 enough that people with ordinary skill in the art are not even going
9 to care if 50 percent of the stuff they have to throw away.

10 And in the case of, you know, those -- that Neanderthal,
11 some of the time they were throwing away 95 percent. This is
12 kind of maybe one of the hearts of some of the argument, which is
13 in Shapero, I guess Patent Owner has been claiming, well, it's high
14 off target.

15 Now, when they did the Brooks declaration, they didn't
16 actually look at the Shapero data. They didn't actually look at
17 Jones and say what the prediction there is. They said, oh, the
18 commercial product I'm only predicting. And as the Board
19 identified in its institution decision that it wasn't comparing it to
20 the right thing.

21 But in Shapero, there is data that shows you that the on-
22 target rate is actually kind of high. So Dr. Bustamante identified
23 two possible sources of spurious results. There's the primer
24 dimers, which is the primers. The primers that are used interact
25 with each other. And we know that in Shapero he's eliminated one

1 of those primers, he's eliminated one of the target specific primers.

2 So now, you only have one target specific primer and
3 two common primers. And he actually gives a mathematical
4 formula later in the -- in his article, which, like, tells you just
5 mathematically what the chances of forming primer dimers are
6 when you start reducing the number of primers, so primer dimers
7 are one. And then the second one is the target-specific primers just
8 mispriming.

9 So, you know, PCR has been around by the time of
10 Shapero for, like, 30 or 40 -- 30 years. I think it was '85 that Kary
11 Mullis came up with it. People have been designing target-specific
12 primers for a long time. They know how to design target-specific
13 primers so that they hit the target. But for some reason, Dr.
14 Brooks is saying, well, the state of the art now is, like, if you
15 design your target-specific primer, you're only going to get it right
16 50 percent of the time.

17 Now, Dr. Bustamante didn't agree with that. But we
18 actually have data in the Shapero reference that shows you that the
19 two sources of spurious results, which would drive down your
20 enrichment levels, are actually not present. So you have this gel,
21 Figure 1A, which is -- we're on Slide 54 right now. It's actually
22 Figure 2A. So Figure 2A is a gel. And Dr. Bustamante admitted
23 that, like, you know -- and people still use it. Gels are kind of like
24 the first step in analysis to see if what you got is really what you
25 were driving for.

1 And in Figure 2A, Dr. Bustamante admitted -- and we
2 have the testimony there -- that if you're going to get primer
3 dimers with the primers are interacting with each other, they're
4 going to be about 100 base pairs or less. And in that middle
5 rectangle where we have the testimony, Dr. Bustamante was asked
6 at line 13, well, there's this 100 base pair marker annotated in
7 Figure 2A, and the markers are in the column labeled MW. And
8 his answer was, and it's not very bright.

9 So Dr. Bustamante actually sees the marker. He says, it's
10 just not very bright; and it's not. There's actually a piece of tape
11 there, you can see kind of like a broad outline. But the experts,
12 you know, the people who look at these kind of things all the time,
13 they see the marker, it's just not very bright.

14 And then he was asked, well, do you see anything in
15 lines 1 to 9, essentially, that indicates anything that's 100 base
16 pairs or less, which would be indicative of primer dimers. And his
17 answer is no. So that's actual evidence that shows you that there
18 are no primer dimers being formed. And that is one of the major
19 sources of the problem with multiplex PCR.

20 So what does Patent Owners say given that information?
21 So they come up with two arguments. First, they say, well, the
22 primer dimers are just missing because they ran off the gel. And
23 they say that Dr. Metzker admits that. There's no way. Dr.
24 Metzker didn't admit that. He said, well, it's possible that
25 something ran off the gel -- and we're on Slide 56 -- but that's not

1 the way the data is presented. And it wouldn't be presented in that
2 way. It's like you wouldn't have the base -- 100-base pair marker
3 submit this in a peer review journal if everything ran off the gel
4 and it was essentially useless.

5 The other argument they make is, well, there are no
6 primer dimers in there because there's this step in there that's
7 identified in the caption of Figure 2A, where this enzyme chops up
8 all the primer dimers. Now, they make that argument with no
9 expert support.

10 We're not sure we necessarily agree with their science.
11 But what it boils down to is they're saying, there are no primer
12 dimers because there are no primer dimers because Shapero got rid
13 of them. The claim doesn't -- so even if you accept that scientific
14 argument, which we don't really think is correct scientifically, it
15 still comes within the claim and its proof that there are no primer
16 dimers.

17 And Shapero's method has actually gotten rid of one of
18 the major problems because the claim is a comprising claim. He
19 added in a step for enzymatically getting rid of primer dimers.
20 And therefore, what you put on the sequencer is not going to have
21 these spurious things that you have to sequence.

22 The other thing that Dr. Bustamante mentions as the
23 possible is the target-specific primer mispriming. And there's
24 evidence to the contrary in the Shapero reference as well on the
25 gel. And we highlighted this pretty prominently in our briefs.

1 So we're at Slide 59 now. And in the right-hand box,
2 starting at line 19 to 21, looking at that gel, what the gel -- what
3 Shapero said is the fragments that we got are the ones that we
4 expected size wise. So everything that we got is what we
5 expected. And Dr. Bustamante admits that that is strong evidence
6 of on-target sequence or on-target priming and not off target.

7 Now they say, well, you can't tell one way or the other.
8 That doesn't rule out that there may be some off target. But there's
9 zero in Shapero that's actually telling you that they're getting
10 anything but good results.

11 There's a number of references -- and I'm going to have
12 to move along here because I'm going to turn it over to Mr. Smith
13 in about six minutes. So they say that persons of ordinary skill in
14 the art have disregarded single primer extension. And that's a
15 reason that people never would have looked to Shapero.

16 And we went through -- I mean, there's no way we go
17 through all of these in the hearing here today because they just
18 basically dump the kitchen sink. But there's a common theme.
19 And that theme is when they cite to articles, they actually, like,
20 crop the quotes. And just as a general rule, what those references
21 are saying, a lot of times, when there -- if there's any criticism at
22 all, they've either solved the alleged problem or they've -- well,
23 they've essentially solved the alleged problem. So this is just this
24 idea that people have disregarded single primer extensions.

25 So this is Siebert, which is one of the very early ones. It

1 was a method very similar to the enrichment methods that are
2 claimed. But Siebert is actually telling you, they get a high
3 specificity.

4 Miura is one that I really love. I mean, I wish we had
5 come up with that reference, but it's one of Patent Owner's. And
6 they're saying, Miura is showing you that people think that single
7 primer extension is really awful. Actually, what Miura says is
8 some -- you know, in some situations, they were finding off-target
9 things. So what they did was they actually designed their own
10 primer design algorithm by concentrating on a particular region,
11 like the three prime region more specifically.

12 And when they did that, the results that Miura showed,
13 he actually got 90 percent specificity. So how is this a reference
14 that a person of ordinary skill in the art is going to look at and say,
15 oh, Miura is using single primer extension and he's getting 90
16 percent specificity. Why would that dissuade somebody from
17 using single primer extension?

18 Same thing with the Sohn reference, which is 2050. I
19 mean, I can't say anything about Sohn other than he seems to be
20 late to the party. I mean, he's actually describing exactly the same
21 thing as Shapero was describing, the exact same methodology.
22 And he says, well, you know, if you increase your ligation
23 efficiency and you put a blocking group on the adapters, then
24 you'll get rid of any problems that you have.

25 Well, Shapero already did that. There was no ligation

1 efficiency problem with Shapero. He put an excess of adapters in
2 the ligation reaction and he had -- Shapero had an amine group.
3 So even if you were to accept Sohn as identifying problems, he
4 solved them.

5 This is actually maybe my favorite slide. So, like, if
6 there's all these problems that are out there and everyone knows
7 about them, for single primer extension, where in the patent does it
8 ever identify a single one of those problems and offer a solution?
9 It doesn't. We gave Dr. Bustamante gads of time to try to find
10 anything.

11 And he actually admitted it. There is no problems
12 identified with single primer extension in the patent. There are no
13 solutions offered. So how can there be -- how can persons of
14 ordinary skill in the art think that they have to run away from
15 single primer extension? The references allegedly negatively
16 citing to Shapero, they just don't. I mean, when you read them in
17 the context, they actually say the opposite. So this is Howell -- it's
18 also same authors as Dahl.

19 And it's in the first full paragraph where it says -- and it's
20 highlighted -- a variant of the method uses adapters. And it says,
21 to achieve amplification of specific genomic sequences. And that's
22 actually referencing Shapero.

23 Now, it does have a statement that says none of these
24 provide 100 percent specificity. But who cares? The patent
25 doesn't require 100 percent specificity. And Dr. Bustamante

1 admittedly nothing has 100 percent specificity. And even Dr.
2 Brooks' declaration said they were 10 percent off at 90 percent.

3 And one thing that's interesting about Howell as well is
4 he actually tells you that this methodology of using enrichment
5 techniques, when coupled with new forms of sequencing, could
6 replace other forms of genotyping that existed like arrays. Bui is
7 kind of the same thing. And I don't have time to go through all of
8 these in detail. But it's the same thing over and over.

9 The quotes are cropped. And, you know, this is another
10 -- this one really highlights it. We're on Slide 68. And this is
11 Morin. They said that Morin basically tells you that Shapero is
12 really bad and it needs to be improved. What it actually says is
13 Morin has his own method. And he says, our method, we need to
14 improve the multiplexing and the specificity. And he cites to
15 Shapero as an example of that improvement, not that Shapero is
16 bad, but that Shapero is good. So it says the exact opposite of
17 what they claim it says.

18 There's also a claim that you wouldn't use NGS
19 sequencing because it doesn't have -- the error rate is too high.
20 That's just not true either. So this is another one of their exhibits.
21 We're on Slide 70, Moorthie. Moorthie actually tells you that
22 while the raw error rates are higher in next generation sequencing
23 because the sequencing depth is much higher. So you sequence
24 the same thing over and over and over again, that the actual error
25 rates are actually better on NGS.

1 And Tucker, Exhibit 1013, says the same thing. That's
2 Slide 71. So then there's more in the Patent Owner's response -- or
3 sur-reply about, you know, everyone should avoid amplification
4 -- PCR amplification. And they cite to the Bronner and Quail. At
5 page 16 or page 18, this is what they cite, note, unnecessary PCR
6 amplification can exacerbate bias. Well, everyone knows that.
7 Why would you do amplification, like, more than you actually
8 need to do?

9 But what we put in this slide -- and you can see -- is the
10 basic protocol actually is PCR. So it's just avoiding unnecessary
11 amplification doesn't mean avoid any amplification altogether.
12 And this is another article that they cite -- that Patent Owner's cite,
13 which is Arid 2042 for -- avoid amplification at all costs. What
14 Arid actually tells you is you can't avoid amplification at all costs.
15 It's just not practical. You can't automate if you avoid
16 amplification.

17 And they actually tell you that they -- the methodology
18 that they've developed for PCR actually alleviates many of those
19 problems. They do say there are times when not using
20 amplification is actually beneficial. And, you know, we agree with
21 that, but that's not across the board.

22 In the sur-reply, there was a couple of things raised
23 which is Qiagen admitted in other proceedings that SPE is, like,
24 this great thing and it's new. I don't understand their argument at
25 all. Because in the EPO proceedings, which is 22 -- Exhibit 2211,

1 what Qiagen was actually saying is they got a reference cited
2 against them.

3 And they said that reference doesn't really apply because
4 that reference is a dual primer, like the old style, like top and
5 bottom strands. And our invention is in a single primer reaction,
6 the improvement of putting in the reaction mix, magnesium at a
7 certain concentration and this MutS protein, and by doing that,
8 we've created a product or -- you know, a product that actually
9 functions better in single primer extension in certain applications.

10 Now, I'm going to turn it over to Mr. Smith. But just to
11 highlight, you know, a lot of these secondary considerations go to
12 the skepticism and unexpected results. And we've seen going
13 through all this that there just weren't any.

14 MR. SMITH: Thank you. As Mr. Bilsker introduced, I'll
15 be discussing the secondary considerations starting with teaching
16 away and skepticism. Now, Mr. Bilsker has already covered many
17 of Patent Owners teaching away arguments. I'll be focusing on the
18 Brooks declaration and Patent Owner's reliance on the Brooks
19 declaration.

20 Now, Patent Owner points to the Brooks declaration to
21 show that a POSA would be skeptical that the claim methods
22 would provide efficient sequencing data and that high off-target
23 binding would create problems for the sequencer, flood the
24 sequencing system, and confound sequencing analysis. But this is
25 both legally and factually incorrect.

1 As Mr. Bilsker has already gone over, Dr. Bustamante
2 has already admitted that the claims and the patent specification
3 does not outline a specific level of enrichment as required.
4 Moreover, in our conversation with Dr. Bustamante, he admitted
5 that even if you're going to put 95 percent off-target junk on the
6 sequence, like they did in the Neanderthal papers, that is not going
7 to dissuade POSAs from doing that sequencing. And it's not going
8 to be an issue that's going to confound sequencers because as we
9 know they did that.

10 JUDGE YANG: And Counsel, can you confirm if you
11 are on Slide 80 or 81, please?

12 MR. SMITH: I am now on 81.

13 JUDGE YANG: Thank you.

14 MR. SMITH: I was on Slide 80. Again, as Mr. Bilsker
15 has already discussed, many of Dr. Brooks' claims have been
16 pushed back on by the experts in this case who we have cross-
17 examined.

18 Moving on to long felt need, the Patent Owner's long felt
19 need argument focuses on efficiencies in cost and in ease for a
20 library preparation method. But as we know, the library
21 preparation method, to do this already existed. And that was the
22 MARA method. And as Dr. Bustamante confirmed, the MARA
23 method is one example of the broader SPET as described in the
24 patent.

25 And now, the case law says if there's already a solution

1 to the long felt need, that a Patent Owner cannot rely on long felt
2 need. And again, the secondary considerations must be tied to a
3 claimed feature. And here, Patent Owner points to, I think, cost
4 and ease. Neither of these are a claimed feature.

5 Moving on to industry praise. So here, again, the praise
6 is directed to the library preparation method that already exists and
7 to multiplexing. And as we know, Shapero taught how to do
8 multiplexing. And again, I want to point out that while Petitioner
9 brought industry praise for its product, it does not bring any
10 evidence of commercial success.

11 And also, the industry praise is -- again, it's all towards
12 the multiplexing and the library enrichment technique. And again,
13 as Dr. Bustamante admitted, there's no requirement within the
14 limitations that multiplexing takes place within the claims.

15 Moving on to copying. Patent Owner's copying
16 argument points to our answer as evidence of access. Now, Patent
17 Owner's case, Medtronic -- in that case, it says that you need both
18 access and similarities. But here, there's none of that. And in
19 Medtronic I'd like to point out that both parties agreed that there
20 was access.

21 And you can see that at footnote 7 of the Medtronic case,
22 access was not disputed. Here, access is definitely disputed. And
23 outside of this answer, Tecan does not bring any more evidence
24 that we had access to the claim method. Moving on, there's.

25 Moving on, on copying, this is Slide 87. And I direct

1 you to the top two steps that we have highlighted there. Again --

2 JUDGE BRADEN: So Counsel, I noticed that in the
3 response that Qiagen denies that it received unfettered access to
4 confidential information regarding the NuGEN's research and
5 development of technologies, its entire IP portfolio or any other
6 trade secrets that NuGEN possessed. Did Qiagen receive any
7 access to confidential information concerning NuGEN's research?

8 MR. SMITH: I don't know if I can speak to that here. I
9 think we can speak to the answer. I'm not aware -- or yeah, I
10 cannot speak to that here, so.

11 JUDGE BRADEN: All right. Thank you, Counselor.

12 MR. SMITH: Moving on again, it requires evidence of
13 both access and evidence of similarities. And we asked Dr.
14 Bustamante about the similarities between the Ovation technology,
15 that is the Patent Owner's, and the QIAseq technology. And when
16 we asked him about that, he pointed out two very distinct
17 differences. I point you to the first step there. As you can see,
18 there is an overhang on the Qiagen product that is not present in
19 the Ovation product. And that overhang is created from an
20 enzymatic fragmentation process.

21 On the other hand, the Ovation target enrichment has a
22 sonication process. And that also creates a difference in the next
23 step. As you'll see, the next step, you have to -- with a QIAseq
24 product, you have to go through an in-repair process. On the other
25 hand, with the Ovation target enrichment, you just do ligation.

1 Now, these are not just small differences in the claims,
2 and we actually -- or small differences in the methods, excuse me.
3 We actually asked Dr. Bustamante about this throughout the
4 transcript from 390, line 25 to 402, line 9. But I'd actually point
5 you to specifically page 402 of that transcript, line 6 through 9.
6 And there, we asked Dr. Bustamante, are these differences trivial?
7 Are these substantial differences? And he agreed that these
8 differences are not trivial and that there are substantial differences
9 between the two products.

10 I'd like to move on to Qiagen's marketing statements.
11 Patent Owner points to Patent Owner -- or excuse me, the Patent
12 Owner points to Qiagen's marketing statements as evidence of
13 secondary considerations. Now, I would point out that there is not
14 a case that I'm aware of that allows you to use a competitor's
15 statements about their own product for secondary considerations.

16 But regardless, I would like to point out that all of these
17 statements were statements specifically about the QIAseq SPE
18 technology. This is not about SPE in general, it's about the
19 QIAseq SPE technology.

20 And you can tell that from reading the paper. And this is
21 Slide 88 talking about Exhibit 2148. This QIAseq technology, it
22 allowed for a reduction in primer dropouts. It also allowed you to
23 sequence for more than just hotspots.

24 And now, these are two advantages that are not discussed
25 anywhere in the '012 Patent. And it is something that is specific to

1 the QIAseq product. As Mr. Bilsker already previewed, a lot of
2 these differences are due to the differences in our product,
3 including the use of magnesium and the MutS protein within our
4 reaction.

5 Lastly, I'll touch on unexpected results very quickly.
6 Patent Owner's only evidence for unexpected results is reliance on
7 the Brooks declaration. And this is not sufficient. As you can see,
8 he's talking about his own skepticism and not the skepticism that a
9 POSA would have as required by the legal authority. And as
10 we've already discussed, a lot of his skepticism has already been
11 somewhat torn apart by the experts in this proceeding who have
12 not agreed with him.

13 That's all I have. We'll go over to the rest of our time.
14 Thank you.

15 MS. CIPRIANO: Good morning, Your Honors. Linnea
16 Cipriano for Patent Owner, Tecan Genomics. As you heard from
17 Petitioner, the question before the Board and the question the
18 Board must answer in this proceeding is whether a person of
19 ordinary skill in the art in 2012 would have been motivated to use
20 the library preparation methods used with the Affymetrix
21 hybridization array technology described in Shapero to generate
22 sequencing libraries for NGS platforms?

23 The answer to this question is no. Not only do the cited
24 references themselves lack any suggestion that a person of
25 ordinary skill would want to combine the techniques to arrive at

1 the claimed method but also the real-world evidence confirms that
2 persons of ordinary skill in the art did not think to combine
3 methods in this way.

4 I will address Petitioner's prima facie obviousness
5 arguments. And my colleague and LEAP practitioner, TJ Beavers
6 will address the secondary considerations including Patent Owner's
7 evidence that the prior art taught away from the claimed methods.

8 So turning to Petitioner's prima facie case. So Ground 1
9 of the petition is based on the combination of Shapero and
10 Delseny. Today, Petitioner's arguments have strayed a little bit
11 from the Delseny reference. But the question before the Board is
12 whether Petitioner has met its burden that the challenged claims
13 would have been obvious under Ground 1 of the petition?

14 And to meet that burden, Petitioner must show that a
15 person of ordinary skill in the art in 2012 would have been
16 motivated to extract the library preparation method of Shapero and
17 combine it with NGS platforms reviewed in Delseny.

18 JUDGE YANG: So Counsel, on that, counsel for
19 Petitioner points out that in Shapero itself, it -- the enrichment
20 method is to prepare for the library. And afterwards, however you
21 analyze, that library is not limited by the microarray platform.
22 Counsel actually points to some languages and said at least one or
23 two of them are referring to sequencing. Do you agree with that
24 statement?

25 MS. CIPRIANO: I don't agree that Shapero represents

1 the MARA method as broadly as Petitioners points out. And if we
2 could skip ahead to Slide 10. So if we look at how the Shapero
3 authors actually described their results, all of the statements about
4 the methods tie the MARA method to the hybridization array.

5 And so what I put on Slide 10 at the top, Shapero
6 explains that they are not relying on MARA for specificity since
7 that specificity is achieved through the use of the high-density
8 arrays. And similarly at the bottom of Slide 10, Shapero's
9 conclusion is that they were able to achieve higher multiplex levels
10 using MARA in conjunction with the hybridization arrays.

11 Shapero does not report on the use of MARA in
12 isolation. And indeed, Shapero's own statements in the discussion
13 section of the article acknowledge the importance of using MARA
14 with the arrays to achieve that specificity. So on page 7 of Exhibit
15 1006 in the right-hand column, the authors summarize the role of
16 MARA in their experiments.

17 And they make three critical points. One, they explicitly
18 acknowledge that while MARA accomplishes their goal of
19 reducing the number of primers for their multiplexing, it
20 introduces nonspecific primer target and primer interactions.
21 That's from Shapero's own words. And I don't have a slide on that,
22 but that's on page 7 of Exhibit 1006.

23 And in the same section, Shapero states that with their
24 MARA method, specificity achieved by hybridization to target
25 specific arrays does not rely on MARA for hybrid -- for the

1 specificity. And it is the hybridization arrays which resolves the
2 issue of the nonspecific interactions that Shapero pointed out.

3 And third, in the same section, Shapero explicitly points
4 out that they did not use MARA with universal arrays. And those
5 universal arrays that Shapero was referring to are one is akin, not
6 -- certainly, not exactly NGS, but akin to NGS where the
7 hybridization array has universal oligonucleotides to bind
8 everything or close to everything.

9 And because those universal arrays would require
10 additional steps to decode if they use that with the MARA method.
11 So I do disagree that Shapero is using MARA for anything other
12 than reducing primers -- the number of primers. And they're
13 achieving all the specificity through -- or they assumed they were
14 achieving the specificity through the hybridization array.

15 JUDGE YANG: So on this specificity part, I need some
16 education. Is there a requirement for the specificity in the
17 challenged claims?

18 MS. CIPRIANO: There is not a requirement for
19 specificity in the challenged claims. But there would be
20 acknowledgment that specificity is important to NGS systems in a
21 person of ordinary skill in the art. And I have a slide on that, too.
22 If we look at Slide 9, Dr. Bustamante acknowledged that
23 specificity would have been important to a person of ordinary skill
24 in the art. And that speaks directly to the motivation of using one
25 particular hybrid -- one particular library preparation method over

1 another.

2 A person of ordinary skill in the art would have
3 understood that if the data that you get out from any particular
4 sequencing reaction is nonsense, or what you're looking for is only
5 a very small portion of what you sequence that creates more work.
6 That is not ideal. Now, in certain circumstances, could you go
7 down that path? Maybe.

8 But that is not what a person of ordinary skill in the art
9 would have been motivated to do. When they're looking for cost
10 efficiency, they're looking for time efficiency and resource
11 efficiency.

12 So when we're talking about Petitioner meeting its
13 burden, Petitioner must show that -- getting back to the burdens
14 here, that a person of ordinary skill in the art would need to extract
15 the MARA from Shapero and combine it with NGS. And in
16 making this argument, Petitioner contends that a person of
17 ordinary skill in the art would make this combination largely
18 because the field was moving in that direction.

19 And while there's no dispute that NGS was certainly
20 being widely adopted and rapidly developing, this process was not
21 as simple as mixing and matching techniques. As the sheer
22 volume of prior art in the record in these proceedings
23 demonstrates, scientists in this field had a lot of options for
24 techniques and were using a lot of different ideas to improve NGS
25 sequencing.

1 But the record shows there is one thing that people in the
2 art were not doing. And that was trying to use Affymetrix library
3 preparation techniques with NGS platforms. And I put a timeline
4 on Slide 3 to help illustrate the point.

5 Now, the Shapero article that Petitioner relies on
6 published at the end of 2004. The first NGS platform became
7 commercially available in, I think, 2004 is what Delseny states that
8 the 454 platform first was sold in 2004. But by around 2007, no
9 one disputes that the field largely had access to NGS platforms.
10 And this was a time that both parties admit was -- is a time of rapid
11 development of many library preparation techniques and NGS
12 techniques.

13 Now, Petitioners point to Delseny's review article that
14 published in 2010. And that discusses various NGS -- the uses of
15 NGS that were happening over the previous several years. Now,
16 Delseny has a review article, it is not presenting any new
17 information. It's presenting on what people were doing in the
18 previous years by 2010.

19 And notably, Petitioners have failed to point to any
20 evidence of someone in the art when there is a lot of trying
21 different things and a lot of experimentation with NGS, that no one
22 suggested the use of Shapero's MARA method with NGS. And it
23 wasn't until 2012, when the inventors of the '012 and '108 Patents
24 filed the challenged applications that the techniques were
25 combined.

1 If this really was a situation where there was a -- there
2 were finite choices in the art to solve a problem, Petitioner
3 provides no explanation why it took until 2012, when the inventors
4 first filed their patent application, for someone to try this
5 combination. Now, if we look closer at the references cited in the
6 petition, it's clear why this is the case.

7 If we look at Slide 4, looking at the Shapero paper,
8 Shapero is a paper reporting on a method for multiplexed SNP
9 genotyping using high-density arrays. Now, this was published
10 before NGS -- the NGS platforms were developed. And there's no
11 dispute that Shapero itself didn't use NGS.

12 Now, in Shapero, they were looking for SNPs or SNPs,
13 single nucleotide polymorphisms, which are known -- they're
14 known single nucleotide differences that exist in the population.
15 And Shapero was looking to distinguish between copies in these
16 -- looking for these SNPs, distinguish between copies of a gene
17 that are almost identical but may include differences at these
18 specific SNP locations.

19 And the high-density arrays or hybridization arrays used
20 for this paper were made by a company called Affymetrix. And
21 Shapero and Jones were scientists at Affymetrix. Indeed, they
22 were the developers of the arrays that were used in the experiments
23 that were reported and touted in this article.

24 Now, you saw in Petitioner's papers that Dr. Bustamante
25 called these scientists experts; and indeed he did. He called them

1 experts in array technology. This is the technology they were
2 developing. This is the technology that they were specialized in.

3 And if we look more closely at what was actually
4 discussed in Shapero, the method that Shapero reports is not
5 simply a library preparation method and a hybridization array.
6 The method Shapero reports is a combination of using the benefits
7 of a particular library preparation method with their specialized
8 hybridization arrays.

9 So as Petitioner's counsel discussed in detail, Shapero
10 reports a library preparation method that uses a target specific
11 primer to introduce a universal primer sequence into the resulting
12 extension products. And those universal primers are used to -- for
13 amplification.

14 JUDGE YANG: So if we just look at this figure, do I
15 understand it's correctly -- it actually does depict all the steps of
16 the challenged claim except the last, which is the sequencing step.
17 Do I understand it correctly?

18 MS. CIPRIANO: Patent Owner does not dispute that.

19 JUDGE YANG: Okay.

20 MS. CIPRIANO: Yes. Now, the library resulting from
21 the MARA method was either further processed with digestion
22 enzymes to remove unwanted material, or it was applied directly to
23 the Affymetrix hybridization arrays. And I'd like to spend a few
24 moments talking through how the hybridization arrays actually
25 work because it's necessary context for the representations that the

1 Shapero authors make in the paper.

2 And I'm looking at an illustration that was in Patent
3 Owner's papers that's reproduced on Slide 5. So hybridization
4 array is a solid -- has a solid support structure that forms the base
5 of what we call a chip. And on that chip are mounted thousands of
6 oligonucleotides with sequences complementary to portions of the
7 genome being targeted.

8 Now, all of those oligonucleotides have to be designed to
9 be complementary to something that they're looking for and
10 looking to bind. And when the sample library is exposed to the
11 chip, the fragments in the sample that are complementary to the
12 sequence on the chip hybridize to the oligonucleotides bound to
13 the chip. And fragments that do not contain sequences
14 complementary are washed away and removed from the process
15 going forward. So then the hybridized fragments from the sample
16 are sequenced and the data is analyzed.

17 Now, let's contrast that with the NGS systems that we
18 have been talking about in this matter. So on Slide 8, I've included
19 an illustration that appeared in Dr. Bustamante's declaration and in
20 Patent Owner's papers comparing the mechanisms of hybridization
21 array with NGS.

22 And so on the left, we have hybridization arrays the way
23 I just talked about it. The light green and lighter purple bars are
24 the oligonucleotides bound to the solid support of the chip. And as
25 you see, only the fragments with the complementary sequence, the

1 little ladder between the rectangles, are adhered to the chip and are
2 moved forward.

3 Now, on the right of Slide 8, we have an illustration of an
4 NGS platform. And here, there are also oligonucleotides bound to
5 the surface, to a solid surface, and these are colored in light orange
6 and light blue. But these oligonucleotides are directed to universal
7 adapter sequences.

8 And while this characteristic makes NGS less expensive
9 and easier to make, it also means that the NGS platform does not
10 provide for any allelic discrimination, as Shapero calls it, or target
11 specificity. So as shown in this -- in the figure, all fragments with
12 the universal adapter sequences in an NGS platform bind
13 -- hybridize to the surface without regard to whether they contain
14 particular sequences of interest or not and all of the fragments are
15 sequenced.

16 So to summarize, the NGS platforms do not provide any
17 specificity the way that the hybridization arrays work. Mm-hm.

18 COURT REPORTER: Judge Yang, I cannot hear your
19 microphone.

20 JUDGE YANG: Sorry, I usually --

21 COURT REPORTER: Thank you.

22 JUDGE YANG: So I was asking to get some help with
23 the -- to connect Shapero with the microarray, these illustrations
24 -- at which step or which component does Shapero provide that
25 makes it better? I guess that's what I'm trying to get.

1 MS. CIPRIANO: Sure. If we can look at Slide 5, I've
2 illustrated kind of the full picture of the Shapero method. So they
3 create fragments. They go through the MARA method to create
4 the library that is used for the sequencing. Then they -- that's
5 where the hybridization array comes in.

6 They use the library and they apply the sample to the
7 hybridization array. So that is going to be -- the sample is going to
8 be the orange, gray, green, gray-blue pieces or the orange, gray,
9 purple, gray-blue pieces on the left.

10 JUDGE YANG: Yeah. Okay. So if that's the case,
11 Shapero happens upstream of these, what you're showing me here;
12 is that correct?

13 MS. CIPRIANO: The MARA method happens
14 upstream. But the hybridization array is a critical piece of
15 Shapero's technology. That is the Affymetrix chip that Shapero is
16 using, the hybridization array that is even in the title of the
17 Shapero paper.

18 So as I was mentioning in response to your question,
19 Judge Yang, the person of ordinary skill in the art would have
20 understood the importance of this specificity. And really,
21 Petitioner's argument here requires the Board to reach a conclusion
22 that a person of ordinary skill in the art would have understood that
23 the MARA portion of Shapero's method could be separated from
24 that Affymetrix hybridization array and used with the NGS.

25 So prior to -- we look at Slide 5 -- the taking all the steps

1 up to MARA method and then removing the hybridization array
2 and sticking up an NGS platform instead of the hybridization
3 -- probe array hybridization that is depicted in Slide 5. And that
4 conclusion is fundamentally flawed because of the portions that
5 even Shapero mentions. The combination of MARA with the
6 hybridization array is how Shapero got its data.

7 So in attempt to undermine the statements that Shapero
8 really highlights this combination, Petitioner points to the text
9 -- one of the things they point to is the text I have on Slide 11.
10 And Petitioner suggests that a person of ordinary skill in the art
11 reading Shapero would consider using MARA alone. But when
12 read in context, the statement is not so broad.

13 Shapero states these results suggest -- and I'll talk about
14 in a minute -- the results that Shapero is talking about are the
15 results generated by using MARA with hybridization array, not
16 using MARA alone. So these results suggest that MARA may
17 serve to allow for greater multiplexing.

18 But immediately following that statement, Shapero notes
19 that when coupled with a method for target specificity, such as
20 arrays, this method may facilitate the use of SNPs in genome-wide
21 studies. So Shapero's goal was to increase their ability to
22 multiplex by reducing the number of primers present in their
23 library preparation method. And Shapero explains that it would be
24 able to do this because they can rely on the target specificity of the
25 hybridization array that they are interested in to get the specificity.

1 JUDGE YANG: Before you go into the data of Shapero,
2 I have a question for you. Do you agree Jones and Shapero teach
3 the same method, the MARA method?

4 MS. CIPRIANO: The MARA method is also included in
5 Jones, yes.

6 JUDGE YANG: Okay. So then Petitioner pointed out
7 paragraph 80 of Jones.

8 MS. CIPRIANO: Yes.

9 JUDGE YANG: Yes. Okay. Go ahead. The show is
10 yours.

11 MS. CIPRIANO: Yes. Let me talk about paragraph 80
12 of Jones. So Petitioner uses -- points -- one of the things that they
13 point to for the argument that you can -- you know, Shapero is
14 applying beyond the hybridization array context. They point to
15 paragraph 80, and I've reproduced that on Slide 12.

16 And Petitioner argues that Jones suggests that the
17 amplified sample could be the -- point to the underlined text on
18 Slide 12, that the amplified sample could be analyzed by any
19 method known in the art. But notably, this is a reference
20 -- specifically, a reference to the method described in Figure 2 of
21 Jones, which contemplates amplifying fragments.

22 Now, I've put the Figure 2 -- the actual schematic of
23 Figure 2 on the right-hand side of Slide 12. Figure 2 contemplates
24 amplifying fragments -- if you see at the bottom of that figure out
25 -- after using a hybridization array for specificity. So there is

1 nothing in Jones that suggests the absence of using a hybridization
2 array for the specificity portion of their methods. So Jones uses
3 MARA to make a library. They apply that library to a
4 hybridization platform.

5 So Petitioner also relies on Shapero's citation to Syvänen.
6 I think you heard that this morning. And Petitioner seems to
7 suggest that we can pick and choose what Syvänen said and what
8 they didn't, and that's certainly not the law. But notably, Shapero
9 cites Syvänen for the unremarkable statement that there are a
10 multitude of genotyping methodologies for SNPs that have been
11 described over the years.

12 Shapero then goes on to explain that many of the
13 methods rely on PCR amplification -- and you'll hear more about
14 that from Mr. Beavers -- and as such are not compatible with high
15 levels of multiplexing. Shapero sought to solve this issue through
16 combining its library prep method with its assays.

17 So if we turn to Petitioner's reliance on the data
18 supported -- presented in Shapero, that, too, does not support a
19 conclusion that MARA could be used on its own with NGS. So as
20 an initial matter, the data presented in table 1 of Shapero -- and I've
21 reproduced that on Slide 13 -- this is all data that is a result of
22 methods that include binding the samples of hybridization arrays
23 and then sequencing them -- sequencing the samples that were
24 bound to the array.

25 And in its papers, Petitioner places significant weight on

1 the discrimination scores and the call rates reported in Shapero.
2 But these are inherently based on the - on this combination of
3 MARA with the array.

4 And as Dr. Bustamante confirmed, the impact of each
5 part of the method, whether it's the MARA method or the
6 hybridization array, cannot be determined from the data presented
7 in Shapero. So a person of ordinary skill in the art would have no
8 way of knowing whether the MARA method would provide
9 similar effects when used with the additional step of eliminating
10 off-target sequencing that is built into -- oh, excuse me, when used
11 with the additional step of eliminating off-target sequencing that is
12 built into the hybridization array.

13 So if we look at -- so Petitioner also spends some time on
14 the gel reads reported in Figure 2 of Shapero, which I reproduced
15 on Slide 14. Now, these gels, importantly, are the only data in
16 Shapero that analyzes the library preparation before it gets applied
17 to the arrays. And I'd like to take each panel of Figure 2 in turn.

18 Now, panel A shows -- that's on the left-hand side of
19 Figure 2, shows the PCR products from Shapero's 250-plex
20 experiment. This gel shows that the PCR reaction produced
21 fragments in the shown size range, producing what's called smears,
22 so -- as opposed to individual bands that you would see if you had
23 individual fragments or specific fragments.

24 And this gel shows, essentially, that the PCR worked to
25 generate amplification products. But it doesn't provide any

1 information about what those sequences are. It doesn't provide any
2 confirmation that it's precisely what they intended to amplify.

3 Now, Petitioner has placed considerable emphasis on the
4 presence or absence of a band representing primer dimers on this
5 show. And I'd like to highlight three points in response. First, you
6 heard earlier that -- I think I heard -- or Counsel say that the
7 experts agree that there was a 100-base pair band. And if you
8 actually look at the testimony that Petitioner's counsel put on Slide
9 54, so Exhibit 1120 at page 230, lines 18 and 19, Dr. Bustamante
10 says, I don't see it, when talking about the 100-base pair band.

11 Second, assuming Petitioner is right that no primer
12 dimers occurred in Shapero's 250-plex reaction, this doesn't speak
13 to the degree of specificity that the primers used in MARA showed
14 in that method. It's possible to not have primer dimers but still
15 have significant off-target binding. There's just no information to
16 tell.

17 And last, there is -- as Petitioner's counsel mentioned, it's
18 not surprising to Patent Owner that the primer dimers were not
19 seen in the 250-plex reaction. Because in this reaction, the library
20 was exposed to digestion enzymes to eliminate unwanted material.
21 And this would have significantly reduced the presence of any
22 primer dimers such that they would not be seen -- not likely to be
23 seen on this gel. So the presence of primer dimers on this gel -- on
24 this particular gel is largely irrelevant to the issue at hand.

25 So if we look at panel B of Figure 2 and this shows

1 Shapero's negative control. And I won't spend a lot of time on it
2 because I think the papers speak for themselves. But the negative
3 control, really, is -- it doesn't speak to whether the target bound in
4 the right spot. It just speaks to whether the primer bound period.
5 Whether it bound to something in the sample and it created an
6 extension product and the reaction was able to amplify.

7 And both experts in this case have agreed with that
8 general understanding of how the negative control works. If you
9 don't have one of the primer binding sequences, then you also
10 would not get an amplification product, and you wouldn't see the
11 information on the gel.

12 JUDGE YANG: On panel A about the enzyme digestion
13 part, Petitioner made an argument saying the challenged claim has
14 the comprising language. So if you could just add a step
15 subjecting the primer extension product to the digestion to get rid
16 of the primer dimer, wouldn't that also solve the problem? So it
17 doesn't matter what is the reason the primer dimers are not there.
18 What's your response to that?

19 MS. CIPRIANO: So this gel is after the amplification
20 process has already occurred. And the primer dimers are an issue
21 when they happen during amplification. I think Petitioner agrees
22 that when the primers stick to each other, they create amplification
23 products that are not intended. So seeing the primer dimer on the
24 gel is an indication that it happened during the reaction, that they
25 were present, and could have disrupted the reaction.

1 The enzymatic digestion that we're talking about is
2 afterward that would get rid of the primer dimers that you would
3 see on the gel. But it wouldn't prevent them from occurring during
4 the amplification step.

5 JUDGE YANG: Okay.

6 MS. CIPRIANO: So I'll just highlight, Dr. Bustamante
7 confirmed that there is just no -- and I have some of his testimony
8 on Slide 18 -- data in the Shapero reference to confirm either way
9 what level of specificity was achieved by the MARA method. So
10 taken as a whole, a person of ordinary skill in the art would
11 understand that Shapero disclosed a successful method for large
12 scale multiplex reaction using the Affymetrix hybridization arrays.

13 And even after NGS was being widely used, the field
14 would not have turned to this successful combination and pick and
15 choose its parts for another sequencing platform. Nevertheless,
16 Petitioner argues that the teaching of Delseny would have
17 motivated a person of ordinary skill to pluck MARA from Shapero
18 and use it with an NGS platform. But the disclosures of these
19 references teach just the opposite.

20 So let's look at Delseny. Now, according to Petitioner,
21 since Shapero is genotyping through SNPs -- and this is what was
22 in the petition, since Shapero is genotyping through SNPs and
23 Delseny suggests that you can genotype with NGS, it would have
24 been obvious to a person of ordinary skill in the art to use a library
25 preparation of Shapero with NGS.

1 But such an argument ignores the details of both Shapero
2 and Delseny, and it oversimplifies the technology. So Delseny is a
3 review article reviewing a number of NGS technologies. And
4 Delseny itself cites over 150 references showing that scientists in
5 this field were actively developing methods for NGS and had a
6 significant number of options. And Delseny includes several pre-
7 NGS techniques in his discussions but notably does not mention
8 MARA or Shapero.

9 So Petitioner specifically relies on Delseny's report of
10 scientists using NGS for genotyping in the petition. So let's look at
11 what Delseny actually says about using NGS for genotyping. I
12 have an excerpt on Slide 20. Delseny suggests that NGS has
13 opened the possibility to genotype by sequencing. And Delseny
14 points to a paper that is -- has illustrated this technique, an article
15 titled high-throughput genotyping by whole-genome sequencing
16 by first author, Huang, and senior author, Han, who is also a
17 coauthor of the Delseny paper.

18 So Delseny concludes that the technique described in that
19 article can substitute for using microarrays for genotyping because
20 of its higher resolution. But if we look closer at the technique that
21 Delseny is referring to in the Han paper that we refer to, Han
22 describes a method for whole genome resequencing with NGS.
23 And Han's goal was to address accuracy concerns that arose from
24 genotyping using individually targeted SNPs, just like Shapero did.

25 Han explained that analyzing SNPs collectively, unlike

1 Shapero, over the entire genome could resolve these issues. So far
2 from signaling that NGS could be used for all genotyping
3 applications, Han is describing a specific genotyping technique
4 and cautioning against -- that itself cautions against using single
5 SNPs the way Shapero did. And this is just insufficient to show
6 that a person of ordinary skill in the art would have been motivated
7 to combine Shapero with Delseny to arrive at the challenged
8 claims.

9 And now, I've put a few quotes from the Virtek Federal
10 Circuit case just to stress the importance of the motivation to
11 combine in this analysis. So as the Federal Circuit has repeatedly
12 confirmed, KSR did not dispense with the requirement that
13 Petitioner must show that there was a motivation to combine the
14 prior art to arrive at the challenged claims.

15 Indeed, the question is not whether a person of ordinary
16 skill in the art could have come combine the prior art, but whether
17 there is evidence to show that a person of ordinary skill in the art
18 would have been motivated to do so. And the prior art here does
19 not provide any reason other than a generalized trend toward NGS,
20 that a person of ordinary skill in the art would combine these
21 teachings to arrive at the challenged claims.

22 So as you heard today, Petitioner's arguments have a
23 little departed from what is in the petition to incorporate another
24 -- a number of new references and arguments. But in the petition,
25 Petitioner relied on three points to support its motivation

1 arguments: the data in Shapero, the text of Delseny and Syvänen.
2 And as I've discussed here, and Tecan explained in its papers, that
3 none of these would support a finding of obviousness here.

4 Now, one of the new arguments you heard today was
5 regarding Tucker and that Tucker would have provided a
6 motivation to use MARA method with NGS. But Petitioner does
7 not explain how Tucker would have motivated a person of
8 ordinary skill in the art to modify Shapero in the way that removes
9 the target specificity aspect that Shapero relied on. So not only is
10 this argument not in Petitioner's petition, it also lacks sufficient
11 specificity to support a finding of obviousness.

12 So I'm now going to turn the podium over to Mr. Beavers
13 to talk about the teaching away and secondary considerations.

14 MR. BEAVERS: Good morning, Your Honors. My
15 name is TJ Beavers. And I'll be continuing the arguments. So as
16 my colleague mentioned, I will be discussing how the prior art
17 teaches away from key aspects of the claimed inventions. And
18 then I'll go from there to talk about some of the other secondary
19 concerns considerations.

20 And so as you've heard, and you heard this from
21 Petitioner, there are quite a bit of exhibits in this case. There are a
22 lot of references. And that is because this is not such a simple
23 field, right? There are a lot of different methods, a lot of different
24 techniques that people have tried over the years as they've tried to
25 figure out how to resolve various issues.

1 And so on the screen, I put up 26 references that we
2 identified that teach away from various aspects of the claim
3 defense. And you'll see highlighted in green, the references that
4 Petitioner did not bother to address during these proceedings,
5 you'll see there's 14 of them. I will note that as of today, Petitioner
6 first -- finally addressed Bronner, which is Exhibit 2155. That
7 exhibit appeared in the POR as well. So it's incorrect to claim that
8 they're now addressing it for the first time on sur-reply.

9 So what I want to kind of hone in on are two specific
10 areas of prior art references, right, and why they're important: the
11 first considers the single target-specific primer that's used in the
12 claimed invention; and then the second looks at PCR amplification
13 itself. Now, as my colleagues spoke about Delseny and through its
14 incorporation of Han would have taught away from adapting
15 Shapero, which uses MARA for use with NGS, given how Shapero
16 focuses on specific loci with a single primer.

17 But there's also a number of genome walking papers,
18 which you heard from Petitioner earlier, that also discuss these
19 issues. And so just at a high level, genome walking is kind of a
20 loose set of methods that are used to characterize genomes, largely
21 looking at known regions and then from there, kind of trying to
22 figure out what's going on around there, right, what other genes
23 might be around those regions.

24 And a lot of these early methods were very painstaking,
25 you know. They would use a gel to really be able to tell what are

1 the sizes of various genes. And that's the case with Siebert, right?

2 We identified Siebert for a few reasons. So the first is that Siebert

3 comments on earlier prior art methods. And this is key, right?

4 Because as you'll see, and as Dr. Bustamante explained,

5 the art is fluid, right? The art is not just frozen in time. In 2005,

6 2006, inventors are still working at different techniques. And so as

7 we go through these papers, we see a progression of what they say

8 about the papers that came before them. And then sometimes the

9 inventors say, hey, we've got something that maybe works.

10 Sometimes they claim it did work. Sometimes they say it worked

11 in some cases.

12 But then we see a paper that follows -- that talks about,

13 hey, wait, there are issues with that. And that's what Dr.

14 Bustamante was trying to convey, was showing a whole chronicle.

15 So looking at Siebert here, Siebert's telling us some

16 earlier methods when they used them, generated unwanted

17 products, that they would have to use other steps like size

18 separation because they were off-target products that essentially

19 confounded the results they were looking at. And so what Siebert

20 did was that it proposed a method that used a specialized adapter,

21 along with PCR suppression, and then a specific type of nested

22 PCR to be able to try to fix some of the specificity issues.

23 And now you heard Petitioner earlier kind of discuss this

24 as almost like a panacea for target specificity issues. But I want to

25 make the point, as we put on Slide 27 and highlight it, Siebert is

1 using two rounds of gene-specific primers. At no point does it use
2 a universal primer pair.

3 That's important because one of the things the claimed
4 invention sought to address was being able to efficiently PCR or
5 amplify in other ways multiple target regions in an efficient
6 manner that could then be used with NGS. And so it's a key
7 distinction here with respect to Siebert.

8 But fast forward a decade later, right, Siebert reports that
9 these modifications helped. But then you look at papers in 2005
10 publishing around the same time as Shapero, and they talk about
11 how there's still problems in the art, right? If we look, for
12 example, at Miura, Miura noted the conventional PCR as of 2005
13 used a primer pair. And that methods that use a single target
14 specific primer were often plagued with nonspecific amplification
15 products derived from so-called off targets.

16 And in a minute, I'll talk a little bit more about Miura.
17 Petitioner has pointed out how the algorithm worked in one
18 specific experiment. But there's more to the story than that.
19 There's also Tsoktouridis. Tsoktouridis also compared earlier
20 genome walking methods and methods that relied on PCR
21 amplification. And Tsoktouridis reported, the comparison of these
22 methods revealed no simplicity, low reproducibility, high
23 backgrounds in nonspecific PCR products, and described them as
24 laborious and time consuming.

25 Now, I want to talk a little bit more about Miura. You

1 had heard that Miura had used this algorithm and then in one
2 instance was able to obtain 90 percent on target specificity. There
3 are a couple of key points that are missing from that story, the first
4 is the specific type of method that Miura is using. Miura compares
5 two different genome walking methods that use a special targeted
6 adapter ligation. And so in other words, what Miura is able to do
7 is Miura is able to direct the adapter itself where it is ligated. So
8 that it is ligated onto the fragment of interest.

9 And what that is doing is it's creating what is pretty much
10 a second target specific priming site, right, because that's where
11 they're able to control where the second site goes. And it makes
12 sense, right, in the context of genome walking. As I mentioned a
13 moment ago, many of these methods are anchored on we know
14 where one sequence is and we kind of want to see what else is, you
15 know, next to that sequence. But they don't know what the rest of
16 the sequences are.

17 And so the way to fix that is let's install an adapter that's
18 specific to the other end of the fragment so that then we can go
19 about perhaps amplification or other methods to then characterize
20 what is next to the known sequence, right? So that's one key
21 difference.

22 So first off, before Miuri even used its algorithm, it noted
23 that trying to develop or even, you know, fix these methods or
24 adjust them, it still had issues with off-target priming. And it
25 attributed that to the misannealing of gene-specific primers.

1 But then when Miura developed an algorithm to try to
2 predict how the gene specific primer may perform, sure, in one
3 instance, 90 percent on target. But then in other instances, Miura
4 obtained low yield of on targets, and they were plagued with many
5 off-target products. And so what Miura tried to do was adjust the
6 algorithm to fix some of these issues. And in some cases, Miura
7 was able to, but then new issues would appear.

8 And so ultimately, this led the authors of the paper to
9 conclude that they could use this algorithm to eliminate,
10 apparently, poor primers. That's it, right? And as you've seen in
11 the papers, though, Petitioner argued in reply that you could take
12 an algorithm like this and this would solve the issues with target
13 specificity, that by the time you got to the claimed inventions, a
14 POSA didn't care because it was already solved.

15 That's contradicting what Miura is telling us in the
16 publication. But also, it's contradictory as we've identified in our
17 sur-reply to what Dr. Metzker, their expert, testified under oath in
18 2021 where he talked about algorithms like this. And at the time,
19 during his deposition, he said that they create a lot of
20 misinformation. And so that's why he doesn't use algorithms like
21 this to assess mispriming, in other words, off-target binding.

22 And one other point I want to make about Miura -- sorry,
23 I wrote a note about this earlier -- Petitioner focused on a reference
24 that I believe they referred to as Arid, we've been referring to it as
25 Aird, either way, it's the same reference. And so that reference

1 sought to optimize PCR conditions, right?

2 And it emphasized the fact that when you're trying to
3 sequence, you're amplifying specific fragments, you can tinker
4 with things to try to improve the conditions, right? And it was the
5 proponent saying, you got to experiment, it works sometimes, it
6 doesn't work other times, right? And that was ultimately what
7 Arid is telling us is you can, right?

8 But Miura tells us, sure, this is out there, it's not that
9 helpful. It's hard to do that as a mass library preparation method
10 because you're having to experiment each time.

11 Now, another reference we pointed to was Sohn. Sohn is
12 a patent application publication that issued in 2011. And we cited
13 to Sohn because it provides -- this is right on the eve of the priority
14 date. And it provides a summary of where two decades worth of
15 genomewalking methods led us. And as Sohn explains, first --

16 JUDGE YANG: And Counsel, can you please confirm,
17 are you on Slide 30?

18 MR. BEAVERS: I am on Slide 30.

19 JUDGE YANG: Thanks.

20 MR. BEAVERS: Sorry, Your Honor. So Sohn mentions
21 the fact that the most serious problems of the PCR-based genome
22 walking methods are low amplification efficiency and nonspecific
23 amplification. Sohn recognizes that complicated multistep
24 methods were developed. And then Sohn notes, satisfactory
25 performance has not yet been achieved, right? And so Sohn

1 sought to come up with a more simplified method to be able to
2 resolve these issues.

3 And as you heard from Petitioner earlier, they claim that
4 Sohn was late to the party, that essentially, it solved the problems
5 the same way as Shapero, which first off, mind you, as my
6 colleague mentioned, Shapero was not a library preparation
7 method for NGS. And there are a couple nuances in terms of how
8 a library preparation method for a hybrid array differs from that of
9 NGS. And I'll talk about that in a moment.

10 But the other thing, too, is Sohn is a different method.
11 Sohn is again using a targeted adapter ligation approach, in other
12 words, meaning that it's directing where that adapter is going. It's
13 not ligating adapters to every available fragment and solution.
14 And that's key, right?

15 And we've pointed to this. Because as the Federal
16 Circuit has explained, for example, in the Panduit case that we cite
17 in our papers, that the art recognized similar problems and went in
18 a different direction is evidence of the nonobviousness of the
19 challenged claims. And that's the case here.

20 Now, Your Honor, earlier you had mentioned the
21 Syvänen reference. And so I wanted just to discuss a couple of
22 points on that. First, I wanted to highlight some of the key teach-
23 aways from what Syvänen is saying. And then I want to discuss
24 some of what Petitioner had mentioned about the Syvänen paper.

25 So first, as you will see on this paper, in the first block,

1 the future trends aspect, Syvänen is discussing how the principal
2 factor that limits the throughput of assays today is PCR
3 amplification. In the second block, Syvänen writes, the next
4 generation technology for SNP analysis should avoid the PCR
5 amplification step and the technology could be based on the
6 analysis of single DNA molecules.

7 Now, you heard earlier a distinction about library
8 preparation versus analysis for purposes of PCR amplification.
9 The reality is it is the exact same PCR amplification either way
10 you look at it. And in fact, single DNA molecule analysis avoids
11 the PCR amplification altogether.

12 As we pointed to in our papers, Delseny discusses what
13 they refer to as a third generation of next generation technology
14 sequencers that sought to overcome the issues with PCR
15 amplification through using single molecule sequencing. And so I
16 just want to point to this that in fact, people did take what Syvänen
17 said, and others like Syvänen said and invested resources and time
18 in developing entire sequencers that didn't have to rely on PCR
19 amplification.

20 Now finally, as you've heard from Petitioner, they've
21 alleged that Syvänen shows that you could have taken MARA and
22 used it with other analytical techniques besides an array. And of
23 course, my colleague spoke about the nuance with Jones where
24 Jones doesn't separate the array. Yes, there could be other
25 analytical instruments used in combination with the array, but the

1 array is still there.

2 The point I want to make about Syvänen is it also would
3 have reinforced that you need to keep the array. Syvänen wrote
4 that when using -- and I'll summarize here -- labeled allele-specific
5 PCR primers without a consecutive target specific detection
6 reaction or size separation step, the specificity of the method might
7 be hampered owing to primer dimers and other spurious
8 amplification products.

9 This is key because, essentially, what Syvänen is saying
10 is that if you're going to use PCR amplification in an instance, like
11 what Shapero did, you need something that's able to detect, right?
12 And Shapero tells us the allele discriminator in MARA and
13 Shapero, as a whole, is the array. And so Syvänen is telling us,
14 you need to stay with the array in that context.

15 Now, you saw table 2 earlier, and the Petitioner pointed
16 to SNaPshot and to pyrosequencing. And I'll talk about that in a
17 second. But I just wanted to highlight briefly that Syvänen
18 recognizes several methods where Syvänen praises the most
19 significant advantage and the special feature as, for example,
20 alternative to PCR. PCR amplification avoided -- avoids target
21 amplification. And so Syvänen is openly criticizing PCR
22 amplification as part of the process.

23 Now, turning back to the methods that Petitioner had
24 pointed to. As we've explained in our papers, SNaPshot uses
25 essentially just one nucleotide extension process. It is not

1 incorporating the same type of technology, at the end of the day, as
2 NGS. It's not Sanger sequencing either. It is a very specific one
3 nucleotide analysis method. And Dr. Bustamante, at length, talked
4 about it in his declaration and why that method is not telling
5 anyone that you could actually take MARA and use it with NGS or
6 pre-NGS technologies.

7 Now, pyrosequencing, this is something that Petitioner
8 first raised in reply. And as we noted in our sur-reply, Syvänen is
9 critical of pyrosequencing in several regards and most notably the
10 fact that it's not good for multiplexing. The problem is
11 pyrosequencing's demands lead to a situation where you can't
12 really analyze many sequences.

13 And so Syvänen has noted that it is -- in fact, in that
14 same table, I don't have the blow up on this one, but you will see in
15 their slides that Syvänen has, as a critique of pyrosequencing, the
16 multiplex issue. And this is important because Shapero tells us
17 that one of the goals of MARA plus array was to be able to
18 multiplex, higher multiplexing. So Syvänen is telling us
19 something like pyrosequencing is at odds with Shapero's goals.

20 Now, briefly, I want to talk about some of the other PCR
21 implication methods. Petitioner pointed to Bronner and said that
22 Bronner, you know, taught -- disclosed the Bronner reference
23 disclosed other methods beyond PCR preamplification. And that's
24 true, right?

25 And the point here that we were making is that when you

1 look at the art as a whole as a POSA would, a POSA would be
2 aware of all these other articles. A POSA would be aware that
3 Bronner and Quail worked together and developed technologies
4 that omitted PCR amplification. And the Quail papers and the
5 Kozarewa paper discussed the benefits. It criticized PCR
6 amplification. And it discussed numerous benefits of methods that
7 actually avoided PCR amplification, consistent with what Syvänen
8 was saying.

9 And you heard about Dr. Metzker's publication. As you
10 have seen from the papers, the parties disagree as to the scope of
11 Dr. Metzker's statement that coupling PCR with high-throughput
12 NGS platforms for targeting sequences is not practical.

13 Now, I want to flag for Your Honors -- I can't find
14 anything -- that Dr. Metzker's statement and our interpretation of
15 his statement. As Dr. Bustamante has explained, a POSA would
16 understand it, is consistent with other papers in the record.

17 For example, Mamanova, which is Exhibit 2011, in this
18 proceeding at page 112, states that PCR is difficult to multiplex to
19 any useful degree and said that in practice, it is often more
20 straightforward to perform PCRs in uniplex. You heard from
21 Petitioner earlier today discussing about RainDance. Mamanova
22 identifies RainDance as an example of improved multiplexing in
23 2010. It does not mention Shapero despite Petitioner's claims that
24 Shapero somehow promoted multiplexing.

25 JUDGE YANG: So on this issue -- so besides Patent

1 Owner, did other POSAs move away from PCR in multiplexing, or
2 did they also continue and -- yeah, go ahead.

3 MR. BEAVERS: Certainly, Your Honor. So there's
4 several branches here, right, you can think about. So certainly,
5 there are some people in the art that continued using whether it
6 was multiplexing, maybe two primer multiplexing, or they used
7 other methods to do so, right? You have the branch of Shapero
8 and Co that leverage the hybrid array, the specificity of the array to
9 allow them to reduce the number of primers they were using. And
10 the key there was that they were leaning on the fact that they didn't
11 need to rely on the primers for specificity, they could rely on the
12 array for that.

13 Then you have instruments, like RainDance, where they
14 completely separated. Ultimately, like, the individual reactions to
15 where each reaction occurs in an individual silo. And in fact,
16 earlier, Petitioner had pointed to Syvänen's discussion of PCR
17 amplification and had noted how you could use a microarray as an
18 option for that.

19 I just want to point out that's exactly what Jones and
20 Shapero is doing. Syvänen's recognizing that type of work in
21 2001. That's different, though, than, for example, using a single
22 target specific primer with an adapter -- a partial duplex adapter
23 that's ligated onto every fragment and then from there relying on
24 specific specificities.

25 And so there are differences in terms of multiplexing first

1 as to how people have kind of diverged over time. And then of
2 course, there's the publications discussing whether or not PCR
3 amplification should be used in context there. And of course, there
4 are numerous publications about single molecule as Delseny
5 -- sorry, as Delseny discusses about how you can use single
6 molecule sequencing as an alternative to multiplexing.

7 So I want to discuss briefly the long felt needs that we've
8 identified. And so Dr. Bustamante identified a number of papers
9 that published near the priority date discussing various issues with
10 NGS target capture technology. And he identified that these
11 papers echoed the exact same needs that the patent sought to
12 resolve.

13 And I just want to read briefly what the patent articulates
14 as the needs in the art. The patent stated that there was a need for
15 improved methods for selective target enrichment that allow for
16 low cost, high-throughput capture of genomic regions of interest
17 without specialized instrumentation -- in other words, without the
18 use of an array -- and a need for high efficiency nucleic acid
19 library generation.

20 These are stated in the context of NGS target capture
21 methods. As we have discussed, Shapero is not an NGS target
22 capture method. Shapero relies on specialized instrumentation to
23 actually promote target specificity.

24 And so one other point here is with the Moorthie paper.
25 So this one was published in October of 2011. This is Slide 36,

1 this is going to be at the bottom left. And so you'll see that
2 Moorthie identifies a bunch of problems with all these target
3 capture methods. And ultimately, Moorthie pretty much just says,
4 it may ultimately be more cost effective to sequence a whole
5 genome.

6 As you heard from Petitioner earlier today, they
7 discussed the Garber paper. And they talked about how Garber
8 was telling you, genome sequencing is getting cheaper and
9 cheaper. If anything, that's a motivation to follow what Moorthie
10 is telling you, give up on target capture methods, go ahead and just
11 sequence the whole genome.

12 And now, Petitioner has insisted that Shapero resolve the
13 same issues. I put a timeline on Slide 37 that shows Shapero's
14 publication in 2004 and the fact that years later, there are multiple
15 publications discussing how these needs still persisted in the art.

16 But as Tecan has identified, there are numerous papers
17 that have praised Tecan's inventions for solving these issues. For
18 example, Barchi described the patent -- the technology as new,
19 robust, customizable and explained that it greatly simplifies primer
20 design. Smith published, essentially, echoing the same praise.

21 And while Petitioner has argued that this should be
22 disregarded because Smith also interviewed an employee of
23 NuGEN, the -- essentially, the company that invented the
24 technology that was later then purchased by Tecan. The reality is
25 that this statement comes from Smith. This is not a quote from any

1 employee of Tecan or NuGEN. This is Smith articulating what her
2 view was of the technology.

3 Similarly, Scaglione had noted in multiple places how
4 the technology improved the art. And that's consistent with the
5 famed Jackson Laboratories, which described Tecan's technology
6 as widely used for genotyping, quantitative, straightforward, and
7 cost-effective.

8 Now, I want to briefly touch on what the art said about
9 Shapero. Now, the Petitioner has argued that the art was
10 complimentary of Shapero. And as we have identified, there are
11 multiple references that criticize Shapero, some recognizing
12 specific issues with Shapero, others wholesale criticizing Shapero.
13 For example, Bui, in 2009, stated that it was impractical for
14 assaying a selected set of SNPs in specific genomic regions and
15 mentioned that there was a need to come up with something for
16 small to medium sized laboratories with limited resources.

17 Palka-Santini, in 2009, described Shapero as time
18 consuming and prone to contamination. And Liu, in 2012, months
19 after the priority date, described Shapero as expensive and
20 requiring specialized equipments and stating then that there was a
21 need for a simple and accurate genotyping assay that could be
22 implemented in laboratories lacking access to sophisticated
23 equipment.

24 Now, Petitioner has argued --

25 JUDGE YANG: Wait, sorry --

1 MR. BEAVERS: Yes, sorry, Your Honor.

2 JUDGE YANG: Yeah. And question about this lacking
3 access to sophisticated equipment, that's the array step, correct?

4 MR. BEAVERS: So that possibly could be right. There
5 are many different types of technology. So one is the array, right,
6 saying there's a need to something beyond the array. But there are
7 also other methods.

8 For example, RainDance is a very sophisticated type of
9 technology, which the patent discusses as being something
10 expensive, right? The patent wanted something simple that didn't
11 require use of some type of hardware that, you know, would, in
12 often cases, be too expensive for a lot of smaller to mid-sized labs.

13 So as you heard from Petitioner, they've argued that
14 because the MARA method, in large part, discloses similar library
15 preparation steps with the claimed inventions, that you should just
16 ignore our evidence of secondary considerations. That's an
17 incorrect reading of the law. We pointed to the Medtronic case, in
18 which the Medtronic case had, essentially, concerned a patent
19 where the individual claim elements were all known in the art.

20 But the point the Federal Circuit made was that the
21 combination was not known. The combination was not
22 appreciated in the art. It was not known in the art. And so sure,
23 maybe individual pieces might have been known. But nexus was
24 not to be disregarded there because of the fact the prior art did not
25 essentially show the combination.

1 And that's the point here, right? Dr. Bustamante
2 explained that it's a combination of limitations, right? It's a single
3 target specific primer. It's the universal primary amplification. It's
4 the fact that the library preparation method is designed seamlessly
5 to then be attached to, for example, the flow cells of an Illumina
6 for sequencing. It is all of this combined that is the unique and
7 characteristic features of the patents. And this is what is driving
8 the nexus here with respect to the secondary considerations.

9 Now, another point you heard, the Petitioner focused a
10 lot on multiplexing and focused on the benefits. And I'm going to
11 steal a little bit more time. So the Petitioner focused on various
12 benefits and conflated the benefits with features, right? The
13 Petitioner said that you should essentially disregard benefits
14 because they're not claimed.

15 That's not the law, right? At the end of the day, what
16 they're citing to -- the case law they're citing to concerns
17 unclaimed features of an invention. That is different from the
18 benefits that are derived from the invention.

19 And in fact, we cite to the WBIP case where the Federal
20 Circuit affirmed a finding of long felt unmet needs, where the need
21 that was addressed was carbon monoxide poisoning, even though
22 the claims to the challenged patent had nothing to do with carbon
23 monoxide. And this is consistent across the Board with Federal
24 Circuit cases where they have looked, for example, Apple v.
25 Samsung, where the need that was addressed was pocket dialing.

1 And the claims were not directed specifically to pocket dialing.

2 But the Federal Circuit affirmed the need because at the
3 end of the day, it was the features that satisfied that problem. And
4 so it's our position, as we've explained in the papers, the Petitioner
5 is incorrect on the law with respect to whether or not the benefits
6 must be claimed expressly in the claims.

7 Now, turning to copying, you heard Petitioner earlier talk
8 about how there was not evidence. And Judge Braden, you had
9 asked about this question of unfettered access. And I want to first
10 jump ahead to the same response that Petitioner showed you.

11 At the beginning of that response, the Petitioner admitted
12 that NuGEN and -

13 JUDGE BRADEN: When you say you jumped ahead,
14 where did you go?

15 MR. BEAVERS: Oh, I'm sorry, I'm on Slide 48. I'm
16 sorry. My apologies.

17 JUDGE BRADEN: Okay. Thank you.

18 MR. BEAVERS: So the Petitioner admitted that NuGEN
19 and Qiagen entered into discussions relating to Qiagen's potential
20 acquisition of NuGEN. They admitted that they had received
21 certain detailed information on NuGEN technologies. They
22 admitted that they performed some level of due diligence and that
23 they had had discussions with employees.

24 And as you heard, Petitioner cannot represent to you that
25 they did not receive technical documents concerning the patented

1 inventions. This was in 2013. As we noted earlier --

2 JUDGE BRADEN: What evidence has Patent Owner
3 put into the record that shows that they did get those confidential
4 documents?

5 MR. BEAVERS: Certainly, Your Honor. So I first like
6 to highlight Medtronic. Medtronic explains that -- because
7 essentially, what Petitioner is driving at is a demand for direct
8 evidence. What we put into the record --

9 JUDGE BRADEN: Right. That's the case. I want to see
10 the evidence.

11 MR. BEAVERS: So what we put into the record is
12 Petitioner's own admissions that they have conducted due
13 diligence, they had access to the technical documents, and at the
14 end of the day, the same workflow was publicly available in 2013,
15 2015. And then I'll talk about briefly in a moment, the substantial
16 similarities between the products. So we have put forward
17 evidence that they had access to the materials.

18 And so as the Federal Circuit has explained, you don't
19 have to show pictures of them tearing down devices or physically
20 in possession of them. Evidence of access and substantial
21 similarity is a presumption of copying there. And Petitioners put
22 forward no rebuttal evidence with respect to that. They've only
23 just demanded direct evidence.

24 Now, I want to briefly touch on the substantial similarity.

25 JUDGE BRADEN: I just want to make sure, when you

1 say they admitted, you mean the admission in the answer to the
2 complaint?

3 MR. BEAVERS: Exactly, Your Honor, yes.

4 JUDGE BRADEN: Okay.

5 MR. BEAVERS: This is their -- yes, their answer to our
6 complaint in the District Court litigation. So Dr. Bustamante did
7 an analysis comparing the workflow to the Ovation system, which
8 is listed in the patent specification as a commercial embodiment
9 and compared that to QIAseq targeted DNA panels and the RNA
10 panels as well in his declaration.

11 And Dr. Bustamante examined how those two compare
12 to one another with respect to Claim 1. And Dr. Bustamante
13 determined that there was substantial similarity.

14 You heard from Petitioner earlier that Dr. Bustamante
15 had discussed with them a deposition that there were other
16 differences. Those differences are irrelevant when it comes to
17 Claim 1. For example -- and I wrote this down -- the Petitioner
18 cited to Dr. Bustamante's deposition transcript at page 402, line 6
19 through 9.

20 If you look there, Dr. Bustamante is talking about
21 different types of fragmentation. Claim 1 does not specify what
22 type of fragmentation need to occur. In fact, Claim 1 does not
23 even require fragmentation. It only requires obtaining the
24 fragment. And so our point here is that Petitioner is just pointing
25 to what we would consider to be superfluous issues that are not

1 directed to the claim, to Claim 1 or to the analysis.

2 JUDGE BRADEN: But is it non-superfluous to
3 determining substantial similarity between the processes?

4 MR. BEAVERS: So Your Honor, we would believe that
5 it's superfluous for purposes of this proceeding, and here's why.
6 So first, when you're looking at the products and what matters,
7 right, the mapping of the commercial embodiment -- so Ovation
8 -- to the patent claim is in relation to Claim 1, right?

9 JUDGE BRADEN: Mm-hm.

10 MR. BEAVERS: And so from there, we're looking at,
11 for those features, comparing that to the mapping between ovation
12 and the defendant's -- or Petitioner's products. And so that's where
13 the mapping aligns. That is the substantial similarity is with
14 respect to Claim 1, the independent claims here. And so we would
15 argue that essentially, they are focusing on other limitations that
16 are beyond the scope of the claims.

17 And so briefly, I just want to note a couple of points real
18 quick. As we have noted in our papers, the Petitioner for years,
19 after copying the inventions, talked about how single primer
20 enrichment was revolutionary, how it was different than the
21 technology at the time. They described it as new. This starts in
22 2016 on.

23 And in this proceeding, they've argued that they didn't
24 copy because their workflow is somehow similar to Shapero's
25 workflow. And this is something that Dr. Metzker adopted at his

1 deposition.

2 And so we have introduced exhibits calling into question
3 the veracity of those statements. And we've introduced essentially
4 various statements that show that the Petitioner, in the District
5 Court litigation at the Federal Circuit is and at the patent offices,
6 made statements about how their single primer technology defied
7 expectations of the industry, how it was different, how they
8 developed it, never once did they attribute it to Shapero or Jones.
9 And so we've asked you to consider that for purposes of
10 credibility.

11 And finally, I just want to highlight, Petitioner in 2018
12 published unexpected results with respect to using a single target
13 specific primer versus a primer pair. Dr. Bustamante analyzed this
14 paper. Dr. Bustamante analyzed how this would be the closest
15 prior art as a system. And Dr. Bustamante also analyzed,
16 ultimately, whether the POSA would have found these results
17 surprising or unexpected.

18 All of that analysis is unrebutted. If you look at
19 Petitioner's reply, they pretended like this publication didn't exist
20 and instead, they focused on the Brooks declaration. We would
21 submit that this is evidence of unexpected results.

22 And so unless there are further questions, I will yield my
23 time. Thank you, Your Honors.

24 MR. BILSKER: How much -- do I have 14 minutes left?

25 JUDGE YANG: You have 14 minutes and 15 seconds.

1 But go ahead and we'll see how --

2 MR. BILSKER: So I'm just going to address kind of in
3 the order that he last raised. So if we go to slide -- I guess I'm the
4 one that can do that -- Slide 58 where - this is Patent Owner's
5 slides where he says this is evidence of unexpected results.

6 Now, as Mr. Smith explained and as stated in those new
7 exhibits that they introduced, which are the European Patent Office
8 filings, we further improved on single primer extension by saying
9 in certain situations, you can get rid of hotspots and primer
10 dropouts and have more efficient extension and -- with sync primer
11 extension if you add high levels of magnesium and this MutS
12 protein.

13 That's not something that's anywhere in the patent.
14 That's not somewhere that's anywhere in the prior art. And that's
15 how it was distinguished. There's nothing in those -- in this
16 statement that they got good results that shows unexpected results
17 from, quote, "SPE of the claimed invention."

18 JUDGE YANG: So now you finished that one. I would
19 like you to address one argument Patent Owner made. That is
20 Shapero was published in 2004, and the priority date was 2012.
21 And in between those two dates, despite the voluminous
22 discussion, you know, in the prior art about improving NGS,
23 nobody actually referred to MARA or anything similar to that.

24 MR. BILSKER: So we addressed this in our initial
25 response. If somebody actually said, take MARA and use it for

1 NGS, we wouldn't be talking about obviousness. There'd be no
2 such thing as obviousness, why bother even having it if that's the
3 argument? You can't have obviousness if something's been around
4 and no one specifically said to combine them.

5 The one case that they cited for that proposition, in that
6 case, the fact showed that over multiple, multiple decades, there
7 was no suggestion to combine. I mean, here, what we've got is
8 you've got MARA published in 2004. And you've got NGS really
9 just kind of coming into vogue around, like, 2007, 2008, 2009. So
10 we're not even talking about a decade here.

11 And in this situation, you know, I was trying to think of
12 an analogy of, really, what are we arguing about? If you had a
13 situation where you had a recipe to make a cake, right? So I say,
14 here's my recipe to make a cake, you know, mix these ingredients
15 this way and that way, put this one in first, put that one in first.
16 And you can bake it by any method known in the art.

17 And at the time I make that statement, you know, you've
18 got coal-fired ovens, you've got a steam oven, and maybe you have
19 a gas oven. And then a few years later, somebody comes along
20 and invents the next generation of ovens, a convection oven, an
21 induction oven.

22 Are we really going to say that there -- when you've got a
23 statement that says, combine it with any method of cooking known
24 in the art because someone develops a new oven, that there's -- all
25 of a sudden, you can't make that combination. Unless there's some

1 very specific reason as to why it won't work, it doesn't make any
2 sense. And there's -- there is no suggestion here.

3 I want to get back to this issue about copying. So there's
4 a couple of things. I think Judge Braden said where -- essentially,
5 she said, where's the beef? Where's the evidence that they actually
6 had access to this? If you look at that, the allegation and the
7 complaint and then the denial, what it says is Qiagen had access to
8 certain technical information. Certain technical information.

9 Are we claiming that NuGEN is a single product or
10 technology company, that prior to this due -- they didn't even have
11 this product available, right? This is not actually a product at the
12 time diligence was done. Are they saying there's no other
13 technical information that they -- that Qiagen would have looked at
14 other than the technology about this? That answer is completely
15 devoid of anything that establishes copying.

16 And you get back to this is Slide 51 from their
17 presentation.

18 JUDGE BRADEN: But Counsel, whose burden is it?

19 MR. BILSKER: To establish copying? Theirs.

20 JUDGE BRADEN: Yes.

21 MR. BILSKER: Theirs.

22 JUDGE BRADEN: Thank you.

23 MR. BILSKER: This is Slide 51 from Patent Owner's
24 presentation. And they say, this workflow shows similarity, and
25 the similarity must show copying. You know what, this doesn't

1 even align with the patent claims. This is the steps of enrichment.
2 Where's the step that shows the Ovation being sequenced? It's not
3 even there. So it doesn't even align with the claims of the patent.

4 And again, if you're trying to use this to say, the
5 similarity in this process shows that you must have copied. Well,
6 no, the similarity in the process as compared to things in the prior
7 art, it's identical to the Shapero method on those first two steps. I
8 mean, you've got -- one, two, three, four, five -- five steps shown
9 in the Qiagen methodology, and two of them are not the same as
10 what's shown in Tecan. And those steps are not trivial. So how
11 does that establish copying when it's more similar to Shapero than
12 it is to theirs?

13 You know, I actually -- I mean, it's a little like whack-a-
14 mole here. And I don't have that much time. But just as a matter
15 of record, I am going to object to certain technical arguments they
16 made about the Jones reference. Scientific arguments on what
17 Figure 2 showed when Jones was actually saying, hey, literally,
18 you know, the only way to do this is not putting it on the array.

19 There are multiple other ways to do the allele
20 discrimination in the analysis. And they made a number of
21 technical arguments. There was one made by Ms. Cipriani (sic) at
22 -- there was 39 minutes and 17 seconds remaining, and then by Mr.
23 Beavers at 19:51 and 13:12 saying somehow this technically really
24 wasn't the same process. Those arguments were never made in the
25 briefs, and if they were, we would have refuted them with our own

1 expert declaration.

2 I heard Ms. Cipriani say that the only way that specificity
3 is achieved in the Shapero MARA method is through the
4 hybridization to the array. That's just flat wrong. And it's flat
5 -- it's totally contradicted by the words in the paper itself.

6 If you go to Exhibit 10 -- and I don't have this pulled up
7 on a slide. But Exhibit 1006, which is Shapero, page 8, right-hand
8 column, about four lines up from the body -- or from the bottom.
9 And I will read it, "Importantly, MARA does not require absolute
10 specificity of primary annealing and elongation since target
11 recognition and allele discrimination is achieved through
12 hybridization to high density arrays."

13 So what it's saying is all specificity is not achieved by
14 hybridization. It's actually saying there is specificity achieved
15 through the MARA method. It just doesn't have to be 100 percent
16 specificity, which again is the same thing that Howell said that no
17 method achieves absolute specificity. And even their Brooks
18 declaration, which she pulled out of thin air with no support, where
19 he said, oh, the unexpected result is 90 percent. Well, what about
20 the 10 percent that you were off?

21 The other thing is as far as what the data in Shapero
22 shows -- so in Shapero you have those gels which, before you ever
23 get to the hybridization, the gels are evidence that you are
24 achieving specificity. You're getting extension products that are of
25 the right size and you're not seeing any primer dimers.

1 And, you know, I put that slide up, and I'm just going to
2 read the testimony rather than trying to switch back and forth
3 between presentations. But it was the testimony that we read from
4 Dr. Bustamante when he was looking at the slide in Shapero. And
5 they say -- well, he says it's not there. Well, I read it, it's our Slide
6 54. The question, at -- it's at page 230, line 13.

7 Question, well, there is 100-base pair marker annotated
8 in Figure 2A, right? Answer, and it's not very bright. Well, if you
9 can't see it and it's not there, you can't say it's not very bright.
10 Saying it's not very bright means you saw it, right? I mean, maybe
11 he try to correct it later on. But what he said is it's there and it's
12 not very bright.

13 There is further evidence of specificity and that further
14 evidence comes from the analysis method that Shapero perform.
15 In the '012 and the '108 Patent, what they say is the only way you
16 can determine what your level of enrichment is, is you have no
17 idea what it is when you've gone through all the steps prior to the
18 sequencing. The only way you can do it is sequence it. Sequence
19 it with the enrichment method and without -- and see how many
20 reads you get that map.

21 Well, what Shapero did was he used the array
22 hybridization method as a proxy for how much specificity there
23 was. Now, how did he do that? Dr. Metzker explains it in detail
24 and it's in our papers. But I'll just go through it briefly. And table
25 1 is important to this. So he had a prior methodology which he

1 -- which they identified SNPs. And I don't know how many there
2 were. There were, say, well, hundreds of them, right, for the 250-
3 plex locus or 250-plex experiment. So that was kind of -- we'll
4 call that quote, "the gold standard."

5 And then what he did was he ran the enrichment process.
6 And the enrichment process is you have to actually amplify what
7 you're looking for. If you don't amplify what you're looking for,
8 you're not actually going to see it on the hybridization array. And
9 he even did something more. And you can see it in the caption of
10 table 1.

11 In the thing that he was comparing MARA to, at the end,
12 even with the allele discrimination, there was a threshold set. And
13 that threshold was 0.03. It's in the caption of table 1. And he
14 actually says, when we ran MARA, we actually kicked up the bar.
15 We put the bar up almost three times as high to 0.08. And what
16 that means is on the prior methodology, when it's at 0.03, well, it
17 doesn't have to be that bright for you to say, yeah, there's a SNP
18 there.

19 When you kick it up to 0.08, it has to be really, really
20 bright for a SNP to be there. And even with that higher hurdle,
21 they were still finding the same things that they were finding in the
22 lower threshold one that they were to going comparing it to. So
23 Dr. Metzker actually explains how those scores, those concordance
24 scores of -- in the 99 percent range do show that you're amplifying
25 what you want to amplify.

1 If your primers are in there just amplifying willy-nilly a
2 bunch of nonsense stuff, you're not going to be finding all of those
3 SNPs. It's just not going to happen, you know.

4 And again, I mean, one thing that the silence is kind of
5 deafening. So we had that slide which I said was my favorite
6 slide. So you've heard them now, two attorneys go through
7 -- there's all these problems. Everyone knew about all these
8 problems. Where in the patent does it ever have say like, hey, with
9 single primer extension, the prior art has known that you've got a
10 problem?

11 And the problem is you've got this and you've got that.
12 But here, we solve the problem. Nowhere. So what does that tell
13 you? It tells you the inventors never believed there was a problem.
14 So, you know, a POSA is a hypothetical person. They're charged
15 with knowledge of the entire set of prior art. There's no one
16 arguing that Shapero is not in the art field.

17 I mean, if you know about Shapero, it's kind of the cake
18 analogy. Shapero and Jones tell you, look, there are two parts of
19 this, there is a preparation part and there is a detection or
20 discrimination part. The preparation part is the same as the recipe,
21 you know, mix these ingredients together. The discrimination part
22 is cook it in existing ovens.

23 The discrimination is --he tells you, one way you can
24 figure it out is look at all the methods that exist today. One of the
25 methods is pyrosequencing. And, you know, I mean, actually, it's

1 in our slide. Well, it's kind of towards the end, it's that Bronner
2 reference. And, you know, I have trouble saying the name of that
3 reference, Syvänen.

4 But they said, well, Syvänen criticizes pyrosequencing.
5 Well, it doesn't criticize pyrosequencing, it says multiplexing is
6 difficult. It was a prior generation. It doesn't say multiplexing is
7 impossible. And everyone is striving for multiplexing. That's the
8 whole goal of Shapero. It says, hey, I've got a method now where
9 I can multiplex that avoids all the problems.

10 It's our Slide 74. It's that Bronner paper, which is their
11 -- one of their exhibits, Exhibit 2155. If you look at page 5 of that
12 paper -- actually, the first next generation sequencing in Shapero
13 was 454. One of the things it says is 454 can actually multiplex
14 now. You put things on a bead, you had millions of beads, they
15 had millions of copies of things. And that was one of its benefits,
16 it could multiplex.

17 So unless you have any further questions, I think I am --

18 JUDGE YANG: Since you have 30 seconds left, I do
19 have a question.

20 MR. BILSKER: Sure.

21 JUDGE YANG: Regarding your cake analogy, say, you
22 know, somebody developed this recipe with an eye to the coal
23 oven --

24 MR. BILSKER: Yes.

25 JUDGE YANG: Later when you have the convection

1 oven, you cannot use the exact recipe. You have to tinker with it.
2 Because otherwise, I don't know, something, you know, isn't going
3 to work.

4 MR. BILSKER: Yup.

5 JUDGE YANG: And I think that's the gist of Patent
6 Owner's argument, right? You --

7 MR. BILSKER: It is not. There's no statement that said
8 -- and they've admitted it. You heard her -- you heard Ms. Cipriani
9 admit it when you asked her the question, does Shapero have all
10 the elements of the enrichment that are necessary? So all the
11 elements that are necessary, there is no modification that you have
12 -- all you're doing is not putting it on the array.

13 JUDGE YANG: Right. But as far as I understand, all
14 the limitations there in Shapero was designed with the eye of the
15 following up the microarray assay. So it's --

16 MR. BILSKER: I disagree, Your Honor. There's no
17 difference. So you have adapters on the fragments that come out
18 of the MARA method. You have adapters sequence, A1 and A2.
19 A1 and A2 can be -- for example, P5 and P7, that attach the
20 molecule to the flow cell and Illumina sequencer. There's
21 absolutely no difference.

22 Actually, I don't know if it was you that wrote it, but this
23 Board actually identified that in its institution decision. They said,
24 these -- there's no reason these adapters can't be -- for example, the
25 Illumina P5 and P7 that attach to the flow cell. There's never been

1 an argument that you actually have to modify the enrichment steps
2 of MARA to make it allowable to put on a next generation
3 sequencer.

4 And again, it's what you put on next generation
5 sequencers, whatever platform, because it's not even identified in
6 the claim. They just say any next generation sequencer you always
7 have to put an adapter. It's basically just like you have to put the
8 key for that machine on there.

9 JUDGE YANG: Whenever you're ready.

10 MS. CIPRIANO: Thank you. So I'd like to make just a
11 couple of points here. First, on that last point Mr. Bilsker was just
12 talking about. There is a difference between the adapters used in
13 Shapero and the adapters claimed. The adapters claimed require
14 that it has a sequence complementary to a sequence on a surface.
15 And that's the important part for binding or adhering to an NGS
16 system.

17 So while technically, there are adapters there that could
18 be the Illumina or those sequences, Shapero didn't use those
19 adapters. So that is one point that there would need to be that
20 change.

21 JUDGE YANG: Wait. Okay. I need to take a closer
22 look at that. Do you have anything that could show me that point?
23 The P7 -- P5, P7 adapters and only array are the sequences specific
24 to the --

25 MS. CIPRIANO: Yeah.

1 JUDGE YANG: Sorry, you have to fill in the --

2 MS. CIPRIANO: Yeah. If we look at the MARA
3 method, the -- Illumina wasn't invented when Shapero made its
4 MARA method. So the adapters that Shapero used were not
5 directed to the Illumina sequencing platform. In order to -- I'm
6 sorry.

7 JUDGE YANG: Go ahead. Yeah. No.

8 MS. CIPRIANO: In order to use MARA with the
9 sequencing platform, you would need to incorporate those
10 sequences into the adapters instead of using the exact sequences
11 that Shapero used.

12 JUDGE YANG: Correct. But this is not like -- counsel
13 for Petitioner said, this is not anticipation. You don't have to use
14 the exact -- the same, right? I'm a little confused with -- about this
15 argument.

16 MS. CIPRIANO: No, absolutely. And I just wanted to
17 clarify the record that we haven't -- there is no evidence in the
18 record that Patent Owner has said that MARA is exactly what the
19 claims are. The enrichment steps of the MARA method, we do not
20 dispute that they align with the patent claims.

21 JUDGE YANG: Okay.

22 MS. CIPRIANO: Sure. So a couple of points, first, I
23 wanted to talk a little bit about copying and Judge Braden's
24 question about the evidence of copying. Here, the evidence in the
25 record shows that Qiagen was trying to purchase NuGEN, the

1 original developer of this technology. And they've admitted that
2 they had access to technical documents.

3 It defies logic that Qiagen didn't ask for and have access
4 to information about NuGEN technology that was published in a
5 patent application shortly after this diligence was taking place. So
6 I just call into question the reality of the admissions that were
7 made in the answer to the complaint and the timeline of public
8 disclosures of this information.

9 JUDGE BRADEN: Counselor, there's nothing in the
10 record that shows or gives a list of the confidential information
11 that was provided to Qiagen during this process, correct?

12 MS. CIPRIANO: Not in the record in this case, no.

13 JUDGE BRADEN: All right. Thank you, Counselor.

14 MS. CIPRIANO: And so to address what Mr. Bilsker
15 has talked about my statements about Shapero, if I said it was the
16 only method of target specificity, I certainly misspoke there. But I
17 do think that I represented that it was the only specificity aspect
18 that Shapero relied on, that the statements in Shapero talked about
19 the hybridization array providing the allelic discrimination,
20 providing the target specificity. They were questioning the
21 specificity of MARA and relied repeatedly throughout the
22 reference that the hybridization array was what was giving them
23 assurances in target specificity.

24 And finally, I just want to talk about the realities of the
25 facts in this case and talk a little bit about the timeline and maybe

1 address some of your question, Judge Yang. The reality is that
2 secondary considerations are important because they help
3 eliminate a hindsight look at the prior art. And that's exactly what
4 we see here, that the Petitioner's claims are a hindsight compilation
5 of the prior art.

6 And the real-world evidence shows that. And I'll try to
7 fill in what we talked about throughout this morning. So Shapero
8 was published in 2004. Between 2004 and 2012, there was no
9 mention of using Shapero with NGS even though that there was
10 significant development in the field. And not only -- and, you
11 know, Petitioner takes issue that that's what obviousness is for, to
12 compile different ideas.

13 But not only does the art not point to Shapero, we've
14 identified numerous references that point away from Shapero.
15 And even Shapero itself says, don't -- we're not using MARA with
16 the universal arrays, we're using it with target-specific arrays. And
17 that certainly, all of the art combined would teach a professional
18 person of ordinary skill not to broadly construe and broadly
19 interpret the MARA method.

20 So the art repeatedly taught away in this period from
21 2004 to 2012 -- or at least 2007 to 2012, teaching a way using
22 non-target specific method and a PCR-based method with NGS.
23 Then after this timeline, if we think about the realities of what
24 happened after the patents were published and the Tecan's products
25 came out, there was praise for the product.

1 Qiagen came out with a similar product. And we claim
2 that that is that -- copies. Qiagen made public statements about the
3 improvements on the NGS systems regarding the single primer
4 enrichment technologies. So this is a quintessential cause
5 -- excuse me, this is a quintessential case of hindsight. It is not as
6 -- the question before the Board is not whether a person of
7 ordinary skill could have used MARA with NGS. The facts of the
8 case and the secondary consideration show that a person of
9 ordinary skill would not have been motivated to do so, and the
10 petition must be denied.

11 If you don't have any questions, I'm going to wrap it up.

12 JUDGE YANG: Okay. Any questions?

13 MS. CIPRIANO: Thank you.

14 JUDGE YANG: Thank you. All right. So we are all set
15 for this morning's argument. We thank the parties for your
16 excellent presentation. And these cases are submitted, we will
17 issue the final decisions in due course.

18 (Whereupon, the above-entitled matter went off the
19 record at 12:42 p.m.)

IPR2025-00028 (Patent 10,036,012 B2)

IPR2025-00029 (Patent 10,876,108 B2)

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