

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC,
Petitioner

v.

PERSONALIS, INC,
Patent Owner.

IPR2023-00545 (Patent 11,299,783 B2)
IPR2023-00546 (Patent 10,450,611 B2)

Record of Oral Hearing
Held: May 7, 2024

Before ULRIKE W. JENKS, ROBERT A. POLLOCK, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

IPR2023-00545 (Patent 11,299,783 B2)

IPR2023-00546 (Patent 10,450,611 B2)

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The above-entitled matter came on for hearing on Tuesday,
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Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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2 JUDGE POLLOCK: Good afternoon. I am Judge Pollock. With me
3 are Judges Jenks and Majors. This is the final hearing in IPR2023-00545
4 and IPR2023-00546, which relate to U.S. Patent Numbers 11,299,783 and
5 11,450,611, respectively. This hearing is open to the public. Petitioner is
6 Foresight Diagnostics, Incorporated. Patent Owner is Personalis,
7 Incorporated. Counsel for Petitioner Foresight, would you kindly identify
8 yourself and your colleagues?

9 MR. KRAUSE: Good afternoon, Your Honor. On behalf of
10 Petitioner Foresight, you have Andrew Krause from Irell & Manella, and I'm
11 joined by my co-counsel, Amir Naini from Naini P.C.

12 JUDGE POLLOCK: Good afternoon.

13 MR. KRAUSE: Good afternoon.

14 JUDGE POLLOCK: Counsel for Patent Owner Personalis, would
15 you kindly identify yourself and your colleagues? Mr. Derek, you're on
16 mute. Would you start over, please? I'm sorry, Mr. Walter, I can't hear you.

17 Charles, can we address this?

18 CHARLES: Yes, sir. Mr. Walter, I believe if you have a touch panel
19 system, you need to star 6. If you don't, and you're on a web browser, it's
20 just a mute. You're double muted. It doesn't look like you're muted inside
21 of Webex, so it'll be locally there. Stand by, please.

22 Mr. Walter, can you give me some audio, please?

23 MR. WALTER: Can you hear me? Charles, can you hear us?

24 CHARLES: Thank you.

1 MR. WALTER: Apologies, Your Honor. Your Honor, this is Derek
2 Walter of Weil, Gotshal & Manges for Patent Owner, and I'm also joined by
3 Nate Luman from Knobbe Martens Olson & Bear.

4 JUDGE POLLOCK: Good afternoon, Mr. Walter. As set forth in our
5 order of March 27, Petitioner will have a total of 45 minutes to present
6 argument in this case, and Patent Owner will have a total of 45 minutes to
7 respond. Petitioner will open the hearing by presenting its case regarding
8 the challenged claims for which the Board has instituted trial. Thereafter,
9 Patent Owner will respond to Petitioner's argument.

10 Mr. Krause, would you like to reserve any time for rebuttal?

11 MR. KRAUSE: Yes, I would like to reserve 10 minutes, Your Honor.

12 JUDGE POLLOCK: Mr. Walter, would Patent Owner like to reserve
13 any time?

14 MR. WALTER: Yes, Your Honor, I'd like to reserve five minutes.

15 JUDGE POLLOCK: Very good. A few matters of housekeeping
16 before we begin, though I'm sure counsel has heard this before.

17 First, the Panel will attempt to keep an accurate account of the time,
18 but we suggest that the parties do the same. For the courtesy of all parties,
19 and to minimize technical interference, please mute your microphone when
20 not speaking.

21 For clarity of the record, please identify yourself each time you
22 speak and refer to each demonstrative by page number. The panel has
23 digital access to the full record, but to the extent you are referring to
24 something other than a demonstrative, please give us time to locate a copy as
25 we may not be able to clearly read the text or context of what you're posting
26 to video.

1 If the counsel wish to raise any objections to argument or
2 demonstratives, you may raise them at the conclusion of any portion of
3 opposing counsel's presentation, and we will take them under advisement.

4 Petitioner will go first, as it bears the burden of showing
5 unpatentability of the challenged claims.

6 Mr. Krause, I believe you have 35 minutes on the board, and any
7 more than that, you'll be eating into your rebuttal time. I'll try to give you a
8 warning, but I'm sure you have people taking charge of your time as well.
9 Are you ready?

10 MR. KRAUSE: Understood. If you can see my screen, then I should
11 be ready.

12 JUDGE POLLOCK: Very good.

13 MR. KRAUSE: Thank you, Your Honors, and may it please the
14 Board. Andrew Krause, on behalf of Petitioner Foresight Diagnostics.

15 So we're here today for the hearing on the '611 and '783 patents from
16 Personalis. There's some overlap in both the grounds of challenge and in the
17 general contours of the claim. So we intend to begin with the '611 patent
18 today and address those issues, and then address the remaining issues in the
19 '783 patent.

20 For some general overview, we thought it would be helpful just to
21 sort of situate ourselves in what's claimed here, so we put up the '611 patent
22 first here. And it's a claim that generally involves a number of steps. It's an
23 initial sequencing step of tumor to identify cancer variants. From that
24 sequencing, a probe set is created that probe sets used to enrich a sample for
25 those variants, and then those variants are sequenced at a deeper level in a

1 later step. And there's some numerical limitations that we will address in the
2 full argument.

3 The '783 patent is similar, but slightly different. It involves the
4 creation of a probe set with a variable portion that includes information that's
5 a result of the sequencing, and then some of the probes are a fixed portion
6 that are created independent of the sequencing. Similarly, the probe set is
7 used to amplify or enrich a subsequent sample. That sample, the library
8 that's created, is sequenced and the variants are reported out. So essentially,
9 the claims generally relate to methods of informing a cancer assay based on
10 mutations from the tumor.

11 Now, the context of all this is important because, as we see in a
12 recently filed proceeding after the POPR and -- after the POR in this case,
13 this is exactly the type of method that Patent Owner's counsel asserted is, on
14 its face, not remotely inventive. So that's the context and now we'll dig into
15 the substance of the arguments here.

16 So we'll turn first to *Ley*, the *Ley* reference on the '611 patent, which
17 we believe anticipates and renders obvious all the challenged claims. Here
18 we're showing a general overview of what *Ley* did. So *Ley* did an initial
19 whole genome sequencing step of matched tumor and normal tissue from a
20 skin sample. It filtered out some variants that it had identified in that whole
21 genome sequencing. And it also included some probes for known cancer
22 genes, the BRCA2 and TP53 genes, it targeted. It created PCR primer sets
23 and it used those to create amplicons of multiple samples and then sequence
24 those amplicons -- sequence the sequencing library by deeper sequencing,
25 and generated a report of results. And this is our slide 7.

1 So here back to claim 1 of the '611 patent. So the first four steps and
2 the preamble are not in dispute on *Ley* here. The disputes relate to the
3 claimed step 1(e), which has a number of parts as well as the dependent
4 claims, and this is slide 8.

5 We'll start with the overview of what's in these limitations. So we've
6 broken it down into subparts that track sort of how we did it in our briefing.
7 So the first numerical limitation is the requirement that the sequencing of (e)
8 is subjected to a sequencing at a coverage of 175 kilobases or less. And as
9 we'll go through, that's met because *Ley* sequenced single exons in its
10 resequencing step, and even if you accounted for each and every exon
11 present, that sums to less than the 175 kb claimed.

12 The second part is this idea of sequencing to identify a presence or
13 absence of genetic variants, which *Ley* does. It finds that the variants that it
14 designed the probes for were, in fact, present in the relapsed tumor sample.

15 And finally, there's the issue of how deep is the sequencing of (e).
16 And that's been calculated, and it's significantly deeper than the whole
17 genome sequencing in step 1. This is claim --

18 JUDGE POLLOCK: Mr. Krause?

19 MR. KRAUSE: Yes.

20 JUDGE POLLOCK: One question. You say *Ley* sequenced single
21 exons and so your declarant added up all the length of the exons. How do
22 we know *Ley* isn't sequencing, in part, intron sequence?

23 MR. KRAUSE: So this is -- let me go to slide -- I'll jump right there.
24 We'll go to slide 12. So we have the testimony of Dr. Furneaux, who's asked
25 if the primers were created amplicons of the exons, and that's how Dr.
26 Furneaux understood the disclosure of the reference. There's also *Ley* 's

1 filtering procedure, which rules out intronic and non-genic sequences. I
2 think that's the flowchart. I don't have it on a slide, but that, I believe, is
3 *Ley*'s Figure 2. But I can confirm.

4 And that's also what Dr. Quackenbush testified, this is our slide 13,
5 in his opening declaration, reading *Ley*, a POSA read *Ley* to understand that
6 the panel of genes were targeted to an exon containing the genetic variant.
7 So *Ley* is, as read by a POSA, focused on the exons. It narrows down the
8 locations of the mutations to the specific SNPs that are point mutations that
9 create a protein change. So the reading that Dr. Quackenbush set forth was
10 that it's creating its amplicons based on the sequence that contains those
11 single nucleotide polymorphisms, and that's how it honed in on single exons.
12 Because of that, his calculation of the total coverage of *Ley*'s sequencing
13 library in (e) is a substantial overestimate because it summed up each and
14 every exon.

15 And that's the -- and so I think this goes to the point. So slide 14,
16 rather, right, Dr. Quackenbush's declaration, paragraph 121, rather than the
17 smaller sequence of a variant-containing exon, Dr. Quackenbush calculated
18 the entire length of the genes, which contained multiple exons, to get his
19 overestimate of about 45,000 kilobases of sequencing, which is about a
20 quarter, give or take, of the claimed 175 kilobases or less.

21 In addition to being disclosed in *Ley*, based on Dr. Quackenbush's
22 analysis, we also set forth that it would have been obvious to provide a
23 smaller capture panel. The factors including to simplify the assay, reduce
24 cost. And one would, of course, expect success in doing that because they
25 did it with 12 genes, so doing it with fewer also would have been obvious,
26 and this would have been simply a routine optimization.

1 This is confirmed by the fact that the patent doesn't establish any
2 criticality to the 175 kb or less limitation. In fact, it's not clear that the "or
3 less" part is even disclosed. So when the patent talks about 175 kilobases, it
4 seems like that's more of a floor on sequencing and not a ceiling, further
5 confirming that arriving at the footprint is a matter of routine optimization.

6 Slide 18 just goes through -- apologies. I'll pause there and turn to
7 slide 18, which is the next numerical limitation at issue, which involves
8 whether or not the depth of the sequencing of the amplicons is deeper than
9 the sequencing of (a), the whole genome sequencing. And so we have no
10 dispute over the fact that *Ley's* sequencing of (a), the whole genome
11 sequencing, had a depth of about 13 to 33x. And in this table, Dr.
12 Quackenbush calculated the depth of sequencing for each of the amplicons
13 of the targeted genes. And at the low end, about 588x; at the higher end,
14 12,365x, all substantially higher than the claimed or the sequencing of (a),
15 which was the 13 to 33x.

16 JUDGE POLLOCK: Okay, Mr. Krause, is this sequencing depth one
17 of the disputed terms?

18 MR. KRAUSE: Yes, this is one of the disputed terms.

19 JUDGE POLLOCK: Can you give me a thumbnail of why it's
20 disputed?

21 MR. KRAUSE: Yeah. So I'll turn to slide 19. The dispute that they
22 make involves Dr. Furneaux's contention that to figure out the sequencing
23 depth here, we would have needed to apply the Lander-Waterman equation.
24 But that's not correct, because here we have the actual data of what
25 happened in the experiment. We know how many times each of those
26 sequences would sequence, so we know the depth.

1 And this sort of contrasts with, I think, one of Dr. Furneaux's
2 mantras throughout the proceeding, which is that the Lander-Waterman
3 equation is used for theoretical purposes to predict what might happen in an
4 experiment beforehand, but that's not the same as looking at what actually
5 happened in the experiment. So really here, because we have this data from
6 that table, the Lander-Waterman equation is not necessary. As
7 Dr. Quackenbush testified, depth -- depth of sequencing means the number
8 of times genomic sequencing -- a genomic sequence has been sequenced.

9 So if we go to slide 20, I asked Dr. Furneaux at his deposition, I
10 walked through this table with him to understand, you know, what was in
11 here. And so we can see he agreed that this is showing the number of times
12 a particular sequence was sequenced. So the variant got read 5,672 times the
13 reference 4,890 times. That means that the sequencer read here is in the
14 primary tumor, the combined sequences at that position about 10,000 times.
15 So this confirms that the sequencing is much, much deeper than the whole
16 genome sequencing of (a), where a given position would be read, on
17 average, 13 to 33 times.

18 JUDGE POLLOCK: All right, thank you. You can move on.

19 MR. KRAUSE: The next disputed, and the final disputed, aspect of
20 claim 1 is the idea of sequencing to identify a presence or absence of the
21 genetic variants. And we think this is fairly straightforward and satisfied by
22 Ley 's confirming in the relapsed tumor sample that the variance targeted by
23 the probe set were present in the sample and the foreknowledge of the
24 variance is assumed by the structure of the claim. The claim language in
25 step 1(e) refers to sequencing to identify said genetic variants, and said
26 genetic variants are referred to multiple times earlier in the claim and set

1 forth that you're creating a probe set for the variants, that the probe set
2 amplifies or enriches those variants. No dispute there. And that you're
3 using that enrichment and amplification to create a sequencing library of
4 said genetic variants. So all that needs to happen in (e) is to identify that
5 they're present. And we think, as the Board found correctly in its Institution
6 Decision, that that's satisfied in Table 3 of *Ley* or Figure 3 of *Ley*.

7 JUDGE POLLOCK: So what does it mean to identify?

8 MR. KRAUSE: So we think it means to indicate it's present to find it.
9 Well, we -- certainly the dispute here, Personalis contends that it means to
10 determine the identity of, which we believe does not make sense in the
11 context of the claim when we plug it in.

12 So this is our slide 25. They say identify means "to establish the
13 identity of." So plugging that in, that makes the claim read, "Sequencing to
14 establish the identity of a presence or absence of at least a subset of genetic
15 variants," which doesn't really make sense. How do you establish the
16 identity of something that's not there?

17 So slide 26, we think the much more straightforward reading is,
18 "Does the sequencing data of (e) show whether the genetic variant" was, in
19 fact, identified and the same as the variant that was identified in the whole
20 genome sequencing? So it's --

21 JUDGE POLLOCK: Am I correct that your position is that
22 confirming the identity of is the same as identifying?

23 MR. KRAUSE: I don't think it's confirming the identity. It's you're
24 sequencing and you're confirming that that variant was, in fact, present in the
25 sample. So the sequencing confirms the presence of the genetic variant in
26 the subsequent sample. That's how we're reading it.

1 So I think that the sequence is known before because that's how the
2 probe set was designed and that's what the claim requires and we're relying
3 on identifying the presence of the sample, not the absence here. So
4 amplifying sequencing and confirming the presence of that variant satisfies
5 the fact that the variant was, in fact, identified in that sample.

6 JUDGE POLLOCK: All right, if you turn back to your slide 18, so
7 we have, for example, CDH24. The variant is, I guess, sequenced 5672
8 times. Would you say that that variant was identified 500, 600 -- 5,672
9 times?

10 MR. KRAUSE: I believe that's correct. And it's identifying the
11 presence of that sample, the presence of that variant. Right. It was
12 identified in the sample. Right. If it read zero, perhaps then that would be
13 an absence. But because it was identified that number of times, it was
14 identified in the sample.

15 JUDGE POLLOCK: Okay, I see. Thank you.

16 MR. KRAUSE: So the next main dispute involving *Ley* relates to the
17 fixed and variable portions. Go to our slide 31. And we believe that these
18 are also terms that can be understood readily from the claim language. The
19 variable portion probes are identified from a result of said sequencing of (a),
20 and the fixed portion is independent of the result of the sequencing of (a).

21 So, in *Ley*'s set of 12 amplicons that it creates, the variable probes
22 are those that are based on the discovered somatic mutations that it found in
23 the whole genome sequencing data. And the fixed portion are the two
24 known control amplicons that it added based on knowledge of relevant
25 mutations in the literature.

1 Go to slide 33. On the fixed content, those control amplicons are
2 consistent with what the specification includes as an example of a fixed
3 portion, which is probes for cancer driver genes. So that sort of aligns. And
4 the dispute here is really based on, I think, trying to read aspects of the
5 specification which are simply not claimed into this straightforward claim
6 language.

7 And one of the interesting things, if you go to our slide 32, is that
8 when Personalis applied the claim language to its own assay for secondary
9 considerations, it essentially used analogous teachings to satisfy these claim
10 limitations. So the personalized probes it said satisfy the variable portion.
11 The personalized being based on sequencing and including probes for
12 known cancer-related variants was sufficient in that context for the fixed
13 portion. And that's essentially the same mapping that the petition proceeds
14 under.

15 The next set of disputes revolve around whether *Ley* teaches the
16 treatment limitations. This reports using the testing to inform treatment
17 afterwards. The primary dispute, I think, is that Personalis argues that *Ley*
18 can't possibly teach that because it was a posthumous analysis. But that's not
19 the standard for anticipation.

20 Slide 40, law doesn't require actual performance of the method. It
21 requires that *Ley* discloses the limitations and enables them, and suggests the
22 method to a person of skill in the art. So Dr. Quackenbush testified that a
23 person reading *Ley* would understand that it enabled the use of its methods
24 to inform treatment.

1 And if we go to slide 41, Dr. Furneaux agreed, is enabling because
2 the samples were taken while the patient was alive and the analysis would be
3 applicable going forward.

4 JUDGE POLLOCK: Counsel, I can understand reading informing
5 treatment rather broadly, but can you talk about the '611 patent claims 10
6 and 28, which involve providing a therapeutic intervention, or treating a
7 subject or a biological relative? How do you justify anticipation for those
8 two claims?

9 MR. KRAUSE: So, in Dr. Quackenbush's declaration, he discusses
10 the case report in *Ley*, which discusses the course of treatment and therapy
11 that the patient was receiving while this testing was ongoing. So certainly
12 the POSA reading of the reference would understand that these tests could
13 also inform it in real time. The *Ley* report was based on a sort of mirror
14 (phonetic) look at the data.

15 JUDGE POLLOCK: Well, something that a POSA could do, how
16 does that supply the necessary anticipation? Seems like an obviousness
17 point, isn't it?

18 MR. KRAUSE: So we certainly agree that there is obviousness as
19 well. Let me turn back, slide 40. The *Bristol-Myers* case says that it doesn't
20 require the actual performance. It enables the POSA to perform the method.
21 The abstract of *Ley* expressly informs the POSA that the purpose of the
22 paper is to do genetic testing to inform the use of targeted therapies in
23 patients. So it's describing that that's the goal and is describing the test to do
24 it. So the fact that it's sort of a proof of concept of the assay, looking
25 backwards, doesn't make it non-anticipatory, because disclosures enable the
26 POSA to carry out the method.

1 JUDGE POLLOCK: Well, where does *Ley* disclose any particular
2 therapeutic intervention based on the results of these assays?

3 MR. KRAUSE: I believe it's in the supplemental information. It
4 describes the treatment that the patient was receiving.

5 JUDGE POLLOCK: As a result of the testing --

6 MR. KRAUSE: I think that's --

7 JUDGE POLLOCK: -- or prior to the sampling?

8 MR. KRAUSE: I think the patient's receiving the treatment, and the
9 report shows whether or not it was working. It shows the sort of
10 maintenance of the mutations or the lack of response. And I would point to
11 paragraph 154 of the Quackenbush declaration as an example, discussing the
12 implications of some of the treatments on the indication and contraindication
13 of certain chemotherapies.

14 JUDGE POLLOCK: Okay, you're welcome to move on.

15 MR. KRAUSE: But even if not anticipated, the treatment and
16 therapeutic limitations are, we believe, rendered obvious based on the
17 applications of similar methods on a going-forward basis. That was the
18 purpose of *Ley*. And Dr. Quackenbush testified that these are precisely the
19 sorts of methods that were used going forward in the literature in the time
20 period between 2008 and 2016, the priority date of these patents.

21 We'll turn to the *Newman* grounds and two issues that I want to
22 address. The first is the sequencing of (a) being 12 gigabases or more.
23 That's slide 44 of our presentation. And here, based on the two options that
24 were disclosed in *Newman*, Dr. Quackenbush calculated that the sequencing
25 of (a) was 12 gigabases or more based on the 12.3 and 13.0 gigabase reads
26 of the two options for paired end reads. A POSA would at once envisage

1 using this read, which satisfies the claim and is greater than the 12
2 gigabases.

3 The other main dispute on *Newman* is with the size of the selector.
4 And the testimony from Dr. Quackenbush is that *Newman*'s 157 kilobase
5 selector is targeting a footprint of 157,000 bases, which is less than the
6 claimed 175 kb. And the specification supports the calculation of the 175 kb
7 based on the intended footprint. As an example, giving the size of the
8 exome as the footprint, not the size of a capture panel that would target the
9 exome.

10 JUDGE POLLOCK: Would you expand a little bit about what the
11 controversy is on this limitation?

12 MR. KRAUSE: So the controversy is Personalis contends that the
13 length of *Newman*'s capture probes was 157,000 kb. And Dr. Furneaux just
14 says that; we don't believe that there's any support in the record for it.
15 Dr. Quackenbush's testimony is that the intended targeted region for
16 *Newman* is 157,000 kb. And so, therefore -- and so they argue, if the capture
17 probes were 157,000 bases themselves, then there might be overhanging
18 regions that are pulled down in the process that would somehow expand
19 over the claimed 175 kb. So there's some speculation about what might
20 happen, but we believe the record is strong that *Newman* is targeting the
21 157,000 bases and that's what satisfies the claim. That's what the claim
22 means here. And in any event, for the same reasons as with *Ley*, routine
23 optimization, to use a smaller capture panel and arrive at this claimed less
24 than 175 kb, would have been obvious.

25 JUDGE POLLOCK: All right. Thank you.

1 MR. KRAUSE: We'll turn to the '783 patent unpatentability based on
2 *Ley*. The dispute on the fixed and variable portion and the sequencing to
3 identify are essentially the same as with the '611, so I won't readdress those
4 here. I'll address two of the additional disputes.

5 Turning to slide 54, Personalis disputes that *Ley* applies its probe set
6 to an additional biological sample. We think that *Ley*'s application of the
7 probe set to the relapsed tumor sample satisfies that part of element step
8 1(b). So we think that's a pretty straightforward response to that dispute.

9 The other dispute involves the printed matter doctrine. So I'll turn to
10 slide 56. So we think *Ley* generated the claimed report and that's really all
11 that's required. We do think that it identifies the presence or absence of the
12 health condition or disease, and the genetic invariance can inform a therapy
13 or change in therapy for the subject. But we don't think that the part in
14 parenthetical (ii) is entitled to patentable weight under the *Praxair* case.
15 And so, right, claim limitations directed to printed matter are not entitled to
16 patentable weight unless functionally related to the substrate on which the
17 matter is printed.

18 And really the -- turn to 58, which brings up this claim against the
19 *Praxair* claim on this generating a report identifying variants which inform a
20 therapy choice or change in therapy is really just calling for a mental step.
21 And the claim found the printed matter in *Praxair* provided a lot more detail
22 about what the therapy was, what symptoms were being evaluated, what
23 information was being provided to the healthcare provider to make this
24 determination, and that was still determined not to be entitled to patentable
25 weight.

1 JUDGE POLLOCK: In the event we were to find element (d) to be
2 entitled to patentable weight, what would be your response?

3 MR. KRAUSE: So I think this goes back to some of the -- I can pull
4 paragraphs. Dr. Quackenbush testified that observing some of these variants
5 were known to have relationships with chemotherapeutic drugs, whether
6 indicating or contraindicating them, and so providing that information would
7 inform the decision of whether or not to use those, because this is just a
8 providing information step. So given the known relationship between, for
9 example, the SLC15A1 and cytarabine, that would be an example of
10 providing information that informs the choice in therapy.

11 Now I'll turn to the ground 3 for the '783 patent is the combination of
12 *Forshe* and *Dawson*. The primary dispute in this ground is really
13 regarding whether *Forshe* discloses the combination of the -- or whether
14 the combination of *Forshe* and *Dawson* discloses and motivates the
15 combination of a fixed and variable portion. So, again, the variable portion
16 is data-derived or based on the initial sequencing. And we think that's the 10
17 variants we rely on in *Forshe* are identified based on the whole genome
18 sequencing of tumor material in the co-pending proceeding. That's exactly
19 what Patent Owner's counsel said as well. And we think there's a motivation
20 from both the *Forshe* reference itself and the related *Dawson* reference that
21 motivate a POSA to include additional variants for TP53, which is a known
22 breast cancer driver gene. So the motivation would be to include those, for
23 example, to increase the accuracy and to further inform the treatment based
24 on this known variant.

25 The primary dispute, I think, appears to be that Patent Owner
26 contends that even though the references teach probes to subsets of the TP53

1 gene, I think they construe the argument as arguing that the proposed
2 combination would require covering the entire TP53 gene, which is not the
3 case. And they argue that because of that length, it would require a
4 significant amount of PCR primers that wouldn't be multiplexable. But this,
5 again, we think even if -- and again, our combination is not that you would
6 target the entire gene, it would be that you would target the known -- some
7 of these known variants indicated in *Forsheew* and *Dawson*. But even if you
8 did target the whole gene, that multiplexing wouldn't negate motivation,
9 wouldn't negate reasonable expectation of success because in the context of
10 *Forsheew*, Patent Owner's counsel has said that multiplexing of this degree of
11 targets was routine and well established by 2015.

12 I'll address briefly the dependent claims in the '783 patent. There's a
13 dispute over whether it would be obvious to substitute capture probes or
14 hybrid capture probes for the PCR primers of *Ley* and *Forsheew*, and there's a
15 dispute over whether it would have been obvious to apply *Ley* to cfDNA.
16 So, on the hybrid capture probes, this is something Dr. Quackenbush
17 testified. He said that by 2016, these techniques were readily available and
18 known to be interchangeable to POSAs as predictably substitutable
19 enrichment techniques, and that given a particular desired target sequence, it
20 would have been obvious to select hybrid capture reagents as opposed to
21 PCR probes for certain experiments. And this is confirmed by the patent
22 admissions that these are essentially interchangeable techniques by that
23 point.

24 On the cfDNA point, and the obviousness ground for *Ley*, Dr.
25 Quackenbush explained, based on the subsequent literature that used a
26 similar approach of an initial whole genome sequencing or whole exome

1 sequencing step to identify tumor variants, designed PCR primers to create
2 amplicons based on cfDNA, that that sort of serial monitoring was an
3 obvious extension of *Ley*, and that a POSA would have found that obvious
4 to do with a reasonable expectation of success, including because of the
5 numerous successful reports of doing exactly that.

6 And unless there are further questions, I will reserve the remainder
7 of my time.

8 JUDGE POLLOCK: Judge Jenks. Judge Majors. Questions?

9 JUDGE JENKS: I do not have any questions.

10 JUDGE MAJORS: I don't either. Thank you.

11 JUDGE POLLOCK: All right. well, thank you. You've got 16
12 minutes for rebuttal. I'm sorry, 11 minutes.

13 Mr. Walter -- Charles, are we getting signal for Patent Owner's
14 counsel, Mr. Walter? Charles, do we have Mr. Walter on the line?

15 CHARLES: Just a moment, sir.

16 JUDGE POLLOCK: Oh, okay.

17 CHARLES: I do see him here. Just a moment. Well, Mr. Walter,
18 you are muted.

19 MR. WALTER: Can you hear me now?

20 CHARLES: Yes, we can hear you now.

21 JUDGE POLLOCK: Yes, we can hear you.

22 MR. WALTER: Your Honor --

23 JUDGE POLLOCK: These technical issues pop up whether we're in
24 person or online, so we take it with a grain of salt and move on. So if you're
25 ready, you have 40 minutes.

1 MR. WALTER: I am ready and thank you. And I apologize again
2 and thank you for accommodating the technical error.

3 JUDGE POLLOCK: Not a problem.

4 MR. WALTER: I'm going to start with the '611 patent just like
5 Petitioner did. And I'm actually going to start with their summary of claim 1
6 of the '611 patent, which is their slide. It's slide 3 from their presentation.
7 It's helpful I think because it shows how specific this claim is. It's a
8 personalized genetic testing assay, requires you to do an initial sequencing
9 process where you sequence more than 12 gigabytes, identify the variants,
10 and then in another sample or a subject from a relative, you sequence with
11 the footprint of 175 kb or less, and the depth has to exceed the initial
12 sequencing process. And this is a very specific method. The specifics
13 they've kind of disregarded and treated as minor points, but these specifics
14 are the things that allow you to do personalized cancer monitoring. So it's a
15 very specific set of claims.

16 Now let's talk about *Ley* and I'm going to show the first page of *Ley*.
17 This is Exhibit 1012. This is the first page and it's entitled, "DNA
18 sequencing of a cytogenetically normal acute myeloid leukemia genome." If
19 you look at the abstract and explain what this method is about, it's about
20 whole genome sequencing for "unbiased discovery". And if you look on
21 page 68 of *Ley*, that's what I'm showing on the slide right here, if you look in
22 the lower right-hand corner there's the decision tree that Mr. Krauss referred
23 to and it talks about how this is done. It finds nearly 4 million variants in the
24 sequencing, does sequence alignment, and it filters them by comparing them
25 to a skin sample and then they filter them more by comparing to a national

1 database. Then they filter out noncoding variants and they filter out false
2 positives and then they come up with their final set.

3 So what this is about, what this reference is really about, it's nothing
4 more than a complex process for doing an initial discovery of mutations
5 related to AML. This isn't a personalized assay in the claims that focuses on
6 reducing your sequencing footprint based on getting an initial certain
7 amount of sequencing data. It's nothing like that. It's just an initial
8 discovery process to figure out what mutations might be causing AML.

9 Now what does *Ley* say about the types of processes that are actually
10 in the claims? Here's what it says. I'm showing our slide 28 now. It states
11 that targeted approaches that use PCR or capture, as in the claims, are
12 inherently limited and they're going to miss key limitations. That's what it
13 tells you about the kinds of methods that are in the claims. And so the
14 notion that *Ley* is a reference that renders obvious the claims, that's far-
15 fetched and that's borne out as we start looking at the individual limitations
16 that are in the claims.

17 And I'm going to proceed much the same way Mr. Krauss did. I'm
18 going to start with the 175 kilobyte limitation. That's shown on their slide 3
19 down there at the bottom, a library footprint of less than 175 kb. Now, it's
20 not anticipated. It can't possibly be anticipated because to know how much
21 sequencing done, how big your footprint is, you need to know specific
22 regions you sequence. And we don't know that because it's not in *Ley*. How
23 do we know that? Because Dr. Quackenbush has told us. He says we don't
24 know the primary sequence or the exact exons that were analyzed. He said it
25 over and over and over again. I'm showing slide 21. "Yes, we don't know

1 the exact primers that *Ley* used." We don't even know the approximate
2 primers that *Ley* used.

3 Slide 22. "*Ley* doesn't disclose the parameters used for the PCR
4 parameter design." We don't have any idea what was going into how he
5 selected his primers and hence the size of the resulting sequence.

6 Slide 23. "I could make guesses, but they would only be guesses."
7 That's Dr. Quackenbush.

8 Slide 24. "I can't speculate on what *Ley* did or did not do." This is
9 in response to a question about how is he designing the PCR. We just don't
10 know.

11 So there's no anticipation here. They have a theory that you can set
12 an upper bound by assuming that only the little itty-bitty exons are getting
13 amplified, but this is just an assumption. Those exons are part of genes and
14 they're only tiny parts of the genes. Dr. Quackenbush acknowledges that.
15 He says the gene may span thousands of bases. And this is slide 111. But
16 that can be distributed over sometimes tens of thousands of bases of DNA.
17 So the actual exons can be tiny fractions of the actual genes. And we have
18 no idea where the primers were placed in order to amplify those exons.

19 So what they're really trying to make here is an inherency argument.
20 And they didn't use inherency expressly, maybe they should have, and we're
21 calling them out now and saying this is an inherency argument. That's what
22 it is, it's an inherency argument. And it's a poor inherency argument because
23 they haven't established that it's there because Dr. Quackenbush has
24 acknowledged that we don't know how they actually designed those primers.

25 Now, there's also this question that would it be obvious in view of
26 *Ley*? Would this type of approach where you come in and you start with 12

1 gigabytes of sequencing data and you focus in on 175 kilobytes, that have
2 been obviously in view of *Ley*? No, we've seen this before. I'm showing
3 slide 115. "Examination of tumor genomes by PCR-directed or capture-
4 based methods is inherently limited, and will likely miss key limitations."
5 This is not at all advocating the kind of methods in the claim, just telling that
6 you can miss things if you use those methods. It's telling you --

7 JUDGE POLLOCK: Mr. Walter? Mr. Walter, backing up. If *Ley*
8 said he's sequencing exons, why shouldn't we take him at his word? Why
9 does it matter where the primers are? He's sequencing exons.

10 MR. WALTER: Because the claim requirement isn't sequencing
11 exons. The claim requirement is that you use a sequencing coverage of less
12 than 175 kb. Okay? And so --

13 JUDGE POLLOCK: And the length of the exons are known, so we
14 can fix an upper bound to the total of the exons. I'm just not following your
15 argument.

16 MR. WALTER: The issue is that you don't know that because he says
17 he's sequencing exons, that he's not including additional regions of the
18 genome in conjunction with that sequence data. If you include primers that
19 are on the outside of the exons, which you might do if what you're trying to
20 do is make sure that you capture an entire exon, you would reasonably
21 include those primers outside the exon. By virtue of doing that, you're going
22 to be sequencing more than just the exon. There's no way around that. And
23 we have no idea where he put those primers. There's no reason to think he
24 put the primers just right outside the exon. Because in order to design
25 primers for a PCR experiment, there's a lot of considerations that go into
26 that, including making sure the primer is unique, making sure that the

1 annealing temperature is going to be right. And we don't have any idea what
2 considerations went into that. They might have been very far outside the
3 exons in order to capture those exons. That might have been what he needed
4 to do. And we just don't know that. That's why we don't have that. That's
5 why it's not anticipated.

6 Now, it's also not obvious either, based on *Ley*, because this type of
7 approach, if focused in on a tightened region of the genome, is something
8 that *Ley* discourages, tells you that you're going to miss things. What it's
9 telling you is that their results suggest that the range and scope of cancer-
10 causing mutations is broad, it's diverse, wide-ranging, and it's distributed
11 widely across the genome. So it's the idea of trying to target particular
12 genomes isn't going to work. That's the plain language says. Trying to rely
13 upon *Ley* as teaching a footprint of 175 kb when you don't actually have any
14 idea of what was actually done, just hindsight, that's retracing the path of the
15 inventor.

16 Now, I want to point out a couple things we heard from them. One
17 of the things we heard from them is that, well, 175 kb isn't identified as
18 being critical. Well, that's not true. Patent tells you, using the method
19 herein, the footprint of the assay be smaller, calls out 175,000 bases versus
20 35 million. And it tells you that you can do this and make it more
21 affordable, while at the same time having good accuracy and having good
22 sensitivity.

23 Your Honor asked about this, and I want to respond bit by bit to the
24 points that Your Honor asked about. You asked about this. They pointed to
25 slide 13 from their presentation. They said, hey, look, here's Dr.
26 Quackenbush. He said, we only sequence the exons. Well, go back and

1 look at slide 13, and what you'll see on that slide is not a single citation to
2 the pact (phonetic). It's just Dr. Quackenbush's say so.

3 They point to Dr. Furneaux. Dr. Furneaux says, oh, they sequenced
4 amplicons of exons. Well, that proves nothing, because sequencing an
5 amplicon of an exon doesn't mean that you're not going to include additional
6 information with that. Like I said, you may design those primers well
7 outside the exons to make sure you capture it. That would be generating
8 amplicons of the exons, but there would be other things as well.

9 And then finally, they pointed to the decision tree. They said, well,
10 the decision tree shows that they're actually getting rid of the exons -- or the
11 introns. No, it doesn't. What the decision tree shows is they found certain
12 mutations, certain variants that were in the introns, and they decided they
13 didn't need to focus on that for further study. But that doesn't tell us
14 anything about where they actually designed their primers, whether they
15 have the 175 kb. Right?

16 To move on now to the deeper sequencing depth. This is the
17 requirement that the sequencing depth in step (e) is greater than the
18 sequencing requirement in step (a). This is not anticipated either. In fact,
19 *Ley* doesn't say anything about this. It's not even thinking at all about what
20 the right sequencing depth be for identification in a targeted personalized
21 asset. It's not thinking about that because it's only focused on trying to
22 discover these mutations for the first time. So they point to these read
23 counts, and these are just the read counts for the validation process. And,
24 you know, what you should note about these read counts is that they're all
25 over the map. You know, one of them is zero, one of them is one, another
26 one is in the tens of thousands.

1 JUDGE POLLOCK: Mr. Walter, aren't these read counts intended to
2 determine frequency in the sample, not discovery? Maybe we have a
3 different idea of why we have read counts here.

4 MR. WALTER: Yes, the read counts are, you're absolutely right, the
5 read counts are only for the validation process. And we're going to hit these
6 read counts again. We're going to talk about this when we get to the
7 identification step. But for now, I'm only focusing on the notion of whether
8 these read counts satisfy the increased sequencing depth limitation, which is
9 what they're relying upon them for, but we are going to come to that. You're
10 right.

11 JUDGE POLLOCK: I thought you were saying that they were
12 intended for discovery, but -- and I don't see it that way. Maybe I
13 misunderstood you.

14 MR. WALTER: Okay, if I misspoke, I'm sorry. These were part of
15 the validation process. As a whole, what I would say is that the *Ley*
16 reference is only about the discovery process. There's an initial
17 identification, there's the validation step. But overall, the reference is only
18 about trying to identify the mutations. What I'm just trying to convey is that
19 *Ley* is not about trying to provide a personalized assay, and it's not about
20 how to optimize a personalized assay and what the right parameters might
21 be. And for that reason, it doesn't actually have any discussion of what the
22 right sequencing depth might be for that purpose.

23 These read count data, it's all over the map. The thing to understand
24 is that read count data for an individual locus, that's not sequencing depth.
25 The sequencing depth is, in fact, computed by this Lander-Waterman
26 equation. And the sequencing depth, it's not a property that's measured by

1 an individual locus. It's an aggregate property of your sequencing run where
2 what you look at is the read length for your sequencing process of the total
3 number of reads for your sequencing process divided by the length of the
4 genes that are actually being studied. And that's what the sequencing depth
5 is for a sequencing run. And none of that information is provided. It's
6 nowhere.

7 How do we know that that information isn't provided? Well, because
8 Dr. Quackenbush tells us. He doesn't tell us the primer sequences or the
9 exact exons. We have no way of knowing what this denominator is on slide
10 108 in the Lander-Waterman equation. We have it many times. Slide 21.
11 "we don't know the exact primers," slide 22, slide 23, slide 24.

12 Going to go through it all in detail again. Put up this slide. This is
13 their slide 19, where they tried to establish this was satisfied. They point to
14 Dr. Furneaux's testimony about coverage being empirical. This is about
15 coverage. Okay, remember, in this claim, there's coverage and depth.
16 Coverage is the 175 kb or perhaps the 12 kb in step (a). This is depth.
17 Those are different concepts, so it's not quite clear why they're relying upon
18 that.

19 And then they point to Dr. Quackenbush, paragraph 66. They say
20 coverage is "the number of times a genomic sequence has been sequenced."
21 What's important, though, is that they only showed you the first sentence of
22 this paragraph. Here is the actual expert report from Dr. Quackenbush.
23 Okay? And the sentence right after is this, "The coverage can be calculated
24 by the Lander-Waterman equation." They left that out. So they tried to
25 characterize this as just a theoretical thing, not a practical thing. This is a

1 practical thing. This is how Dr. Quackenbush says it's done. And he made
2 no effort to show that *Ley* actually satisfied that.

3 Okay. Now, unanticipated, is it obvious? No, it's not obvious either.
4 As I mentioned in response to your question a moment ago, *Ley* doesn't
5 provide any guidance on what you can or can't do or what you ought to do in
6 terms of sequencing depth when you're trying to do a personalized assay,
7 because it's not concerned about that. It's not thinking about that. It doesn't
8 mention anything about the benefits of increasing sequence depth. *Ley* is
9 contemplating a process where you go through a decision tree. That's the
10 decision tree in the lower right-hand corner.

11 Here are the things a POSA would be thinking about. It comes from
12 their expert. A POSA in trying to implement one of these assays would be
13 thinking about accuracy, cost, simplicity of the assay, the simplicity of the
14 analysis. Those are the things the skilled artisan would be thinking about.
15 You see this in Dr. Quackenbush's testimony. Here's slide 114, because all
16 of these factors are important. You can't say that one factor is more
17 important than the other. He says they're all important.

18 The thing to note is, if you look at slide 113, I'm listing those factors:
19 accuracy, cost, assay simplicity, and analysis simplicity. At least three of
20 these weigh against this approach. If you increase the sequencing depth, as
21 the claim requires, that's going to increase the cost of the assay, it's going to
22 increase the complexity of the assay, and it's going to make the analysis
23 more complex. So it's just -- it's really hard to understand how they could
24 possibly meet their burden in view of *Ley*, a reference that says nothing
25 about what the appropriate sequencing depth ought to be in the context of a
26 personalized genetic assay for cancer, have their own experts saying a

1 skilled artisan is going to be thinking about all these factors, three of which
2 weigh against.

3 And what I would note is in the presentation we just heard from
4 them, they didn't address any of the testimony from Dr. Quackenbush on this
5 space, nor did they address any of the testimony from Dr. Quackenbush
6 about how we don't know anything about what *Ley* was actually doing in
7 terms of the sequencing regions or the overall number of genes that are
8 being studied.

9 I'd like to turn to the identification point. There is this claim
10 construction issue that I'd like to spend a little time talking about. This is the
11 requirement that when you do your sequencing at a coverage of 175 kb or
12 less, with the increased coverage, you need to identify the mutations. And
13 there's a dispute about how this should be understood. The dispute is
14 whether identifying means you have to learn of the presence of the variant in
15 the sample, which is what our position is, or if you can satisfy this, having a
16 sample where you know the variant is present, but you just sequence it and,
17 as expected, it pops up in your sequencing data. We don't think that's
18 identification. We don't think that's what the claim is talking about, and we
19 don't believe the word "identifier" remotely brings to mind the latter
20 situation.

21 Let's look at the claim language to help understand that. This claim
22 was only about sequencing something they already knew was there. The
23 language wouldn't say identify, it'd just say subjecting said sequencing
24 library to sequencing at a coverage of 175 kb or less on said variant. But it
25 doesn't. It says that you're identifying it. The next sample, you're
26 identifying it in that sample that's sequenced in step (e). And that

1 identification, that use of the word "identification," that brings to mind the
2 concept of learning that it's actually there in the sample, not sequencing it.
3 We already know it's there.

4 Now, the other thing to note is what's more is the whole point of
5 increasing the sequence depth here is to make sure that you're going deep
6 enough to pick up those variants. Okay? And so if what we were talking
7 about was sequencing something that you knew was already there, you
8 wouldn't be including claim elements directed to having a depth that's
9 enhanced to make sure that you actually do pick it up and learn that it's
10 really there.

11 Now, I think we know that however they're trying to interpret this,
12 it's not correct. I don't know if Your Honors had a chance to look at the
13 transcripts of the experts, but we asked their expert. You know, we had our
14 understanding of what this was, and we asked Dr. Quackenbush on cross
15 examination. We asked him clearly and straightforwardly, what was your
16 understanding of what it means to identify something in the context of this
17 claim language? It's a clear, simple, fair question for a deposition of an
18 expert who's opining on in the validity. And what we got was 14 pages of
19 nonsense. If you get a chance to look at it, I think this is telling.

20 We asked him this question, you know, embedded within this 14
21 pages of nonsense. He says, "I'm able to offer an opinion on what it would
22 take to meet the claim limitation. I can't set out the width or length of what
23 'to identify' might mean." He says, "I can't, you know, testify as to the
24 extent of how one might interpret this." And this is on slide 60 and 61 of our
25 presentation. And again, "What is your understanding of what it means to
26 identify a presence or absence of at least a subset of said set of genetic

1 variants within the context of all the claim language?" A fair question for
2 this kind of a deposition. And here we are on slide 62. The only answer we
3 get is, well, "the claim is obvious in view of *Forshe* and *Dawson*."

4 This is telling. Their own expert can't give a straight answer on what
5 this means and what this establishes, that however they want to interpret
6 this, I haven't explained yet, it can't be right. If they had a clear
7 understanding, if they had a defensible position for what this would be, that
8 would stand as a fair rebuttal to what our position is, you wouldn't see
9 something like this. You know, we understand that in the Institution
10 decision, the Court came out a different way. But in view of the record
11 that's developed, we think our construction is the right thing.

12 Now, in view of that construction, anticipated, no, it's not. Here
13 we're showing on slide 63 their petition. They say, "Once the invariants of
14 interest, the 'putative variants,' were identified, *Ley* then describes
15 validation." The process they're relying upon is the validation step, which
16 they themselves distinguish from identification. Again, it's not surprising
17 that this is the language they would use, because *Ley* is not interested in that
18 validation step, in trying to identify them. They already identify them. It's
19 just a validation step to quantify, to do a little bit more study on the relative
20 amounts of the mutations that are present.

21 Obvious? No, it's not obvious either. The reason that I mentioned,
22 *Ley* is not focused at all how to find mutations that may or not be present in
23 a sample taken down the road from a patient. There's no meaningful
24 explanation for them as to why it would be obvious to do this in view of *Ley*.
25 What *Ley* tells you, that these kinds of targeted approaches might miss
26 mutations. As our expert explained at the time, issues with this kind of

1 approach, including read length, tumor heterogeneity, and cost, and what he
2 does when it does its validation, is it does kind of an artificial example
3 where they're using an atypical example that's almost 100 percent tumor
4 cells. They sidestep the issues that would have been seen for a real-life
5 sample. They don't propose that. They say, this is not the way to go.

6 I'd like to move now to the fixed and variable claim elements. We
7 have the claim construction dispute on fixed and variable. And the dispute
8 here is whether the terms ought to be given their plain and ordinary meaning
9 or their definition from the specification. I don't recall them addressing this
10 in much detail.

11 Expert, this is on slide 15, he says the best place to look is the
12 specification. And that's not controversial. That's actually correct. And if
13 you look at the specification, it says the variable portion defined based on
14 the genetic characteristics originally determined for the individual subject.
15 (Inaudible) portion, change from (inaudible) subject to another. So what do
16 you take away from this? What you take away is that the variable portion is
17 defined based on the characteristics for the subject, so it's going to change
18 from the subject to the subject. And that's contrasted with the fixed portion,
19 which does not change. You see that elsewhere, which is variable, subject to
20 subject, and another portion which is fixed. In other words, the fix doesn't
21 change from subject to subject. The variable does.

22 Slide 17. Here's another example, invariable. Variable is person,
23 subject. Now, no reason to think that in *Ley* we're actually talking about
24 something that might vary from subject to subject. Well, *Ley*, doesn't tell us
25 what fiber sequences we're analyzing here. Go through it again. That's on
26 slide 20, 21, 22, 23, and 24.

1 And the other thing *Ley* tells us is that the AML patient was
2 representative of most patients. In other words, the genes they identified,
3 they might have been the type of fixed content that you would use in an
4 assay. But *Ley* doesn't say anything about that because it's not thinking
5 about a type of assay where you would be testing a cancer patient and
6 multiple samples at different time points based on fixed and variable
7 content. All it's really trying to do is identify mutations that might cause
8 AML.

9 It's not obvious either, because, as we've said many times, *Ley* tells
10 you personalization, another hypothesis-driven, candidate gene-based
11 examination of tumor genomes by PCR-directed or capture-based methods is
12 inherently limited. It tells you this is not the way you should go. That
13 wouldn't be an approach a person of skill in the art would try based on *Ley*.

14 Then we have Dr. Quackenbush, too. He tells us the key thing
15 someone's interested in, cost. Slide 29, 30 from their petition, "increasing
16 accuracy," "reducing sequencing costs was desirable"; slide 31, "we've
17 always striven to be as cost-efficient as possible"; 32, trying to be as cost-
18 effective as possible; 33, always trying to simplify the assay; 34, all of these
19 factors are important.

20 And so the notion that we're going to come into *Ley* and start
21 augmenting this small set of primers that was used to do validation and start
22 doing fixed and variable primers down the road by adding primers for genes,
23 that's contrary to all this.

24 JUDGE POLLOCK: Mr. Walter, where do your claims require a
25 larger number of primers, or any number in these claims?

1 MR. WALTER: Oh, so, no, no, all I'm trying to say is relative to *Ley*.
2 So in the *Ley* reference, what you have is a small set of primers, none of
3 which you can either characterize as fixed or variable. You can't really say
4 which group they fall into. And their obviousness approach, just so we're
5 clear, their obviousness approach is that someone of skill in the art, even to
6 some sense -- even to the extent someone of skill in the art doesn't believe
7 that *Ley* discloses one of these fixed or variable portions, someone who's
8 still in there would just come in and add that in. I'm addressing that
9 argument now. That's what I'm trying to respond to, is the notion that
10 someone would come in and add additional primers to *Ley* to fix up the gap
11 to the extent it doesn't disclose fixed, invariable. That's what I'm trying to
12 address. Okay? And so it's not -- it's not the --

13 JUDGE POLLOCK: Well, I'm really not grasping how you're
14 differentiating primers from what *Ley*'s 10 variants are driven by. Right?
15 You need to spell that out a little bit more for me. For variants, right?

16 MR. WALTER: Let me take a step back.

17 JUDGE POLLOCK: That's unique to the patient, or as you seem to
18 want to put it, unique to M1 AML patients.

19 MR. WALTER: Yes, and that's the issue. If all we're doing is talking
20 about a set of primers that's well known in AML-1 patients, that's the type of
21 stuff that's going to be fixed, that's the fixed content, the stuff that's not
22 going to vary from patient to patient.

23 JUDGE POLLOCK: How does your claim exclude patients that are
24 outside of a very small subtype of cancer patients? I'm just not seeing how
25 you're getting all these things packed into the claim.

1 MR. WALTER: Oh, it's simply because, listen, if you're doing this
2 kind of assay, the assay is going to depend on the type of cancer, naturally.
3 If you've got a leukemia patient, you're not going to load up the assay with
4 primers for lung cancer. And that's what they do later on down the road, is
5 they do try to mix and match and say things would be fixed. Someone
6 wouldn't be motivated to make that kind of combination.

7 JUDGE POLLOCK: So even taking your presumption, if we look at,
8 say, the CDH24 gene from Table 3 of *Ley*, he shows that 5,672 variant runs
9 and 4890 non-variants. So 53 percent showed a variant. So isn't that varied
10 as the cancer waxes and wanes?

11 MR. WALTER: No, I don't think that --

12 JUDGE POLLOCK: Well, that percent is specific to the patient.

13 MR. WALTER: I don't think the fact that the percent varies is
14 something that determines whether something's fixed or variable. Fixed or
15 variable is a distinction between the type of content that's in the assay that
16 you're always going to be testing for, independent of the subject. Because --
17 and this is, just to be clear, none of these concepts are in *Ley* at all. None of
18 them are in *Ley* at all. And that's the bigger point.

19 But as I was saying, fixed content is the type of content that's not
20 going to change from patient to patient because it's known that it's precisely
21 the type of thing that is always involved in the cancer. Okay? It's something
22 that's so common in a particular type of cancer that you always include it in
23 your panel. The point I'm trying to make is that the panel may or may not
24 vary. The data will always vary. The data in the panel are two distinct
25 things. This claim element is talking about the panel. That is the genomic
26 target you're going after, and what you're asking about is the data point.

1 The main point, you know, putting aside the questions you asked
2 about, the main point is that in *Ley*, there is no concept of fixed and variable.
3 It's just not there at all, because he's not thinking about trying to develop an
4 assay anything like the claims. All they're trying to do is figure out what
5 mutations cause AML. That's it. So there's no concept of fixed and
6 variable. It's just not there. Now --

7 JUDGE JENKS: Mr. Walter? Mr. Walter, can we -- this is Judge
8 Jenks. Can we step back just one more, a little back? I'm still struggling
9 with this whole identify thing. And can you point out where in your
10 specification you define identify? So I can understand how *Ley* does not
11 identify variants in these AML patients.

12 MR. WALTER: So identify. Our position is that this is not a term
13 that's uniquely identified in the specification. The patentee did not act -- in
14 fact, that's one of the things I want -- I'll step back a little bit here. This is
15 one of our key points, Your Honor, is that the patentee didn't act as a
16 lexicographer in the specification with regard to the term "identify". And so
17 given that that's the situation we're in, we're the plain and ordinary meaning
18 that applies here. Okay? That's where we're coming from on this, not that
19 the specification has a term.

20 The best place, I think, to make clear, to help understand that this use
21 of the term "identify" is not about simply seeing that it pops up in your
22 sequencing data when you already know it's going to be there, is the claim
23 language itself. Earlier, if this claim was about simply observing that a
24 variant was in a set of sequence data where you knew it was already going to
25 be there, the claim wouldn't say this, and it wouldn't include a claim element
26 directed to increasing the sequencing depth to make sure you find it. It

1 wouldn't even be relevant to include that. So this "identify," what it's really
2 referring to in the context of this claim language, and this is I think the best
3 evidence, is pushing (phonetic) the identity of the variants that are present or
4 absent. And it's establishing that for the first time, not simply seeing that it's
5 in your sequencing data. That's our position that we're coming from. And
6 so we are relying heavily on the plain meaning of the word "identify".

7 JUDGE JENKS: But the way I look at *Ley* is *Ley* went out and said,
8 hey, I'm going to sequence DNA from these AML patients, and we're going
9 to look for things that are different, and then we're going to go back and
10 double check that it's really there. And that's how I understand *Ley* to have
11 done it. So I'm still struggling how identifying variants might be (inaudible).

12 MR. WALTER: Okay. And that is -- and I think your understanding
13 is incorrect. In *Ley*, if you look on page 69 of *Ley*, they were actually
14 sequencing not just the original tumor sample, but the relapse sample as
15 well. That relapse sample was included as part of their identification
16 process. So they knew those mutations were actually part of the relapse
17 sample. And then they did, they went back and they did do targeted
18 sequencing on the relapse sample. Not to say, hey, is it really there? They
19 did it to find out the extent to which it was there.

20 They wanted to look at the allele fraction. Okay? And they were
21 very gratified to see that it was present at about 50-50 allele fraction. That's
22 what they were doing. It wasn't to confirm that it was there and to identify
23 that it was there, they knew it was there because it was part of the original
24 sequencing process.

25 So I'd like claim 10 and 28 very quickly because Your Honor asked
26 about it. They require a therapeutic intervention. That's not anticipated in

1 *Ley*. We know it's not anticipated in *Ley* because the patient was dead when
2 the experiments were done. You can't have a therapeutic intervention on a
3 dead patient. And we know that because to do the experiments, they had to
4 get consent from the next of kin. That's slide 51. That means she was dead.
5 The patient was dead.

6 Now, does *Ley* render obvious preparing a report? No, it doesn't.
7 How do we know that? This is what *Ley* tells you. It says that these
8 hypothesis-driven approaches to identify mutations are going to miss things.
9 This is not a reference that says, hey, we can go do targeted sequencing and
10 decide how to treat someone. It says, well, we should be careful about
11 targeted sequencing because we might miss things.

12 What else does it tell you? That the mutations it found were of
13 unknown clinical relevance. *Ley* can't possibly be teaching or rendering
14 obvious a therapeutic treatment based on this. It can't possibly. It's telling
15 you, don't do the targeted screen. And it's saying that the contextual
16 relevance is unknown.

17 Okay. So I want to hit real quickly *Forshe* and *Newman* on the
18 '611 --

19 JUDGE POLLOCK: Mr. Walter, I'm not sure that *Ley*'s discussion of
20 contextual relevance is the same as that the relevance of these individual
21 variants is unknown. I think you might be over reading that sentence.

22 MR. WALTER: I mean, I disagree. The language says, "The
23 contextual relevance of the mutations found in these genomes would be
24 unknown." What I take that to mean is we don't understand what role these
25 mutations might or might not be playing in cancer. That's what I take that to
26 mean. And if you don't know what the role is and you don't know what

1 drugs might be useful for them, it's hard for me to believe that you would --
2 that this suggests, hey, here's how we're going to treat someone.

3 JUDGE POLLOCK: Well, how do you deal with Dr. Quackenbush's
4 testimony that one of these variants was associated with cytarabine
5 resistance?

6 MR. WALTER: Repeat that, Your Honor.

7 JUDGE POLLOCK: Well, how does that square with
8 Dr. Quackenbush's testimony that one of these variants was associated with
9 cytarabine resistance?

10 MR. WALTER: They might have learned that after the fact, but what
11 they certainly didn't do in *Ley* was suggest any sort of therapeutic treatment
12 or therapeutic adjustment based on that. There just wasn't anything like that.
13 So figuring it out after the fact and then coming in and saying, hey, we could
14 use this, what that sounds to me like is a hindsight reconstruction. That's
15 what that sounds like to me.

16 If *Ley* was thinking about doing a therapeutic treatment, it would
17 have said, hey, look, we found a mutation that's associated with the
18 condition Your Honor mentioned, and we can do the treatment. But *Ley*
19 doesn't say anything like that. It just notes it after the fact and then trying to
20 come in afterwards and say, hey, we could use this for therapy. That's
21 hindsight -- that's my response on that.

22 I only have about a minute left, and so I want to respond real quickly
23 on one point, and I want to move to the '783 patent on *Forshe* and *Dawson*
24 for the (inaudible) patent. And what's noteworthy about this is -- I'm sorry,
25 Your Honor. I didn't mean to interrupt you.

1 JUDGE POLLOCK: Oh, no, you didn't. I have some allergies. I was
2 clearing my throat. I'll go on mute.

3 MR. WALTER: Okay. I want to note real quickly the argument that
4 the '783 patent is obvious in view of *Forshe* and *Dawson* is very, very
5 interesting. You know, they spent a lot of time saying, hey, look at what
6 Mr. Walter said in another case. You know, I don't know that that's entitled
7 to much weight at all here, but let's look at what is entitled to weight, what's
8 not hearsay, what is an admission of the party opponent.

9 Their own founders, they criticize *Forshe*. They say *Forshe* has
10 technical limitations related to multiplexing with PCR, amplicons that can be
11 carried (phonetic) data. There's a small combination of amplicons. There's
12 (inaudible) related to multiplexing of PCR.

13 JUDGE POLLOCK: You're into your rebuttal time, Mr. Walter.
14 Sorry to interrupt.

15 MR. WALTER: And I'm going to finish up in just the next couple of
16 seconds. They criticize *Dawson* as well as having the same problems. They
17 do it multiple times. The methods have been limited by modest sensitivity
18 applicable to only a minority of patients, the need for patient-specific
19 optimization and/or cost, you know, and so the notion that *Forshe* and
20 *Dawson* had it all figured out and rendered the '783 patent, that's just really
21 hard to believe in view of what their own founders, what Foresight's own
22 founders who authorize these proceedings have said about those very prior
23 art references.

24 And with that, I will resume my last four minutes or whatever I have
25 remaining for short rebuttals.

1 JUDGE POLLOCK: Mr. Krause, give me a second. I'll put 11
2 minutes on the clock for you.

3 MR. KRAUSE: Okay. Thank you, Your Honor.

4 JUDGE POLLOCK: When you're ready.

5 MR. KRAUSE: All right. I think I'll begin where counsel left off
6 with some statements about multiplexing and *Forshe*. We believe that
7 goes to the ultimate issue of Patent Owner's characterization of the
8 combination as requiring some thousands of primers. But really, the
9 combination requires, you know, on the order of 10 to 15 primers as we set
10 forth in our reply. So these discussions of multiplexing are really besides
11 the point of the claim and the combination.

12 JUDGE POLLOCK: Well, Counsel, I would tend to agree with you
13 about not requiring thousands of primers, but where does your 10 to 15
14 come from?

15 MR. KRAUSE: Well, so the *Forshe* reference itself, we rely on the
16 10 variable primers that it uses, and then we propose using one or more of
17 the fixed primers disclosed in *Forshe* and *Dawson* for TP53. So the
18 combination is not proposing using the thousand primers that Patent Owner
19 contends would cover the whole gene. It's based on electing a handful of
20 relevant primers. So it's a really small, non-multiplexed universe, and that's
21 something that Dr. Furneaux testified, and we cite this in our reply, doesn't
22 even require multiplexing because you could do parallel PCR on that, on that
23 order of magnitude.

24 I want to address the [inaudible]. I'll go to -- this is Personalis' slide
25 28, which we saw a number of times. And I think the suggestion was that
26 this passage suggests not using a personalized assay. But we think the

1 import of this is that *Ley* was emphasizing the importance of its personalized
2 whole genome sequencing as opposed to solely using hypothesis-driven
3 approaches. So this little snippet doesn't include the passage from *Ley* that
4 talks about how important the whole genome sequencing to identify patient
5 specific mutations was. And we think this passage actually supports the
6 notion that you would want to combine a fixed and variable portion.

7 I'll turn back to slide 31. I believe counsel suggested that there was
8 no suggestion of the concept of fixed and variable portions in *Ley*, but we
9 believe -- this is our slide 31 shows that actually precisely taught these
10 concepts. It said it wanted to use "discovered somatic mutations," so the
11 mutations that were discovered as a result of the sequencing, and then
12 control amplicons based on what was known. So fixed was these known
13 amplicons. Variable was the somatic mutations that tracks the claim
14 language.

15 I'll go to slide 37. This is a passage from the POR where we believe
16 Patent Owner's construction really is requiring reading in this exemplary
17 language about a probe set changing from one individual to another or not.
18 We don't see anything in the claim language or any definitional language in
19 the specification that essentially would require looking at different probe
20 sets and recreating two probe sets in order to determine whether or not there
21 was a fixed and variable portion. The claim simply requires, as we've
22 highlighted, the variable portion from a result of the sequencing and the
23 fixed portion independent of the result of the sequencing, such as the cancer
24 driver genes.

25 And we see this in the dependent claims, which further define the
26 fixed portion. So, for example, claim 17 of the '783 patent, this is slide 34,

1 recites that the "fixed portion comprises one or more known tumor variants."
2 And this wasn't disputed. And we point out that *Ley* identified the BRCA2
3 and TP53 mutations as the fixed portion when it's further defined.

4 Similarly, slide 35 shows claim 18, and this includes the fixed
5 portion being selected from the group, including inherited genes relating to
6 cancer and genes involved in the pharmacogenomics of cancer drugs. And
7 again, citing testimony from Dr. Quackenbush, we identified the TP53 and
8 BRCA2 as satisfying this limitation on that basis.

9 Turn to the issue of sequencing to identify. Judge Jenks had asked a
10 question and I wrote down -- I think counsel said that they were reading the
11 claim as requiring establishing the identity of the variants. But we think this
12 is sort of the key point on this claim construction issue. The claim doesn't
13 say that. The claim says to identify a presence or absence of the variants.
14 So I think the way that they're trying to read the claim removes the presence
15 or absence from the claim language. And when that language is actually
16 included, this simply does not make sense to say you're establishing the
17 identity of a presence or absence.

18 I think we heard a lot about Dr. Quackenbush's deposition. I think
19 the primary issue there is that counsel, I believe, was hoping that
20 Dr. Quackenbush would give their dictionary definition. But this is Exhibit
21 2163, the exhibit page. The one thing that they didn't do, that they didn't
22 show him this dictionary definition or ask him if that would be an
23 appropriate definition to use here. That was not done. And we think that
24 given all of the context in the claim language, that this dictionary definition -
25 - I'll go back, 29, the dictionary definition that counsel picked and

1 Dr. Furneaux adopted really just is not an applicable definition or
2 appropriate definition for "to identify" in these claims.

3 Further questions? I believe that's all I have.

4 JUDGE POLLOCK: Do you have further questions?

5 JUDGE JENKS: I do not have further questions. Thank you.

6 JUDGE POLLOCK: Judge Majors?

7 JUDGE MAJORS: No. Thank you.

8 JUDGE POLLOCK: Very well. Thank you, Mr. Krause. If you'll let
9 me put four minutes on here, we'll get started.

10 MR. WALTER: First, let me start by saying it's a relief that we have
11 this working properly this time.

12 So I'm not going to say too much, but I am going to start with one of
13 their slides that they used in connection with *Ley*. Brought up the -- it's this
14 one. I think this helps illustrate --

15 JUDGE POLLOCK: Slide 53 for the record.

16 MR. WALTER: Slide 53 for the record. It's their presentation. And I
17 think this helps illustrate how their approach to this whole analysis is really a
18 hindsight-driven approach. They say, look, *Ley*'s definitely got the variable
19 and it's definitely got the fixed. And they say there's 10 discovered variants.
20 And these are the ones that are coming from the common AML patients.
21 There's no reason to think they're the kind of thing that might vary from
22 person to person. But then they say that there's the fixed variants, there's the
23 two known variants, the BRCA2 and the TP53.

24 Well, what's interesting is they don't tell you what those mutations
25 actually pertain to. Patients in BRCA2 and TP53, those M372H and P72R,
26 that's for ovarian cancer focused on trying to identify mutations. The notion

1 that someone who's looking for AML mutations would try to design an assay
2 where you've got allegedly variable mutations directed to acute myeloid
3 leukemia and then include with that a fixed set for ovarian cancer, that
4 makes no sense. Why would anybody ever do that? And the reason that the
5 combination they're making is based on that is because this is a hindsight-
6 based approach. They're picking things that seem whatever combined and
7 saying, let's throw it in there in a Frankenstein sort of way. And that's not
8 how you do obvious. It's not how you do anticipation.

9 And unless there are further questions, that's all I have.

10 JUDGE POLLOCK: Thank you, Mr. Walter. Judge Majors? Judge
11 Jenks, do you have a question?

12 JUDGE JENKS: I also do not have any further questions. Thank you
13 very much.

14 JUDGE POLLOCK: Okay. Thank you to both parties for very
15 helpful and well-argued presentations today. This matter is submitted to the
16 Panel for determination and preparation of a final written decision.
17 Adjourned. We will take our leave. If you would kindly stay on the line for
18 the court reporter if she has any questions.

19 (Whereupon, the proceedings at 2:22 p.m. were concluded.)

IPR2023-00545 (Patent 11,299,783 B2)

IPR2023-00546 (Patent 10,450,611 B2)

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