

EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

NATERA, INC.,)
)
Plaintiff,)
)
VS.) NO. 1:23-cv-629
)
NEOGENOMICS LABORATORIES,)
INC.,)
)
Defendant.)
-----)

-- C O N F I D E N T I A L --
IN-PERSON VIDEOTAPED DEPOSITION OF
DR. MICHAEL METZKER
TUESDAY, FEBRUARY 11, 2025

STENOGRAPHIC REPORTER: CHRISTA YAN, CSR NO. 14316, RPR

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1 BE IT REMEMBERED that on TUESDAY, the 11TH DAY OF
2 FEBRUARY, 2025, at the hour of 8:57 A.M., of said day, at
3 555 Twin Dolphin Drive, 5th Floor, Redwood City,
4 California 94065, before me personally, CHRISTA YAN, a
5 Certified Shorthand Reporter, State of California,
6 personally appeared DR. MICHAEL METZKER, who was examined
7 as a witness in said cause; that said transcript format
8 was prepared in accordance with California Code of
9 Regulations Section 2473.

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1 THE VIDEOGRAPHER: We are now on the record. This
2 begins Videotape Number 1 in the deposition of Michael
3 Metzker in the matter of Natera Inc., vs. NeoGenomics
4 Laboratories Inc., in the United States District Court For
5 the Middle District of North Carolina, Case
6 Number 1:23-cv-629CCEJLW.

7 Today's February 11, 2025, and the time is
8 8:57 a.m. This deposition is being taken at 555 Twin
9 Dolphin Drive, 5th floor, Redwood City, California, at the
10 request of Morrison Foerster LLP. The videographer is
11 Emily Murphy of Magna Legal Services, and the court
12 reporter is Christa Yan of Magna Legal Services.

13 Will counsel and all parties present state their
14 appearances and whom they represent.

15 MS. DURIE: Daralyn Durie from Morrison & Foerster for
16 NeoGenomics.

17 MS. LEE: Annie Lee from Morrison & Foerster for
18 NeoGenomics as well.

19 MS. SRINIVASAN: Tara Srinivasan from Quinn Emanuel on
20 behalf of the witness and Natera, and with me at some
21 point will be Sean Boyle from in-house counsel at Natera.

22 THE VIDEOGRAPHER: Okay. Thank you.

23 Will the court reporter please swear in the
24 witness.

25 DR. MICHAEL METZKER,

1 the Witness, called on behalf of the Defendant, being duly
2 sworn to state the truth, the whole truth, and nothing but
3 the truth, testified on oath as follows:

4 EXAMINATION

5 BY MS. DURIE:

6 Q Good morning. And, Dr. Metzker, good morning.

7 A Good morning.

8 Q If we could please have marked as Exhibit 1 a
9 copy of the declaration of Dr. Michael Metzker in support
10 of plaintiff Natera's response of claim construction
11 brief.

12 (Whereupon Deposition Exhibit 1 was
13 marked for identification.)

14 BY MS. DURIE:

15 Q Dr. Metzker, you recognize what's been marked as
16 Exhibit 1 is a copy of the declaration that you submitted
17 in this litigation with respect to claim construction of
18 the '596 patent?

19 A I do.

20 Q If you turn to the first substantive page of your
21 declaration, paragraph 1, you note that you also submitted
22 declarations in connection with Natera's opening and
23 responsive claim construction briefs in a prior round of
24 claim construction, right?

25 A That's correct.

1 Q And you note that you're incorporating the
2 material in those declarations by reference; is that
3 right?

4 A That's what I state, yes.

5 Q Okay. And I take it you have reviewed those
6 declarations in preparation for today's deposition?

7 A Yes.

8 Q Did you find anything in those declarations that
9 you believe to be inaccurate?

10 A No.

11 Q Now, you also submitted declarations in
12 connection with preliminary injunction proceedings in
13 connection with this litigation; is that right?

14 A That's correct.

15 Q Did you review those declarations in connection
16 with preparing for today's deposition?

17 A I did.

18 Q Did you find anything in those declarations that
19 you believe to be inaccurate?

20 A No.

21 Q Now, if we turn to page 3 of your declaration
22 that is Exhibit 1, at the top of page 3 you note that
23 Natera's proposed construction in this case for the term
24 that begins performing high-throughput sequencing and ends
25 from the sequence reads incorporates three requirements.

1 Do you see that? Little one, little two, and
2 little three.

3 A I do see that. I think the paragraph starts on
4 page 2 and carries over to page 3.

5 Q Correct.

6 A Yes, I do see that.

7 Q And I want to start by focusing you on the
8 requirement that is set forth in little one. The terms
9 are all part of the performing high-throughput sequencing
10 to obtain sequencing reads step.

11 What do you understand that to mean?

12 A Well, so it's based on the way the claim has been
13 structured. And if I could actually look at the claim, I
14 could probably answer that --

15 Q Sure.

16 A -- a little better.

17 Q Let's have marked as Exhibit 2 a copy of the '596
18 patent.

19 (Whereupon Deposition Exhibit 2 was
20 marked for identification.)

21 THE STENOGRAPHIC REPORTER: Here you go.

22 THE WITNESS: Thank you.

23 Okay. Can you repeat the question, please?

24 BY MS. DURIE:

25 Q Sure.

1 When it says that the terms are all part of the
2 performing high-throughput sequencing to obtain sequence
3 reads step, what does that mean?

4 A The way I look at this through the lens of a
5 person of ordinary skill in the art would understand that
6 the performing high-throughput sequencing of the amplified
7 DNA includes obtaining reads and detecting an SNV mutation
8 that's present in less than or equal to 0.015 percent of
9 the cell-free DNA having the locus -- the SNV locus is
10 detected from the sequence reads. So it includes both of
11 those steps.

12 Q How do I know if the detection of the SNV locus
13 is happening as part of the sequencing step?

14 A Well, I explain that in my declaration, and it's
15 based on the claim as a whole in the way the claim is
16 constructed.

17 Q And I'm not asking you about why you believe the
18 claim requires that the SNV locus detection happen as part
19 of the sequencing step. We'll get to that. I just want
20 to understand what it means and how I would know in a
21 given instance whether that is happening or not.

22 A Sure. So I guess I was trying to explain the
23 claim as a whole. So the claim requires that you perform
24 sequencing on a tumor biopsy sample. That's Step A. And
25 then Step B, you're evaluating the results to identify

1 loci, which are known positions in the genome, and within
2 those loci are SNVs where you know the location of those
3 SNVs.

4 And then Step C is assaying cell-free DNA where
5 the target specific primers to find the first position of
6 the amplicon, the last position of the amplicon, and by
7 design by identifying SNVs, knowing the position of the
8 SNV. And so I provide an example. For example, if the
9 SNV mutation in a given loci is at base 12 in the amplicon
10 when the sequencer is at Cycle 12 the detection of the
11 fluorescent light will tell you the presence or absence of
12 that SNV mutation.

13 Q And so in your view of the world, that is an
14 example where the detection of the SNV is happening as
15 part of the sequencing operation; is that right?

16 A Yes. In the way I've just described it, that is
17 correct.

18 Q And in that example, the -- in your view of the
19 world, the SNV is detected at the point in time that the
20 base is called; is that fair?

21 A Well, it's not necessarily my point of the world,
22 but given my background and understanding how sequencing
23 technology works, and the way that the assaying cell-free
24 DNA is performed using target specific primers looking for
25 known SNV mutations, you will know which cycle the SNV

1 appears, and the fluorescent color based on which
2 nucleotide is incorporated will tell you whether the SNV
3 mutation is present or absent.

4 Q Got it. And so in every case in which there is
5 targeted amplification followed by sequencing, is it your
6 view that the SNV will always be detected as part of the
7 sequencing step?

8 A So in the broad view, if I am looking to detect
9 de novo SNV mutations, I won't know where the position is.
10 But in the context of Claim 1 of the 050 -- of the '596
11 patent, because I've previously identified the SNV
12 mutation and I know what I'm looking for, in that
13 instance, I will know the position of the SNV mutation.

14 Q So it's your -- is it your view that in any
15 situation in which the location of the SNV mutation has
16 been determined, and in which you are engaged in targeted
17 amplification, you are necessarily detecting the SNV locus
18 as part of the sequencing step?

19 MS. SRINIVASAN: Objection; vague.

20 THE WITNESS: Well, if the SNV location is the known
21 location that I have previously identified, yes, I would
22 know the location. And based on the sequencing process,
23 at that particular cycle, the incorporation of a
24 fluorescent nucleotide will tell me -- based on its
25 fluorescence because these nucleotides have four different

1 colors, the color will tell me -- it will tell the
2 detector, the sequencer, which nucleotide was
3 incorporated, it makes a base call, and it also assigns a
4 quality to that base call.

5 BY MS. DURIE:

6 Q Now, is assigning -- so you referred to assigning
7 a quality. That's a reference to a quality score or Q
8 score, right?

9 A That is correct.

10 Q Is it necessary in your view to have a Q score be
11 assigned as part of the sequencing operation in order to
12 have detected the SNV locus?

13 MS. SRINIVASAN: Objection; vague.

14 THE WITNESS: No. But I would qualify that answer
15 with any next generation sequencing technology that I know
16 every system assigns a quality score associated with base
17 call. So it just happens. It's not whether it's
18 necessary or not. It's just part of the system.

19 BY MS. DURIE:

20 Q I get it, but I want to understand how you think
21 about what it means to detect an SNV.

22 And I take it then, in your view, a Q score may
23 get assigned, but that isn't a necessary prerequisite to
24 the SNV having been detected?

25 MS. SRINIVASAN: Objection; misstates testimony.

1 THE WITNESS: So I think my testimony was at the
2 position where the SNV mutation occurs when a polymerase,
3 which is an enzyme, that incorporates these dye-labeled
4 nucleotides based on which -- based on the complementary
5 template base, the polymerase will incorporate its
6 compliment base, which is an indication of whether the
7 wild-type base is present or the mutated base is present
8 in the sequencing. And that's all detected by
9 fluorescence, and the detector will then generate a base
10 call.

11 BY MS. DURIE:

12 Q Okay. I want to see if I can put this in
13 somewhat simpler terms because I don't think you actually
14 addressed the quality score issue in your answer to my
15 question.

16 So you know -- let's take a concrete example.
17 You know that the SNV mutation, if it is present, will be
18 present in Position 4. Are you with me so far?

19 A Sure, I understand your example.

20 Q Okay. You perform the sequencing operation and
21 you get a fluorescent signal at Position 4 that is blue.
22 With me so far?

23 A So far so good.

24 Q Let's say that we know that blue corresponds to
25 T. Okay?

1 A Yep, I understand that.

2 Q Okay. A T I know already corresponds to an SNV
3 mutation at that position based on a prior analysis that
4 I've done. With me so far?

5 A Yes, I'm still with you.

6 Q Assume that those things happen, and nothing
7 more. Have I detected the presence of an SNV?

8 MS. SRINIVASAN: Objection; incomplete hypothetical.

9 THE WITNESS: In my mind, when I describe things like
10 this to graduate students, color is enough to identify a
11 base. In the next generation sequencing world, it's
12 always associated with a quality score.

13 BY MS. DURIE:

14 Q But I want to -- that's fair, but I want to
15 understand, in your mind, is it necessary to have the
16 quality score in order to identify the SNV?

17 A I don't think it is.

18 Q Okay. Now, you said when you're explaining this
19 to graduate students, you say color is enough to identify
20 a base. In your mind, is there anything required to
21 identify an SNV other than identifying the base and
22 knowing the position of that base and the -- and what you
23 expect to be present at that location, an A, a T, a C, or
24 a G?

25 MS. SRINIVASAN: Objection; compound.

1 THE WITNESS: I don't understand the question.

2 BY MS. DURIE:

3 Q Sure. You said that color is enough to identify
4 a base. Is color enough to identify an SNV?

5 A Yes. And because a base at a given location is
6 either going to be represented by the normal base or the
7 SNV mutated base.

8 Q Got it. And so when Natera's construction of
9 this term says, The terms are all part of the
10 high-throughput sequencing to obtain sequence reads step,
11 that doesn't add any limitation to what the claim
12 otherwise requires; is that right?

13 A I don't understand what you mean adds any other
14 limitation.

15 Q Sure.

16 So when the claim requires that -- strike that.

17 Natera's construction says that the term
18 performing high-throughput sequencing through detected
19 from the sequence reads is all part of the same step, does
20 that requirement add anything of substance to the claim?

21 MS. SRINIVASAN: Objection; vague.

22 THE WITNESS: Well, I think as I'm reading it on
23 page 3, Number 1, little I, the terms are -- the terms are
24 all part of the performing high-throughput sequencing. So
25 it's the terms of this whole performing step.

1 BY MS. DURIE:

2 Q Right. And what I'm asking is, does that piece
3 of the construction add anything to what the claim
4 elsewhere requires?

5 MS. SRINIVASAN: Objection; vague.

6 BY MS. DURIE:

7 Q In other words, does the fact that this is all
8 part -- must all be part of the same step add anything
9 substantive to the claim, or is that something that's just
10 always inherently going to be true?

11 MS. SRINIVASAN: Same objection.

12 THE WITNESS: So I don't understand what you mean by
13 inherently always be true. I think the way the claim is
14 drafted in this particular subset, sub step of 1C of the
15 '596 patent is all being performed as a step.

16 BY MS. DURIE:

17 Q But I think what you said is that anytime that
18 you have already determined the locus of the SNV mutation
19 and you're performing targeted amplification, you will
20 detect the SNV when you see the color coming off of the
21 sequencer, right?

22 MS. SRINIVASAN: Objection; misstates testimony.

23 THE WITNESS: Well, it's when the detector detects the
24 fluorescent signal that's coming off --

25

1 BY MS. DURIE:

2 Q Fine.

3 A And I said generally the way I will explain it to
4 a graduate student is based on color.

5 Q Sure.

6 A But the detector -- excuse me -- is a scientific
7 piece of equipment. It's measuring -- taking measurements
8 directly from the sequencer -- I mean from the -- sorry,
9 from the flow cell that has the fluorescent signal.

10 Q Right. So can you think of a way that one could
11 perform all the other steps of the claim but not have the
12 detection of the SNV occur as part of the sequencing step?

13 A So if I can just -- so you're asking me how can I
14 perform Step 1A without performing Step 1C where the --
15 detecting the SNV mutation is not part of the sequencing?

16 Q Right. Could you perform all the other steps of
17 the claim but not have the detection occur as part of the
18 sequencing step?

19 A Not the way I understand the claim as drafted.

20 Q Okay. And so when Natera says the terms are all
21 part of the high-throughput sequencing to obtain sequence
22 reads step, that's not an additional requirement that
23 narrows the scope of the claim in some way. That's
24 something that is inherent in practicing the other steps
25 of the claim. Right?

1 MS. SRINIVASAN: Objection; vague.

2 THE WITNESS: Well, I think the step of performing
3 high-throughput sequencing is described sufficiently, that
4 it's part of the overall claimed method. And so I don't
5 know -- I don't know how to answer your question more than
6 that.

7 BY MS. DURIE:

8 Q If you deleted from the construction the
9 requirement that the terms are all part of the performing
10 high-throughput sequencing to obtain sequence reads step,
11 would that in your view have any impact on the scope of
12 the claim?

13 A I don't think I've offered that opinion, and I'm
14 not prepared today to just think on the fly of how I could
15 change the wording of the claims to see if there's a
16 different scope or not.

17 Q Okay. And I'm not asking about changing the
18 wording of the claims. I'm saying -- assume the wording
19 of the claims is exactly the same, but that we removed
20 that requirement from the construction. So the
21 construction did not require that the detection occur as
22 part of the sequencing step. Would that, in your view,
23 have any impact on the scope of the claim?

24 MS. SRINIVASAN: Objection; incomplete hypothetical.

25 THE WITNESS: Again, I haven't thought about -- again,

1 adding a requirement or removing a requirement, and,
2 again, it sounds like how that would impact the scope of
3 the claim, I haven't formed an opinion on that.

4 BY MS. DURIE:

5 Q Okay. Now, I think you referred a little while
6 ago to grammar or something about the way the claim is set
7 up. So let me ask you this: If we take a look at the
8 claim, we see that there are various, I'll call them,
9 indented paragraphs; is that fair?

10 A Yes. And I do talk about that in my report.

11 Q Right. And one of those indented paragraphs
12 pertains to the sequencing step, right?

13 A Yes, it does.

14 Q And a requirement, the -- what we're calling the
15 wherein clause appears as part of that indented paragraph,
16 right?

17 A Well, the wherein clause appears in the paragraph
18 of performing high-throughput sequencing.

19 Q Right. Does the fact that the wherein clause
20 appears in that indented paragraph matter to your opinion?

21 A Yes.

22 Q Why?

23 A Well, it's the way that the claim has been
24 structured. So -- and if I can go to the -- my report --

25 Q Sure.

1 A -- and look at where I write about that -- oh, I
2 don't know if I have a completed table of contents or not.

3 Q I think you do. I -- at least my copy of your
4 report, the table of contents is one page.

5 A Oh, it is?

6 Q Yeah.

7 A Okay. I know it goes -- if I go to page 60, but
8 it looks like page 53 is the last.

9 Q If you look at the bottom, you'll see there's
10 page 1 of 60, page 2 of 60, page 3 of 60, as it was filed.
11 So you can confirm that you've got the whole thing if you
12 look at the bottom right-hand corner.

13 A Yes, I can confirm that. And it just looks like
14 it's truncated.

15 MS. SRINIVASAN: May I help him?

16 MS. DURIE: Sure. I mean, if there's -- I don't -- I
17 actually don't know what he's looking for, but...

18 THE WITNESS: I have a section that I actually talk
19 about the structure from a grammar standpoint.

20 MS. SRINIVASAN: I would look at page 31.

21 THE WITNESS: Okay. I'm sorry. Could you repeat your
22 question?

23 BY MS. DURIE:

24 Q Sure.

25 So my question is, how does the fact that the

1 wherein clause appear as part of that indented paragraph
2 affect your opinion?

3 A Well, so, first, just from a grammatical
4 standpoint, and this is on page 32 at the bottom of
5 paragraph 55, it's proceeded by a common -- a comma and
6 not introduced by separators used earlier in the claim.
7 And my understanding is, reading the claim, that the
8 wherein clause informs how the sequencing process is
9 performed.

10 Q Well, let me ask you this: If before the
11 wherein, there was a hard return so that it was also set
12 off as part of its own paragraph, would that make any
13 difference to your opinion?

14 A I haven't considered that, but it's very possible
15 based on the way I've described how other paragraphs are
16 set off and are separated by semicolons, for example.
17 But, again, I haven't really considered that in forming an
18 opinion.

19 Q Well, you said that, in your view, an SNV locus
20 is detected from -- you said from the color or from the
21 signal, right?

22 MS. SRINIVASAN: Objection; misstates testimony.

23 THE WITNESS: It's known because it's targeted --

24 BY MS. DURIE:

25 Q Yeah.

1 A -- multiplex PCR. I know the start and stop
2 sites of the amplicons. I know the position of the SNV
3 mutation I'm looking for. And based on which cycle I am
4 in, in the SBS method, the detection of the fluorescent
5 signal will provide a base call of whether it is a normal
6 base or an SNV mutated base.

7 Q Right. Now, all of that would be true even if
8 the wherein clause were in its own paragraph, right?

9 A Again, I haven't considered rewriting the claim
10 to have a different structure, and what the -- how, if
11 any, of the scope of the claim would be changed.

12 Q Well, you said it was significant to your opinion
13 that this wherein clause was part of the paragraph about
14 performing high-throughput sequencing. And I want to
15 understand why you think that is significant to your
16 opinion.

17 So do you have an opinion about whether the claim
18 scope would be different if that wherein clause was in its
19 own paragraph?

20 MS. SRINIVASAN: Objection; misstates testimony.

21 THE WITNESS: Again, I haven't formed an opinion on
22 that, but just sitting here right now, it could very well.
23 But I have no idea of the extent of the way the scope of
24 the claim would change or not. I haven't really thought
25 about that.

1 BY MS. DURIE:

2 Q Okay. So you haven't thought about the
3 significance with respect to claim scope of whether the
4 wherein clause appears in the same paragraph as performing
5 high-throughput sequencing or in a different paragraph?

6 A Well, I've considered the claim scope as the
7 claim as written, and I've tried to interpret the way a
8 person of ordinary skill in the art would understand the
9 claim scope based on the way within -- with wherein is
10 used in Claim 1 of the '596. I haven't thought changing
11 the structure of the claim and what impact that could
12 potentially have on the scope of the claim.

13 Q Okay. So if we were to put a hard return in
14 front of wherein and have that be in its own paragraph, as
15 you sit here today, you don't have an opinion as to
16 whether that would change the claim scope?

17 MS. SRINIVASAN: Objection; outside the scope.

18 THE WITNESS: My opinion is I haven't formed an
19 opinion. I haven't thought about that. But it's quite
20 possible it might change the scope. I just have no idea
21 to tell you to what extent that scope could be changed or
22 not.

23 BY MS. DURIE:

24 Q Okay. Same question about the comma that appears
25 immediately before wherein. I take it you don't have an

1 opinion as to whether the claim scope would change in any
2 way if you replaced that comma with a semicolon?

3 MS. SRINIVASAN: Same objection.

4 THE WITNESS: That's correct.

5 BY MS. DURIE:

6 Q Now, your opinion that an SNV locus is detected
7 from the fluorescent signal depends on knowing in advance
8 the location of the base in question, right?

9 A That's one consideration that is required and is
10 part of the claim scope.

11 Q And that is part of the claim scope in the
12 portion of the claim that is above the performing
13 high-throughput sequencing requirement, right?

14 A Well, I think that comes into play in performing
15 Step 1A where --

16 Q Perfect.

17 A -- we're doing sequencing, Step 1B where we're
18 evaluating the results that then allow Step 1C to actually
19 take place.

20 Q Right. So as a function of performing Steps 1A
21 and Step 1B, you know where the target loci is, right?

22 A Yes, that's my understanding.

23 Q And that means as a function of performing
24 Steps 1A and 1B, you know where the SNV mutation is if it
25 is present, right?

1 A For a given loci, that is correct.

2 Q Okay. And the claim requires in Step 1C, in the
3 first part of Step 1C, that you perform targeted PCR
4 amplification, right?

5 A Well, it requires performing targeted multiplex
6 PCR amplification.

7 Q Right. Right. But for these purposes, the thing
8 that you think is salient is that the PCR amplification is
9 targeted, right?

10 A Well, that's what the claim requires in Step 1C.

11 Q Right. And so as a function of Steps 1A, B, and
12 the first part of Step 1C, we know the location of an SNV
13 mutation if it is present, we know what that SNV mutation
14 is if it is present, and we are performing targeted PCR
15 amplification.

16 In that circumstance, in your opinion, it will
17 always be the case that detecting the color or the
18 fluorescence will detect the SNV, right?

19 MS. SRINIVASAN: Objection; incomplete hypothetical.

20 THE WITNESS: So it's based on a given loci, those
21 have been identified in Step 1A and 1B where the SNV
22 mutation actually occurs. And then based on the targeted
23 multiplex PCR that defines the start and stop boundaries
24 of the amplicon, and knowing the exact position of the SNV
25 that's been identified previously, in the sequencing

1 process, for that template for that particular loci at --
2 for example, you're -- you gave me an example of Cycle 4.
3 Based on the fluorescence, which is because the polymerase
4 is incorporating nucleotides based on the complementary of
5 the template, the fluorescent signal, i.e., the color,
6 will determine the base call. And that will determine
7 whether there's a wild-type base or a normal base or an
8 SNV mutated base.

9 BY MS. DURIE:

10 Q So I think that was a yes, but let me ask the
11 question again just to confirm that.

12 As a function of Steps 1A, 1B, and the first part
13 of Step 1C, we know the location of an SNV mutation if
14 it's present, we know that the SNV mutation -- we know
15 what the SNV mutation is if it's present, and we're
16 performing targeted PCR amplification. In that
17 circumstance given those predicate requirements, is it the
18 case that the fluorescent signal will necessarily
19 determine the base call, and thereby determine the
20 presence of an SNV mutation?

21 MS. SRINIVASAN: Objection; incomplete hypothetical.

22 THE WITNESS: The reason why I gave a much longer
23 answer is because I felt like there were details missing.
24 You know, I was trying to fill in some of the details of
25 how you can -- how the sequencer can detect an SNV

1 mutation based on some other parameters that I did not
2 hear in your question.

3 BY MS. DURIE:

4 Q And so the other parameters that you referenced,
5 you said based on the targeted multiplex PCR that defines
6 the start and stop boundaries of the amplicon, those are
7 just features of having it be targeted multiplex PCR,
8 right?

9 A That's correct.

10 Q Okay. And then you say that you've previously
11 identified in the sequencing process the template for that
12 particular loci. You're saying that is inherent in
13 practicing Steps 1A and 1B, right?

14 MS. SRINIVASAN: Objection; misstates testimony.

15 THE WITNESS: I don't understand that question.

16 BY MS. DURIE:

17 Q Well, you're saying practicing Steps 1A and 1B of
18 the claim is what results in what you called identifying
19 the template for that particular loci?

20 A So Step 1B is evaluating results of the
21 sequence -- of the sequencing on the tumor biopsy sample
22 to identify target loci --

23 Q Right.

24 A -- that will have an SNV mutation.

25 Q Right.

1 A Step 1C, which is performing targeted multiplex
2 PCR, involves designing around that SNV mutation such that
3 the primers define the start and stop side of the
4 amplicon. And that's not really performed in Step 1B, I
5 think it's performed in Step 1C.

6 Q Fine.

7 In substance, though, it is your opinion that
8 once you have performed Step 1A and Step 1B and the first
9 part of Step 1C and then you sequence, you will
10 necessarily have identified the SNV if it exists?

11 MS. SRINIVASAN: Same objection.

12 THE WITNESS: Yes, it will.

13 BY MS. DURIE:

14 Q Okay. Let's go back to your report at page 3.

15 So at the top of page 3, a little two, you say,
16 The wherein clause -- Number 2 is, The wherein clause
17 informs the mechanics of how the high-throughput
18 sequencing is performed.

19 How does the wherein clause inform the mechanics
20 of how the high-throughput sequencing is performed?

21 A So it's just stated in the claim wherein an SNV
22 mutation that is present in less than -- and we haven't
23 talked about the percentages yet, but less than or equal
24 to 0.015 percent of the cell-free DNA having the SNV locus
25 is detected from the sequence reads. So this is happening

1 as the sequencing process is occurring, as the way we've
2 just been explaining it.

3 Q So you -- but you say it informs the mechanics of
4 how the sequencing is performed. When you're talking
5 about mechanics, what do you mean there?

6 A I'm talking about the step-by-step process in the
7 SBS method where one nucleotide is added, the fluorescence
8 is detected, a base call is given, and then the cycle
9 repeats. And knowing the position of where the SNV
10 mutation is then allows for the detection of that SNV
11 mutation if it exists in the sample.

12 Q So when you say the wherein clause informs the
13 mechanics of how the high-throughput sequencing is
14 performed, you mean that it is requiring sort of a next
15 gen sequencing approach that is base by base?

16 MS. SRINIVASAN: Objection; vague.

17 THE WITNESS: That's a good question. I would say --
18 I'm trying to think of all the next gen sequencing methods
19 out there, and I think most of them do a base-by-base
20 method. So I would say yes.

21 BY MS. DURIE:

22 Q Right. Okay.

23 And when you say the wherein clause informs the
24 mechanics of how the sequencing is performed, are you
25 referring to anything other than the fact that the

1 sequencing needs to be base by base, in your view?

2 A Any -- can you repeat that question, please?

3 Q Sure.

4 When you say that the wherein clause informs the
5 mechanics of how the high throughput sequencing is
6 performed, what you mean by that is that the sequencing
7 needs to be base by base; is that right?

8 MS. SRINIVASAN: Objection; misstates testimony.

9 THE WITNESS: I don't think it needs to be. I think
10 I've used examples such as Illumina, which is an SBS
11 base-by-base method, and just sitting here thinking about
12 other platforms, most of them perform sequencing on a
13 base-by-base method.

14 BY MS. DURIE:

15 Q Fair enough. But I'm not asking you about the
16 platforms that exist in the world. I'm asking you about
17 what that claim requires.

18 And so when you say the wherein clause informs
19 the mechanics, I want to understand what the mechanics are
20 that you think are informed by that wherein clause.

21 A Well, I can only think of practical examples that
22 I have in front of me and that I've considered, and the
23 most dominant sequencing platform out there is the
24 Illumina system, and I've used that as an example of
25 explaining how the mechanics are performed based on the

1 wherein clause.

2 Q Well, does the claim require the use of the
3 Illumina platform?

4 A It does not.

5 Q Does the claim require the use of sequencing by
6 synthesis chemistry?

7 A I would say no as well.

8 Q Okay. Does the claim require the use of a
9 base-by-base sequencing protocol?

10 A It does not.

11 Q Okay. So what, if any, are the mechanics of the
12 claim that are required as a function of the wherein
13 clause?

14 A Well, the mechanics are performing some kind of
15 sequencing process where base calls are being made, and in
16 that process, given amplicons that have the fine start and
17 stop sites, which have known -- known SNV mutated
18 positions within those amplicons, performing the
19 sequencing process where at that particular position,
20 whether it's a cycle or there's some other hypothetical
21 sequencing platform out there, the mechanics are going
22 through that process of being able to identify the base at
23 that location, and the ability to either determine or to
24 detect the presence or the absence of the SNV mutation.

25 Q Okay. So the first part of what I'll call

1 Step 1-C2 in your lexicography is performing
2 high-throughput sequencing of the amplified DNA to obtain
3 sequence reads.

4 What you just described is performing that
5 high-throughput sequencing, right?

6 A I'm sorry. What part did I describe?

7 Q So when you talked about having identified a
8 particular target loci, then in the sequencing process
9 having a template, having cycles, and having fluorescence,
10 that's all performing high-throughput sequencing, right?

11 A That is part of that, yes.

12 Q Okay. So I want to understand what the wherein
13 clause adds with respect to how the sequencing is
14 performed, the mechanics of the sequencing that is not
15 already inherent in performing high-throughput sequencing
16 to obtain sequence reads.

17 A Well, the wherein clause is where the sequencing
18 process as it's building the sequence read is also
19 detecting whether the SNV mutation is present or absent.

20 Q But isn't that always going to happen from
21 obtaining the sequence reads if you have followed through
22 Steps 1A, B, and the first part of Step C of the claim?

23 A I don't understand that question.

24 Q Well, so let me try to back up.

25 When you talk about informs the mechanics, just

1 specifically what are the mechanics that are informed by
2 that wherein clause?

3 A I'm trying to explain, and it's the actual
4 sequencing process of obtaining a sequence read of --
5 because a DNA sequence is in order of nucleotides, you go
6 through that order of nucleotides determining what each
7 base is, and that's why I think it's easiest to describe
8 it as a base-by-base method.

9 Q Yeah.

10 A And by design what was -- I previously
11 identified, knowing the position of the SNV mutation, the
12 base calls, based on the fluorescence because I'm using
13 Illumina as an example, results in detecting the presence
14 or absence of that SNV mutation at that particular
15 position.

16 Q So I want you to take the claim and imagine --
17 put a period after sequence reads. Okay? So
18 performing -- you have all the same predicate
19 requirements, and then it says performing high-throughput
20 sequencing of the amplified DNA comprising the plurality
21 of target loci to obtain sequence reads. Period.

22 Wouldn't everything you just said still be true
23 as to what was required by the claim?

24 MS. SRINIVASAN: Objection; outside the scope.

25 THE WITNESS: So, again, I haven't thought about how I

1 can change the claim language and how it affects the
2 scope, but I just want to understand your question.

3 So after obtain sequence reads, I put a period --

4 BY MS. DURIE:

5 Q A period.

6 A -- and then I don't do anything else?

7 Q Right. Exactly.

8 A I don't do the wherein --

9 Q Right. Delete the wherein clause from the claim.

10 You said the wherein clause informs the mechanics of how
11 the sequencing is performed. So delete the wherein
12 clause.

13 How does that change the mechanics of how
14 sequencing is performed in the claim?

15 MS. SRINIVASAN: Same objection; outside the scope.

16 THE WITNESS: Well, you know, I haven't considered how
17 changing the claim language would affect the scope, but if
18 I don't have a requirement of an SNV mutation that is
19 present in less than or equal to 0.015 percent of the
20 cell-free DNA, clearly, I can just imagine that's going to
21 change things. And I think --

22 BY MS. DURIE:

23 Q How would it change things?

24 A And I think that the wherein clause informs the
25 sequencing mechanics because, for example, to get to a

1 0.015 percent, I have to -- and I talk about this in my
2 report -- the math ends up being 1 in 7,000 sequence
3 reads, for example.

4 So that informs, for example, that I have to
5 produce some number of sequence reads that I can actually
6 obtain something less than or equal to 0.015 percent.

7 Q Okay. So that wherein clause is requiring that
8 you obtain some threshold number of sequence reads; is
9 that right?

10 A I think that's correct. I mean, there is a
11 percentage there in doing math, just detecting one SNV
12 mutation, I would have to also -- I would also have to
13 generate at least 7,000 sequence reads that were normal
14 such that I could get a percentage of 0.015 percent or
15 less.

16 Q Okay. Now, I want to imagine that we are
17 performing the claim and we have a sample, and we are
18 starting the sequencing operation. And we do our very
19 first sequencing run, and we see coming off of the
20 sequencer a signal that corresponds to the position at
21 which an SNV mutation is expected and the base that we
22 have determined constitutes that SNV mutation, and assume
23 that this is the first sequencing round.

24 Have we detected an SNV mutation?

25 A If we perform all the steps in the claim and we

1 do it in the way that I've described it of knowing the
2 start, the stop position of the amplicon, knowing the SNV
3 mutation, performing cycles, and at the cycle or the
4 position is for the SNV mutation detecting that
5 fluorescent signal, it would detect the presence or
6 absence of that SNV mutation.

7 Q Okay. And that is true even if it is -- if there
8 is only one sequencing operation that has been performed
9 and one base that has been detected in that location,
10 right?

11 A Okay. So I think I now understand your question.
12 Because in the next generation sequencing world, one
13 sequencing operation will sequence billions of reads, am I
14 to assume I'm only sequencing one template?

15 Q Right.

16 A I think if you have one template and it has all
17 the definitions that I've gone through of the amplicon and
18 knowing the SNV mutation, you may be able to detect the
19 presence or the absence of that mutation at that position.

20 Q Okay. Now, the claim language talks about --
21 talks about detecting that SNV mutation from the sequence
22 read. I take it -- well, strike that.

23 What do you understand the word from to mean in
24 the context of the claim?

25 A Well, I think the way I've described it as the

1 mechanics of the sequencing where you're performing base
2 by base, and that will start building the sequence read,
3 that as that sequence read is being built at that
4 position, if you know the SNV mutation exists based on the
5 fluorescent signal, determining or detecting whether the
6 SNV mutation is present or not. And that would be from
7 the sequence read.

8 Q Now, Dr. Lennon at NeoGenomics proposed a
9 construction that the phrase means wherein an SNV mutation
10 is determined to be present from the sequence reads,
11 right?

12 A That generally sounds true, but I don't know if
13 word for word that's true or not.

14 Q Sure. Turn to page 30 of your report --

15 A Thank you.

16 Q -- just to make sure we're on the same page about
17 the precise language. And if you see in paragraph 51, you
18 refer to NeoGenomics' construction.

19 A Yes.

20 Q And you see it as wherein an SNV mutation is
21 determined to be present from the sequence reads.

22 Now, what do you understand to be the difference
23 between detected and determined to be present?

24 A The way I understand the mechanics of the
25 sequencing process is the detection is the detection of

1 the fluorescent signal at a given cycle in the SBS method,
2 and I don't think the claim -- I don't think detect and
3 determine are equivalent terms in this context.

4 Q And why not? What is it about determined to be
5 present that you think is wrong?

6 A Well, for one -- and I say this in my report, but
7 there's really no support in the specification to support
8 that determine is the same as detect.

9 Q I'm just trying to understand just as a matter of
10 English what you understand the difference between
11 detecting and determine to be present to be?

12 A I'm sorry. In just a general --

13 Q In the context of these definitions, your
14 construction --

15 A Right.

16 Q -- is detected. Dr. Lennon's construction is
17 determined to be present. What's the difference?

18 A Well, I think Dr. Lennon's construction really is
19 when the sequence read is completed, and something else
20 happens, and you're now determining based on some analysis
21 or something other than what's happening in the sequencing
22 process. And so I think that's not the right
23 construction.

24 Q So when you say detected, I take it, you mean
25 something short of determining whether the SNV is present?

1 MS. SRINIVASAN: Objection; vague.

2 THE WITNESS: No. I mean when detected, it's detected
3 during the sequencing process, as I've explained.

4 BY MS. DURIE:

5 Q And then you think at some later point in time,
6 that SNV mutation is determined to be present?

7 A Well, I haven't offered that opinion whether it's
8 present -- determined to be present or not.

9 Q Well, I'm just trying to understand why you think
10 Dr. Lennon's construction is wrong, and why you think
11 detected and determined to be present mean different
12 things. So you said you understand that the SNV mutation
13 is detected at the point that there is a detection of the
14 fluorescent signal, right?

15 A Yes.

16 Q Okay.

17 A That is correct.

18 Q And I take it you also think that the SNV
19 mutation is not determined to be present at that point,
20 right?

21 A That's correct. And that's based on the claim
22 itself and the support in the specification.

23 Q Okay. So what else has to happen in order for
24 the SNV mutation to be determined to be present?

25 MS. SRINIVASAN: Objection; outside the scope.

1 THE WITNESS: I'm not sure because I haven't -- those
2 aren't my words, and that's not the way I would have
3 characterized it.

4 BY MS. DURIE:

5 Q Yeah, but you think he's wrong. And I want to
6 understand why you think he's wrong. So what is it that
7 you think has to happen in order for the SNV mutation to
8 be determined to be present over and above seeing the
9 fluorescent signal?

10 MS. SRINIVASAN: Objection; incomplete hypothetical.

11 THE WITNESS: Well, I -- I think he's wrong because,
12 first, I don't think you can substitute determine for
13 detected based on the claim, which is detected. It
14 doesn't say determined. And the support that he's looked
15 at in the patent itself doesn't support that determine is
16 the equivalent of detected. So I just think all of that
17 is wrong.

18 BY MS. DURIE:

19 Q But I'm trying to understand why. I mean,
20 sometimes words are synonyms and sometimes they're not,
21 right?

22 A Outside the claim --

23 Q Just in general --

24 A -- yeah, I can agree with that generally, yes.

25 Q Right. And so in this case, you think that

1 detected and determined to be present are not synonyms,
2 right? You think they mean different things?

3 A Well, I -- I'm looking at the claim language, the
4 way the claim language is written, and then the best guide
5 to understand what's in the claim is the specification.
6 And so I've looked in the specification. I've looked
7 where Dr. Lennon has pointed in saying that these words
8 are equivalent, and I don't find the support for that at
9 all.

10 Q And we'll get to -- we may get to the spec
11 depending on time, but I'm not there yet. I just want to
12 understand as a matter of English what you understand the
13 disagreement between yourself and Dr. Lennon to be in
14 substance.

15 So you say that the SNV is detected when you see
16 the -- or when the machine, I guess, sees the fluorescent
17 signal, right?

18 A That's correct.

19 Q Okay. You're saying Dr. Lennon is wrong because
20 he's adding some additional requirement, right?

21 MS. SRINIVASAN: Objection; misstates testimony.

22 THE WITNESS: I would give you the answer I've given
23 before, but in addition to that, I think examples that
24 Dr. Lennon has provided are when you're trying to find
25 mutations versus when you know something is present. And

1 I think the determined is when you're looking for new
2 mutations. We call those de novo. When your map reads to
3 a genome, for example I think you then can determine the
4 presence of an SNV or not.

5 BY MS. DURIE:

6 Q Okay. But even in the context of an assay where
7 you already know the SNV that you're looking for, you
8 would agree that you can determine whether that SNV is
9 present or not, right, in the particular sample?

10 A So after I've detected the SNV, then some other
11 analysis downstream I can then determine the presence of
12 the SNV?

13 Q No. I'm asking sort of a more straightforward
14 question. We know the SNV we're looking for. We run a
15 sequencing operation. We're looking for it. You would
16 agree that we can determine whether that SNV is or isn't
17 present, right, just in general?

18 A Again, I think the details actually matter here.
19 In the context of the claim that we've been discussing,
20 we've already detected the SNV. We may -- we may do some
21 downstream analysis to get more information, but I think
22 it's already been detected.

23 Q Okay. But, again, that's -- I'm trying to
24 understand the difference between detecting the SNV, your
25 construction, and Dr. Lennon's construction determining

1 whether it's present. You think you're right. You think
2 he's wrong. I want to understand what the space between
3 the two of you is. Okay?

4 A Yes.

5 Q So you go through the claim steps, you detect the
6 fluorescence, you make the base call, you have in your
7 view detected the SNV, right?

8 A Correct.

9 Q Have you also in your view determined the SNV to
10 be present?

11 A Well, I've detected it. I think that's the right
12 term to use. That's the claim term. It's been detected.

13 Q Okay.

14 A It's been detected because the fluorescence is
15 a -- I mean, the sequencer is a detector. It is detecting
16 signals corresponding to which nucleotide is added at that
17 position.

18 Q Right. But I want -- the reason I'm asking you
19 about Dr. Lennon's terminology is that you've said it's
20 wrong. Okay? And you've said it's wrong in substance.
21 So I want to understand what you think the substance is.

22 So if I see the fluorescent signal, the machine
23 sees the fluorescent signal and it makes the base call,
24 has it determined whether an SNV is present?

25 A No, I don't think it has.

1 Q Okay.

2 A And I think Dr. Lennon describes it in a very
3 different application of what determine means. But I
4 don't think in the SBS method it's been determined. It's
5 been detected.

6 Q Okay. So what needs to happen in your view to go
7 from detecting the SNV to determining the SNV is present?

8 MS. SRINIVASAN: Objection; incomplete hypothetical.

9 THE WITNESS: I have no idea. I haven't considered
10 what needs to be done to go from one term to another. I
11 just think the construction is wrong.

12 MS. DURIE: Okay. Great.

13 We've been going about an hour. Why don't we
14 take a break?

15 MS. SRINIVASAN: Great.

16 THE WITNESS: Great.

17 THE VIDEOGRAPHER: We are going off the record. The
18 time is 9:58 a.m.

19 (Recess taken.)

20 THE VIDEOGRAPHER: We are back on the record. The
21 time is 10:06 a.m.

22 BY MS. DURIE:

23 Q Now, we've discussed the fact that the claim in
24 this instance requires multiplex PCR, right?

25 A That is one requirement, yes.

1 Q And that means that the system is reading
2 multiple different amplicons at the same time, right?

3 A The sequencer is reading multiple amplicons at
4 the same time.

5 Q Right.

6 And as you note in your report, you can use bar
7 codes and unique index tags during library preparation to
8 help distinguish the unique SNV loci target sequences,
9 right?

10 A That's correct.

11 Q And that allows you to go back after you get the
12 sequencing readout and figure out which sequence
13 corresponds to which target loci, right?

14 A That's one way to do it, yes.

15 Q Okay. Now, in this method, not all SNVs are
16 going to be at the same position in the amplicon, right?

17 A For different loci, it would be expected they
18 could be at very different locations.

19 Q Right. So it might have one sequence where the
20 SNV mutation, if it's present, is going to be at
21 Position 4, for example, and a different sequence where
22 the SNV mutation, if it's present, is going to be at
23 Location 10, right?

24 A For those two loci, they can be at Location 4 and
25 Location 10.

1 Q Okay. And I am running those two sequences
2 through the sequencer at the same time, right?

3 A Yes, you are.

4 Q Okay. Now, when I get a fluorescent signal at
5 Position 4, I don't know which amplicon, which sequence,
6 that position corresponds to until I look at the barcodes
7 and index tags that we were talking about, right?

8 A Well, it depends on the order that you do your
9 sequencing of your index. You could sequence your index
10 first and know the location of every template in the
11 sequencer.

12 Q Okay. Or I could sequence my index at the end,
13 right?

14 A Again, using an index is just one way. You could
15 have a lookup table because the amplicons are defined.
16 Just knowing the order of the sequence can reveal the
17 location or which amplicon is being sequenced at that
18 position in the sequencer.

19 Q So you said one way you could do it is you could
20 have a lookup table, and what you mean is -- let's say the
21 signal that you get out of the sequencer is ACGTC. Okay?

22 A Sure.

23 Q So -- and let's say that I have one sequence of
24 interest in which the SNV is at Position 2 and is a C.

25 A Okay.

1 Q And I have another sequence of interest in which
2 the SNV is at Position 4, and just to make our lives easy
3 I'll say it's also a C. Okay?

4 A Okay.

5 Q So I get an ACGTC out of the sequencer. You're
6 saying one way I could do this is I could have a lookup
7 table that would allow me to figure out whether that
8 sequence corresponds to the sequence where SNV is at
9 Position 2 or the sequence where the SNV is at Position 4?

10 A Well, it would be based on the sequence of the
11 target loci itself because that's known.

12 Q Right. And so I would have a lookup table that
13 would include the sequences of all of the target loci, and
14 I would compare the sequence that I got out of the
15 sequencer to the sequences of those different target loci
16 that are stored in my lookup table, right?

17 MS. SRINIVASAN: Objection; incomplete hypothetical,
18 vague.

19 THE WITNESS: I mean, you can predetermine where
20 things exist before you even start the process of
21 sequencing an SNV mutation.

22 BY MS. DURIE:

23 Q You could, but the claim doesn't require that,
24 does it?

25 A No, it doesn't.

1 Q Okay. So let's go back to your lookup table
2 example. In your lookup table example, you would get the
3 ACGTC sequence out of the sequencer, and you would then
4 compare that sequence to the sequences for each of the
5 different target loci in your lookup table, right?

6 A So I'm not following your example now.

7 Q Well --

8 A So am I doing SNV mutation detection, or am I
9 trying to figure out what loci is present at a given
10 position in the sequencer?

11 Q So I'm trying to understand your example of a
12 lookup table and how that would work. So out of the
13 sequencer, I have this sequence: ACGTC. Now, let me
14 start actually -- let's just do it like this.

15 MS. DURIE: Can you mark that as Exhibit 3?

16 (Whereupon Deposition Exhibit 3 was
17 marked for identification.)

18 BY MS. DURIE:

19 Q So I've handed you Exhibit 3, and it has a
20 sequence written on it, and that sequence is ACGTC, right?

21 A That's correct.

22 Q Okay. Now, I want you to posit that there are
23 several different target loci that we have sequenced as
24 part of the sequencing operation that resulted in this
25 sequencing output. Are you with me?

1 A Yes.

2 Q Okay. And in one of them, the SNV is located at
3 Position 2, and in another one of them, the SNV is located
4 at Position 4. Are you with me?

5 A Yes.

6 Q Now, you got this output from the sequencer. Can
7 you detect the presence of an SNV?

8 A So in this sequence that you've handed me, if my
9 mutation is at Position 2 and I've detected a C, and that
10 is my SNV mutation, I've detected it.

11 Q Okay. And that's true even if you don't know
12 when you look at that whether that represents the loci
13 where there is a mutation at Position 2 or the loci where
14 there is a mutation at Position 4?

15 MS. SRINIVASAN: Objection; incomplete hypothetical.

16 THE WITNESS: Well, I would know based on everything
17 I've done from Steps 1A, B, and C. I would know I have a
18 certain number of target loci, I would know those
19 sequences. I would know the position of those SNVs, and
20 it's the detector as part of the sequencing process that
21 is detecting the presence or the absence of the SNV
22 mutation at any given template.

23 BY MS. DURIE:

24 Q Right. Right. But we've said in some of the --
25 in some of the sequences, the mutation is at Position 2.

1 In other sequences, the mutation is at Position 4, right?

2 A Yeah, that's our example.

3 Q And looking at this output, you don't know just
4 from looking at this output whether the relevant mutation
5 is at Position 2 or Position 4, right?

6 A Well, again, I'm not the one who's actually
7 determining whether it's present or not. I'm saying that
8 the sequencer during the sequencing process when it's
9 measuring the fluorescence, it will detect the presence or
10 the absence of the SNV mutation.

11 Q Right. And you're saying that's true even if at
12 that stage, a person looking at the output doesn't know
13 whether the expected mutation is at Position 2 or
14 Position 4?

15 A Well, I think in this general scenario, a
16 person's not just looking at the fluorescence. It's the
17 detector that's looking -- it's the detector detecting the
18 fluorescence, and based on that, will determine whether
19 the SNV is present or not. Now, there's other things you
20 can do to then figure out which loci is everywhere else,
21 but the detection has already happened.

22 Q So you're saying -- I understand. You're saying
23 the detection is happening at the level of fluorescence.
24 And so in this example, there is the detection of an A.
25 There is then the detection of a C. And in your view, if,

1 in fact, it turns out that that C is at Position 2, and if
2 it turns out that that sequence has an SNV at Position 2,
3 you have now detected the presence of an SNV; is that
4 right?

5 A No, I'm not saying that at all.

6 I'm saying that you perform the steps of the
7 claim, that the amplicons are then provided onto the
8 sequencer. The sequencer is sequencing millions of
9 templates simultaneously, and it determines which
10 nucleotides are incorporated, and based on the
11 fluorescence, it will detect the presence or the absence
12 of an SNV mutation.

13 That's what I'm saying.

14 Q Okay. But in this example, if I get ACT -- ACGTC
15 out of the sequencer, I need to do more work such as
16 comparing that sequence to a sequence in the lookup table
17 to determine whether an SNV is present, right?

18 A No. I disagree with that.

19 Q Okay. So you referenced earlier having a lookup
20 table. You were talking about having sequences that
21 correspond to the various different loci of interest in a
22 lookup table, right?

23 A Well I think what I was trying to explain is you
24 can use a lookup table to figure out different target loci
25 in the sequencing process. You can do that. But the

1 detector -- the sequencing process is detected -- it's
2 already being present or not being present.

3 Q Okay.

4 A That's already being detected.

5 Q Right. So you're saying no matter what other
6 information you do or don't have at your disposal, as soon
7 as you get that fluorescent signal, you have detected the
8 presence of the SNV evince even if based on the
9 information that you've got, you don't know whether it's
10 actually there or not, right?

11 MS. SRINIVASAN: Objection; misstates testimony.

12 THE WITNESS: Well, again, I think we're confusing
13 things here. So on flow cell, you can go through the
14 exercise of figuring out which loci are in which wells on
15 an Illumina sequencer if you need to.

16 I think the point I'm trying to make is in the
17 sequencing process, because of the design of the multi --
18 targeted multiplex PCR amplicons, you will know where
19 those mutations are. And in a given cycle, it will detect
20 the presence or an absence of the SNV mutation for that
21 given template.

22 BY MS. DURIE:

23 Q Well, you said that -- but for that given
24 template is important, right? You said you know where the
25 mutations are, but you know where the mutations are for

1 many different potential sequences, right?

2 Let me withdraw that and try to ask a better
3 question.

4 A Okay.

5 Q We've already established that in this example
6 that you've got in front of you, the mutation might be at
7 Position 2 or the mutation might be at Position 4, right?

8 A No. I disagree with that. So the way I
9 understood your example is I have two different target
10 loci.

11 Q Okay.

12 A One target loci has a mutation at Position 2 --

13 Q Right.

14 A -- and a different loci that has a mutation at
15 Position 4, but it's not one target loci that has one --

16 Q Correct.

17 A -- maybe a two or maybe has four. You know where
18 the positions are --

19 Q Right.

20 A -- for a given target loci.

21 Q For a given target loci.

22 Now, when you get this output from a sequencer,
23 ACGTC, you don't know which target loci that corresponds
24 to without comparing it to the various target loci that
25 are part of your reaction, right?

1 A So I did say that's one way you can do it. You
2 can -- I've put this in my report. You can use sample and
3 gene type-specific barcodes, and you can read the barcode
4 prior to doing any sequencing of SNV locus and know which
5 loci is present. You can do that too.

6 Q Right. So when you get that sequencing output,
7 you might or might not know whether it corresponds --
8 which -- which target sequence it corresponds to depending
9 on how you have set up your protocol, right?

10 A You can do some downstream analysis to figure out
11 target loci, but the SNVs have already been detected.

12 Q Okay. And so just to be clear, you're saying the
13 SNV is detected at the point in time when you detect the
14 fluorescent signal even if you need to do downstream
15 processing in order to figure out the position of the SNV
16 in that particular target loci?

17 MS. SRINIVASAN: Objection; misstates testimony.

18 THE WITNESS: I disagree with that. I don't need to
19 figure out the position of the SNV mutation. So by
20 design, in the targeted multiplex PCR, I already know
21 where all the mutation positions are. And what I'm
22 describing here and what I've suggested is to identify
23 which target loci we're analyzing. There are different
24 ways you can do that.

25

1 BY MS. DURIE:

2 Q And you don't know which position in the
3 sequencing output that you were looking at corresponds to
4 an SNV until you figure out which target loci you're
5 looking at, right?

6 A The target -- the positions of the SNV mutations
7 are already predetermined. They're already built in to
8 the way the targeted multiplex PCR system has been set up.

9 Q Right. But in this example in front of us, we
10 don't which target loci this corresponds to yet, right?

11 A Well, in your example, because it's one template,
12 I know exactly which one it is.

13 Q No, but we've -- we've said this is targeted
14 multiplex PCR. There's multiple templates.

15 A Yes.

16 Q We got this sequencing output. We don't know
17 which template this corresponds to, right?

18 A Again, we do based on as the sequencing read is
19 being generated, we do -- we will figure out which one it
20 is.

21 Q And is it your position that you will figure that
22 out in realtime as the sequencing output is being
23 generated, or will you figure that out through downstream
24 analysis?

25 A I think there are many ways that that can be

1 figured out, and one way that I've suggested is barcoding.

2 Q Sure.

3 A And you can do that up front without ever looking
4 anything up and knowing the position, or which target loci
5 is in the sequencer.

6 Q Or you can do it after the fact, right?

7 A Figuring out which target loci it is, yes. I
8 would agree you can do that downstream, but the mutation
9 has already been detected.

10 Q Right. And so it's your position that the
11 mutation is detected at the point in time when you get the
12 sequencing output, the fluorescence, even if you still
13 have to do downstream processing in order to figure out
14 which target loci that sequence corresponds to, and
15 therefore where the SNV mutation is in that sequence?

16 MS. SRINIVASAN: Objection; misstates testimony.

17 THE WITNESS: I again disagree with figuring out where
18 the SNV mutation is. It's already built in to the
19 different target amplicons.

20 BY MS. DURIE:

21 Q Right.

22 A And I agree there may be some downstream analysis
23 of figuring out which is target Loci 1, target Loci 2, but
24 by design, the SNV mutations have already been defined,
25 they've been detected, and they are in the read. And they

1 don't change after they've been obtained in the read.

2 Q Okay. We'll come back to that in a sec.

3 But when you say they've already been defined,
4 they have been defined for a given target loci, right?

5 A That's correct.

6 Q So I don't know which of those ACGTCs is an SNV
7 unless I know the target loci to which it corresponds,
8 right?

9 A Well, I do know because I've designed it that
10 way, and the detector is detecting the presence or the
11 absence of the SNV mutation based on the color that it
12 detects in a given cycle.

13 Q Okay. So let me just ask you to look at that
14 sequence, ACGTC. Is there an SNV present?

15 MS. SRINIVASAN: Objection; incomplete hypothetical.

16 THE WITNESS: There's no way I can figure that out
17 because this is not -- this doesn't follow the scope of
18 Claim 1 of the '596 patent.

19 BY MS. DURIE:

20 Q And so in order to know that, wouldn't I need to
21 know the target loci to which that corresponds?

22 A Again, the sequencing process is detecting the
23 presence or the absence of the SNV mutation. It's the
24 incorporation of the base corresponding to the
25 complementary nucleotide base in the amplicon that has

1 been generated by multiplex PCR. That's -- that's all
2 defined upfront.

3 The detector is actually detecting whether it's a
4 C, in our example, or whether it might be an A or a G or a
5 T.

6 Q And in your view, the only thing you need to know
7 in order to know whether -- whether you have detected an
8 SNV is detecting a base?

9 A No, that's not true at all. I have explained
10 based on the way the claim is structured, there is a lot
11 of steps upfront to get to the point where I know the
12 position of an SNV in my amplicon.

13 Q Right. But, again, in -- well, if I get a given
14 sequencing readout, I don't know which amplicon -- I may
15 or may not know which amplicon that sequence corresponds
16 to without doing further downstream processing?

17 A That is a possibility. I'd say that's one
18 possibility. You could figure that out upfront by just
19 barcoding the samples and sequencing the barcodes.

20 Q Right. But in your view, it is not necessary to
21 figure that out upfront in order to have detected the SNV?

22 A I'm sorry. What is not necessary?

23 Q It is not necessary to determine upfront the
24 amplicon to which a given sequence corresponds in order to
25 have detected an SNV?

1 MS. SRINIVASAN: Objection; vague.

2 THE WITNESS: The sequencer is identifying the
3 positions of which bases are being incorporated, figuring
4 out downstream which target loci belong to which
5 patient -- because we pool things together -- which loci
6 they belong to, that can take place. I don't disagree
7 with that.

8 But the detection of the SNV being present or
9 absence is already taking place.

10 BY MS. DURIE:

11 Q Right. And I just want to make clear that your
12 position is the detection of the SNV happens at the point
13 of the output from the sequencer even if you haven't
14 designed your assay with barcodes that will be sequenced
15 in advance, right?

16 A I disagree with that. I've already designed my
17 multiplex -- targeted multiplex PCR. Let's use an
18 example. I have 20 loci, and I have 20 SNVs in known
19 positions in those 20 loci. I can pull them all together,
20 put them on the sequencer. The sequencer is actually
21 reading base by base each position. And by design, for
22 example, target Loci 1 that incorporates a C, which I know
23 it's -- Position 6 is the SNV mutation, the SNV mutation's
24 been detected.

25 Q Okay.

1 A You know, putting it all together doesn't change
2 the fact that the SNV mutations have already been detected
3 in sequencing.

4 Q And that doesn't change if you have to do further
5 processing in order to determine that that particular
6 sequencing output corresponds to the first sequence?

7 MS. SRINIVASAN: Objection; vague.

8 BY MS. DURIE:

9 Q Where the SNV mutation is in Position 6?

10 MS. SRINIVASAN: Same objection.

11 THE WITNESS: Can you repeat that question, please?

12 BY MS. DURIE:

13 Q Sure.

14 Your opinion that the SNV mutation has been
15 detected at the point in time that there is an output from
16 the sequencer doesn't change if you need to do further
17 processing in order to determine that that particular
18 output corresponds with a sequence in which the SNV
19 mutation is present at that position?

20 MS. SRINIVASAN: Objection; misstates testimony.

21 THE WITNESS: I'm not following the question. If you
22 could break it down, maybe into steps, so we could go
23 through that.

24 BY MS. DURIE:

25 Q Well, you said, As an example, I've 20 loci. And

1 you've got 20 SNVs in known positions in those 20 loci,
2 and they may be in different positions, right?

3 A Yes.

4 Q Okay. And so you put them all together -- you
5 pool them all together, you put them on the sequencer, and
6 you get a readout in Position 6 of a C, right?

7 A Yes.

8 Q You know that that is an SNV mutation for one of
9 your 20 target loci, right?

10 A That would be correct.

11 Q Okay. And your position is at that point, you
12 have detected an SNV mutation even if you need to do
13 further processing in order to determine whether that
14 sequencing readout is associated with your first target
15 loci or your sixth target loci?

16 MS. SRINIVASAN: Objection; misstates testimony.

17 THE WITNESS: Well, I mean, again, I think there are
18 different ways of doing some downstream analysis to figure
19 out what is target Loci 1, what is target Loci 2, but the
20 SNV mutations have already been detected.

21 BY MS. DURIE:

22 Q And those further downstream steps are what would
23 allow you to determine whether an SNV is present, right?

24 A No. I disagree with that. It's already there.

25 It's -- the SNV mutation is already in the sequencing data

1 by design.

2 Q And so it's -- so is it then your position that
3 the sequencing data in its raw form is sufficient always
4 to determine whether an SNV is present?

5 MS. SRINIVASAN: Objection; vague.

6 THE WITNESS: What do you mean by raw form?

7 BY MS. DURIE:

8 Q The output of the sequencer. The fluorescent
9 signal.

10 A So there's a fluorescent signal, there's a base
11 call, and then there's a quality score. That base call is
12 associated with detecting the presence or the absence of
13 the SNV mutation.

14 Q Fine. And so is it your position that that base
15 call then is sufficient to determine whether an SNV
16 mutation is present?

17 A It is, based on the way the claim is constructed,
18 yes.

19 Q Okay. Now, sometimes, that base call will be
20 wrong, right?

21 A It's possible.

22 Q Okay. And one way that base call could be wrong
23 is that it could simply be incorrect in its assessment of
24 the base that is present at that position in a strand of
25 DNA that is being analyzed, right?

1 A I'm sorry. I don't understand what you're
2 describing.

3 Q Well, the way that a -- explain a Q score. A Q
4 score is a quality score, right?

5 A That's correct.

6 Q And it is an assessment of the likelihood that
7 the base call is correct relative to the base that is
8 actually present in the sample being analyzed, right?

9 A It is -- it is a probability of the base being
10 incorrectly called. So it's usually an error probability,
11 but we turn that around to mean how accurate the base call
12 is.

13 Q Right. And so a Q score of 30 means, in
14 substance, that there is a roughly one in a thousand
15 chance that the base call is incorrect --

16 A That's correct.

17 Q -- is that right?

18 A That's correct.

19 Q And when we say the base call is incorrect in the
20 context of a Q score, what we mean is that the base that
21 is present, actually present in the sample, has been
22 called incorrectly, right?

23 A Wait. I'm sorry. Repeat that question?

24 Q What we mean when we're saying the base call is
25 incorrect in the context of a Q score is that it's -- the

1 output is telling you that it's a C, but it's really a G
2 in the sample itself, right?

3 MS. SRINIVASAN: Objection; vague.

4 THE WITNESS: Usually, it's because the sequencer
5 cannot identify a clear fluorescent signal. Usually,
6 there are multiple signals that are being detected
7 simultaneously, and that will lower the Q score.

8 BY MS. DURIE:

9 Q Right. So -- but it is an error that is
10 happening in the detection of the base that is present,
11 right?

12 A Well, it is detection of multiple fluorescent
13 signals, and that results in possibly a base call being
14 incorrect and -- but then you would see the associated Q
15 score, and you would say that --

16 Q Right.

17 A -- is probably a low quality base.

18 Q But there are other kinds of errors that can
19 happen in the sequencing process, right?

20 A Yes.

21 Q Okay. Errors can come in through the process of
22 library prep, right?

23 A Yes.

24 Q PCR can itself introduce errors, right?

25 A Yes.

1 Q Okay. Now, let us posit a situation in which you
2 know that there is an SNV mutation that may be present in
3 Position 2, and it is a C. Okay?

4 A Okay.

5 Q And let's say that the readout of the sequencer
6 is a C. It is your opinion that you have detected an SNV,
7 right?

8 MS. SRINIVASAN: Objection; incomplete hypothetical.

9 THE WITNESS: So, again, following the claim language,
10 I have an amplicon in that Position 2, my SNV I know is a
11 C, and I've gone to Cycle 2, and I've detected the
12 fluorescent signal associated with the C.

13 BY MS. DURIE:

14 Q Right.

15 A I would say that would have been a detection of
16 the SNV mutation.

17 Q Right. Now, some percentage of the time, no SNV
18 is going to be present, right?

19 A I hope so. For the patient, I hope that's true.

20 Q Some percentage of the time that readout of a C
21 may be a function of an error that was introduced during
22 library prep, right?

23 A There's always a possibility of an error taking
24 place in the sequencing process.

25 Q Right. And some percentage of the time, that C,

1 the readout of the C, will be a function of an error that
2 was introduced during PCR, right?

3 A It's possible.

4 Q Okay. So some percentage of the time, there will
5 not be any SNV present in the patient sample, but in your
6 view, you nevertheless will have detected an SNV if you
7 have seen that C being read out in Position 2 from the
8 sequencer?

9 A Again, it's very, very possible. Errors are
10 typically stochastic, and they happen across the entire
11 amplicon. The chance of it hitting the actual position
12 are much less than the overall error rate of the
13 sequencing process.

14 Q Okay. But nevertheless, I just want to be clear,
15 it is your testimony that even if there is no SNV present
16 in the patient sample, if you get that readout of a C in
17 Position 2 where you would expect the SNV to be if it were
18 there, you have detected an SNV?

19 A If by design Position 2 is a C that you've
20 identified upstream in analyzing the biopsy sample, and
21 for that amplicon, you detect a C at that position, you
22 would call that an SNV mutation.

23 Q Okay. And so you have detected an SNV mutation
24 even though no SNV mutation is present in the patient
25 sample?

1 A Based on the sequence and detection of
2 fluorescent signals in the sequencer, that is correct.
3 Nothing is perfect.

4 Q Okay. One quick question about paragraph 88 of
5 your report. In paragraph 88, you say at the top,
6 Dr. Lennon contends that when scientists perform
7 sequencing to detect circulating tumor DNA, they often
8 combine circulating tumor DNA isolated from multiple blood
9 samples in a single tube for assaying and sequencing.
10 This was true in 2014 and 2015 and is still true today.

11 Do you disagree with that statement by
12 Dr. Lennon?

13 A Well, I disagree in the context that Dr. Lennon
14 has provided this statement, but I don't disagree that in
15 general, samples are pooled and run on a sequencer. But
16 to the extent that these multiple samples represent
17 different time points in monitoring cancer, I disagree
18 with this statement.

19 Q Right. But Dr. Lennon's statement doesn't say
20 anything about different time points, right?

21 A Well, I'd have to -- I've only cited, it looks
22 like, two sentences from his report.

23 Q Right.

24 A I'd have to look at the paragraph to know what
25 the context was.

1 Q Fair enough.

2 But just with respect to the proposition that
3 when scientists perform sequencing, they often combine DNA
4 isolated from multiple blood samples in a single tube for
5 assaying and sequencing, you don't disagree with that?

6 A Well, I don't disagree with that the multiple
7 blood samples typically are from different patients. Not
8 the same patient.

9 Q Are you familiar with instances where there might
10 be multiple blood draws at the same time from the same
11 patient in order to obtain enough blood to analyze?

12 MS. SRINIVASAN: Objection; outside the scope.

13 THE WITNESS: That's a possibility. But in general,
14 if there's not enough blood, everything would be pooled
15 into a single sample, and I don't think they would
16 differentiate the different samples that came from that
17 individual.

18 BY MS. DURIE:

19 Q Fair enough. But I didn't ask you about that.

20 It just -- it wouldn't be uncommon to take
21 multiple blood draws from the same person and then pool
22 them for purposes of analysis?

23 MS. SRINIVASAN: Same objection; vague.

24 THE WITNESS: But that's not what he's talking about
25 here.

1 So when you are pooling samples, you're usually
2 barcoding them because they come from different patients.
3 I think my experience is you can draw two blood tubes for
4 any given patient at any given time point and send them
5 both to the lab. One may be a backup just in case the
6 first sample fails.

7 MS. DURIE: Okay. Let me have Tab 7.

8 MS. LEE: (Indicating.)

9 MS. DURIE: Let me have marked as Exhibit 4 a copy of
10 the declaration of Dr. Metzker in support of Natera's
11 motion for preliminary injunction.

12 (Whereupon Deposition Exhibit 4 was
13 marked for identification.)

14 BY MS. DURIE:

15 Q Do you recognize what's been put in front of you
16 as the declaration that you submitted in support of
17 Natera's motion for preliminary injunction?

18 A I do.

19 Q And I'd like you to turn to paragraph 122. It's
20 on page 69. And this is a --

21 A Sorry. Can I just have a moment to review this?

22 Q Sure.

23 A Okay. Which paragraph?

24 Q Sure. Well, let's start -- if you go to page 67,
25 just to orient you, you'll see you've got a section here

1 where you're discussing Natera's Signatera assay?

2 A Yes.

3 Q And you explain how it works, right?

4 A Yes.

5 Q And if you look at the end of that section, go to
6 page 70, paragraph 124, you express the opinion that
7 Signatera practices Claim 1 of the '454 and Claim 1 of the
8 '035, right?

9 A That's correct.

10 Q Okay. Now, if we go to page 69, paragraph 122,
11 you've broken down the steps of the Signatera assay. Do
12 you see that?

13 A I have based on the figure in paragraph 117.

14 Q Right. And the figure in paragraph 117, the
15 fifth step says, Analyze ultra-deep NGS data in plasma,
16 that's next generation sequencing data, right?

17 A That's correct.

18 Q To detect the presence of circulating tumor DNA,
19 right?

20 A That's what it says.

21 Q Okay. And in your report, you say, In the fifth
22 step, following multiplex PCR amplification, ultra-deep
23 sequencing is performed. Next generation sequencing data
24 are analyzed to detect the presence of circulating tumor
25 DNA.

1 Now, the way that the Signatera assay detects the
2 presence of circulating tumor DNA is to look for SNVs,
3 right?

4 MS. SRINIVASAN: Objection; vague.

5 THE WITNESS: It's to look for SNVs that have been
6 previously identified in their bespoke assay.

7 BY MS. DURIE:

8 Q Right. Just like NeoGenomics, right?

9 A Yes.

10 Q Okay. So you say, Next generation sequencing
11 data are analyzed to detect the presence of ctDNA.

12 What is the analysis that you're talking about?

13 A Well, I don't think I describe it here, but it is
14 a process of identifying at least two SNV mutations in the
15 sequencing data. And as a minimum of two, if two are
16 detected, then they just report -- well, they do two
17 things, but one thing they do is they report a binary
18 result of ctDNA present or ctDNA absent. They also do
19 provide a quantitation of how much ctDNA has been
20 detected.

21 Q And so in the ct -- in the context of the
22 Signatera assay, you analyze the sequencing data to look
23 for the presence of at least two mutations in order to
24 make the determination that ctDNA is present; is that
25 right?

1 A Two mutations that are part of the 16 SNV panel
2 that has been previously developed for that particular
3 patient.

4 MS. SRINIVASAN: I'd like to mark the transcript as
5 confidential, please.

6 BY MS. DURIE:

7 Q Now, let's flip forward in your declaration and
8 go to paragraph 26.

9 So the claim limitation that you're talking about
10 is in the middle of the page, and it talks about
11 performing sequencing to identify tumor specific SNV
12 mutations, right?

13 A To identify a plurality of tumor specific SNV
14 mutations.

15 Q And what it means to identify an SNV mutation,
16 that means the same thing in the context of this claim as
17 it means in the context of the opinion that you're
18 rendering today, right?

19 A Can you be more specific? The opinion I'm
20 rendering today?

21 Q Well, yeah, about claim construction in this
22 case. So identify doesn't mean different things in these
23 different claim limitations, does it?

24 A Well, this is a different patent in a different
25 claim, and this is the upfront step of actually

1 identifying SNV mutations that are specific to a given
2 patient.

3 Q Right.

4 A So this is before I know where anything is.

5 Q Right. But what it means to identify the
6 mutation, that's -- that means the same thing, right?
7 Identify?

8 A The same thing as what?

9 Q As what it means here.

10 A Well, this part of the claim is performing whole
11 exome sequencing or whole genome sequencing on a tumor
12 sample to identify SNV mutations that are specific to that
13 cancer patient.

14 Q Right. And you say here that genomic DNA from
15 tumor tissue is extracted, whole exome sequenced,
16 analyzed, and filtered for patient specific somatic
17 mutations.

18 In this context upfront, do you need to do
19 analysis in order to identify those patient specific
20 somatic mutations?

21 A There is some analysis that needs to be
22 performed.

23 Q What is that analysis?

24 A Well, I don't know all the details of how
25 Signatera does it, but if I think of just cancer biology,

1 one analysis is removing all the germ line mutations that
2 you would identify in the sequencing process because
3 those, by default, are not somatic mutations, which are
4 acquired and typically associated with cancer.

5 Q And so that is something that you need to do in
6 order to determine whether the thing that you were looking
7 at is or is not a somatic mutation?

8 A Again, in the general cancer biology world, yes,
9 that's what you would do.

10 Q Okay. Now, if you go to paragraph 130 of your
11 report, you are now talking about Claim Requirement 1C,
12 right?

13 A I'm sorry. If I just could have a second to
14 review claim -- or paragraph 130.

15 Q Sure.

16 A Okay. I've had a chance to review 130.

17 Q So in paragraph 130, you're talking about Claim
18 Element 1C which is sequencing the amplicons to obtain
19 sequence reads and detecting one or more of the tumor
20 specific SNV mutations, right?

21 A Correct. Claim 1C of the '454 patent.

22 Q Right. But in here, Claim 1C is directed to this
23 idea that you have already determined in an earlier step
24 where the mutation of interest is, right?

25 A That is correct.

1 Q And you are now looking to see whether that
2 mutation of interest is present in your sample, right?

3 A Well, you're -- you're using the sequencing
4 process to detect whether the SNV mutation is present or
5 not.

6 Q And detecting in the context of the '454 patent
7 means the same thing as detecting in the sense that you
8 are using it in your claim construction testimony here,
9 right?

10 A For the '596, that's correct.

11 Q Yeah. Okay.

12 Now, in paragraph 130 you say, Signatera
13 satisfies this claim limitation. And then you say,
14 According to Natera, following multiplex PCR
15 amplification, ultra-deep sequencing is performed with
16 100,000 X average depth of coverage. Signatera also
17 includes detecting one or more of the tumor specific SNV
18 mutations present in cell-free DNA from the sequence
19 reads.

20 Why did you say also?

21 A Well, I think -- so this is based on information
22 from the Signatera white paper, and I was describing first
23 the ultra-deep sequencing is performed. In that claim
24 limitation, 1C, there's a read -- a depth of read of at
25 least 50,000 per target loci or locus.

1 And so I'm first explaining that Signatera meets
2 this claim limitation because they have a depth of read
3 with 100,000 X average coverage. Then I'm also saying in
4 addition to the read depth limitation, Signatera also
5 detects one or more tumor-specific SNVs.

6 Q Okay. But -- and then you go on to say,
7 According to Natera, sample level performance was derived
8 by calculating a binomial probability for detecting at
9 least two clonal mutations at a given ctDNA level,
10 assuming that the majority of the custom panels have
11 between 10 and 16 clonal variants.

12 So when you say calculating a binomial
13 probability for detecting at least two clonal mutations,
14 what are you referring to?

15 A Well, again, I don't know all the details of the
16 Signatera. This is based on information from their white
17 paper, and I think I'm actually quoting from the white
18 paper. But they have some kind of downstream analysis
19 that gets them to the result of ctDNA being present or
20 absent, and if it's present, they give some kind of
21 quantitation of how much is present.

22 Q Is Natera calculating a probability that a given
23 clonal mutation has been detected?

24 A I'm not reading it that way. This is at the
25 sample level performance that they're calculating a

1 binomial probability. I believe this is -- this is -- the
2 SNV mutations have already been detected. This is
3 downstream analysis of generating a final report of
4 whether ctDNA is present or absent in that sample.

5 Q Right. I understand that there has already been
6 a readout from the sequencer as to the base that is
7 present. We can agree as to that, right?

8 A Yes.

9 Q But when it says that it is calculating a
10 binomial probability for detecting at least two clonal
11 mutations, just in English, doesn't that mean a
12 probability that each of those two clonal mutations has
13 been detected?

14 A I don't read it that way. It's a sample level
15 performance, and so it's not -- I think this is a much
16 broader analysis of SNV mutations that have already been
17 detected, and this is now part of a more sample level
18 performance of determining an overall status of whether
19 ctDNA has been detected in the sample or not, and if it
20 is, there's some quantitative information that's
21 associated with it.

22 Q Well, it doesn't talk about the probability of
23 detecting ctDNA. It talks about the probability of
24 detecting at least two clonal mutations, right?

25 A I can agree those are the words. And, again, I

1 don't know all the details of this part of the analysis
2 that I'm relying on the Signatera white paper, and I'm
3 directly quoting from that paper, and I'm giving you my
4 best analysis of what that means.

5 Q And to be clear, when you say it's sample level
6 performance, it's saying what is the likelihood that there
7 is tumor DNA in the sample, right?

8 A Yeah. It's giving some probability that it's
9 there or it's not there.

10 Q And what Natera does is calculate a probability,
11 let's say, that there are two clonal mutations present,
12 right?

13 A Well, again, my understanding is that's kind of
14 their minimum --

15 Q Right?

16 A -- of determining. There could be three. There
17 could be five. I -- you know, that's just kind of their
18 baseline.

19 Q What Natera does is give you a probability score
20 for a given mutation as to the likelihood that it is
21 present, right?

22 A That, I don't know. I mean, I -- this is the
23 extent that I know that -- of what is reported. At the
24 end when a report is being generated, that would go to a
25 patient that a physician would explain the results of the

1 MRD test that had just been performed.

2 Q Okay. But when it says probability for
3 detecting, you don't understand that to mean that Natera
4 is making a probabilistic determination as to whether a
5 given clonal mutation has been detected or not?

6 A I think we're way past that. I think this is a
7 sample level performance analysis to give an overall
8 result of whether ctDNA is present or absent.

9 Q Right. But it doesn't say a probability for
10 determining the presence of a clonal mutation, right?

11 A Again, my understanding, in their baseline, there
12 has to be at least two that have been detected through
13 their process, and -- and this is the output.

14 Q So what does it mean to say a probability for
15 detecting? If the detection has already happened as a
16 function of the output of the sequencer, how can you have
17 a probability for detecting? Isn't detection binary?

18 A Well, I -- I think there's a lot of downstream
19 analysis of getting to a final report that goes to a
20 patient of whether they can detect ctDNA in the sample or
21 not. I think it goes beyond the initial assessment of
22 determining whether the SNV mutation is present or not,
23 and I think this is the final stage of generating that
24 report, as I understand it.

25 Q But it says, A probability for detecting at least

1 two clonal mutations. But in your view of the world, the
2 detection of a given mutation is binary, right? You
3 either detect it or you don't, it's not probabilistic?

4 MS. SRINIVASAN: Objection; misstates testimony.

5 THE WITNESS: Well, I'm reading it from the claim
6 language. We're reading from a commercial product and
7 what Signatera actually does. I've tried to explain with
8 respect to Claim 1 of the '596 patent what it means to
9 perform high-throughput sequencing.

10 Now, what Signatera does as a commercial product
11 and how it reports, I'm not surprised there's other
12 analysis that goes into the final report.

13 BY MS. DURIE:

14 Q Okay. But in your view of the world, detection
15 of an SNV is binary, you either detect it or you don't,
16 right?

17 MS. SRINIVASAN: Objection; misstates testimony.

18 THE WITNESS: In the sequencing process, it is based
19 on the steps of figuring out whether -- what SNV mutations
20 are associated with the patient, doing multiplex PCR,
21 knowing the position, all the things that we've explained.
22 And at a given cycle, the sequencer will detect the
23 presence or the absence of that SNV mutation.

24 BY MS. DURIE:

25 Q And that is a binary decision, right? It's

1 either present or not present?

2 A Well, there are situations, for example, where we
3 said multiple fluorescent signals can occur, and no base
4 call can be made at that position, it gets assigned a low
5 quality score.

6 Q Okay. Let's assume there's a low quality score
7 associated with a given base call.

8 Has an SNV been detected?

9 A Again, from the sequencer detection standpoint,
10 by design if a nucleotide is incorporated at a position
11 with the expected nucleotide being the associated SNV
12 mutation, it would have been detected at that stage.

13 Q So I don't think that answered my question.

14 A I'm sorry.

15 Q Do you need to have a particular Q score in order
16 to say that an SNV mutation has been detected?

17 A Oh, I didn't realize that was your question. I
18 thought I answered that one before. I thought my -- my
19 answer earlier today was, no, you don't need a Q score.

20 Q Right. So let's assume there's a low quality
21 score associated with a given base call. Has an SNV been
22 detected notwithstanding that there is a low quality
23 score?

24 A So maybe that's what I was trying to explain.
25 Usually with a low quality score is because multiple

1 signals are being generated at the same time, and the base
2 caller can't make a call because usually an ambiguity call
3 will represent an in.

4 Q Okay. So any time there is a base call of an A
5 or a C or a T or a G, in your view, an SNV location -- an
6 SNV mutation has been detected if it's at the right
7 position and it's the right base?

8 A The way the claim has been structured, at that
9 position, if it detects the right signal, yes, it would be
10 making an SNV mutation -- it would be detecting an SNV
11 base.

12 Q Okay. And in the Natera assay, at the point in
13 time where you get to this calculation of a binomial
14 probability, you've already either, in your view of the
15 world, detected the mutation or not detected the mutation
16 as a binary yes/no proposition, right?

17 MS. SRINIVASAN: Objection; misstates testimony.

18 THE WITNESS: Well, I think the SNV mutation has been
19 detected or not detected in the early stage. Natera goes
20 through a whole set of analyses in its commercial product
21 to generate a report that it feels strongly -- I mean, has
22 enough confidence, and I think that's why probabilities
23 are being employed here to explain to a patient whether
24 ctDNA is back and maybe recurrence is just down the road,
25 or, you know, no therapy is needed because our results

1 still show there's no detectible ctDNA in your blood
2 sample.

3 BY MS. DURIE:

4 Q Right. And it would be -- and Natera at least
5 talks in that context about the probability that a clonal
6 mutation has been detected at a given position, right?

7 A No. The sentence that I'm quoting says, Sample
8 level performance derived by calculating a binomial
9 probability of detecting at least two clonal mutations at
10 a given ctDNA level.

11 Right? So there's at least two, there could be
12 more that have been detected, but it's also based on a
13 certain level. There's quantitative information that's
14 also provided. And I think all of that is at the sample
15 level performance, and that's why it's described this way.

16 Q Okay. Let me have the reply declaration, which
17 is Tab 8.

18 MS. LEE: (Indicating.)

19 MS. DURIE: Let me have marked as Exhibit 5 a copy of
20 the reply declaration of Dr. Metzker.

21 (Whereupon Deposition Exhibit 5 was
22 marked for identification.)

23 BY MS. DURIE:

24 Q You recognize what's been marked as Exhibit 5 as
25 a reply declaration that you submitted in support of

1 Natera's request for a preliminary injunction?

2 A Yes.

3 Q And in your reply declaration, you talked about
4 the Forshaw 2012 reference. Do you remember that?

5 A Yes.

6 Q And just so you have it in front of you -- yeah,
7 let me get marked as Exhibit 7 --

8 THE STENOGRAPHIC REPORTER: 6. This is 6.

9 MS. DURIE: Exhibit 6, sorry -- a copy of Forshaw
10 2012.

11 (Whereupon Deposition Exhibit 6 was
12 marked for identification.)

13 BY MS. DURIE:

14 Q Great. Now, in your reply declaration in support
15 of Natera's preliminary injunction motion, you explained
16 why Forshaw 2012 was different from the '454 patent,
17 right?

18 A I explained that Forshaw doesn't render obvious
19 the '454 patent claims.

20 Q Now, if you take a look at paragraph 93 of your
21 declaration -- and so feel free to peruse the context, but
22 I want to ask you about paragraph 93.

23 A Okay.

24 Okay. I've read it.

25 Q Okay. So in paragraph 93, you're talking about

1 what you characterize as a limitation in Forshew 2012's
2 approach, right?

3 A Yes.

4 Q And you said that in the approach that
5 Mr. Forshew was using in his 2012 paper, there would be
6 errors in sample library preparation and the sequencing
7 workflow, right?

8 A That's correct.

9 Q So you're saying errors would get introduced
10 prior to the point when the actual sequencing detection
11 operation was happening, right?

12 A Well, I think what I'm saying is errors can be
13 introduced in the sample library preparation, but also in
14 the sequencing workflow.

15 Q Right. So all of these are errors that might
16 mean that the thing that you call, let's say, as a C is
17 actually in the original sample a G, right? That's what
18 we're talking about?

19 A Yes.

20 Q Okay. And you say that those potential errors
21 exceed the technique's ability to detect rare genetic DNA
22 variants, right?

23 A Can you repeat that question?

24 Q Sure.

25 And you can look at the very bottom of page 50.

1 You say, The errors associated with Forshew 2012's sample
2 library preparation and sequencing workflow exceed the
3 technique's ability to detect rare genetic DNA variants.

4 Do you see that?

5 A I do. And then I explain that in greater detail
6 below.

7 Q Right. Now, the rare genetic DNA variants that
8 we're talking about here are SNVs, right?

9 A They can be SNV mutations.

10 Q Yeah. And so what you're saying here is errors
11 that happen during library preparation or as part of the
12 sequencing workflow could impair the ability to detect
13 SNVs, right?

14 MS. SRINIVASAN: Objection; misstates testimony.

15 THE WITNESS: It makes it more difficult. It doesn't
16 impair it, but it makes it more difficult because you're
17 detecting a lot of noise.

18 BY MS. DURIE:

19 Q Right. And so let's say that you set up the
20 system according to the claim that is at issue here, and
21 you have the -- strike that.

22 In the claim that is at issue in this case, there
23 is the potential for errors in library preparation, right?

24 A Yes.

25 MS. SRINIVASAN: Objection; vague.

1 BY MS. DURIE:

2 Q And there is the potential for errors in the
3 sequencing workflow, right?

4 A There is a potential.

5 Q Okay. Now, it is your position that even if such
6 errors take place, you are still detecting an SNV if you
7 see the signal that corresponds to an SNV at the correct
8 location, even if that signal turns out to be an error,
9 right?

10 A In the sequencing process, when fluorescence is
11 being detected, the base call is making the base call
12 based on the nucleotide that's being incorporated.

13 Q Right. And so errors don't impede the ability to
14 detect an SNV in your view, right?

15 A Errors do not impede the ability to detect SNV
16 mutations, that's correct. It becomes more challenging,
17 and there are ways of handling that. But --

18 Q Well --

19 A -- you can still detect SNVs based on the
20 position in the amplicon from the multi -- targeted
21 multiplex PCR.

22 Q Right. Why do errors make the detection harder
23 or more challenging? All you need to do is read out the
24 sequencing information, right?

25 A Right. And what I'm describing here is, again,

1 errors are stochastic. They occur across the entire
2 amplicon. When you're only looking for a known SNV
3 mutation, it makes it easier because the chances of the
4 error actually happening at that position is a function of
5 the size of the amplicon, for example.

6 Q Right. But in your view of the world, errors are
7 irrelevant to your ability to detect an SNV, right?

8 MS. SRINIVASAN: Objection; misstates testimony.

9 THE WITNESS: I didn't say that.

10 BY MS. DURIE:

11 Q Well, all you need to do is know what the
12 expected position of the SNV is, and look at the
13 sequencing readout for that position, and see if it does
14 or doesn't correspond to the SNV of interest, right? At
15 that point, you've detected the SNV?

16 A You absolutely have. And Illumina even tells
17 itself it has millions and millions of error-free sequence
18 reads. So there's many, many sequence reads that are
19 error-free, and you can detect that mutation in that
20 position.

21 Q Okay. But I'm -- I haven't introduced the
22 concept of error yet. Forget about whether there's an
23 error.

24 Your view is as long as you know the position of
25 the SNV and you detect the base that corresponds to the

1 SNV, you've detected the SNV regardless of whether there
2 was an error or not, right?

3 A So, again, the detection is at the sequencing
4 level, and is the detection of the fluorescent signal
5 coming from the sequencing process.

6 Q Right. And so whether there's an error or not
7 has nothing to do with your ability to detect that signal
8 at that location, right?

9 MS. SRINIVASAN: Objection; misstates testimony.

10 THE WITNESS: So if an error is present, most likely
11 it will tell me the SNV is not there instead of it being
12 there. The chances are three out of one that the wrong
13 base is actually called because of an error, and, again,
14 errors are spread across the entire amplicon.

15 So I think in general maybe there's an error
16 that's detected, but most of the time the reads are
17 error-free, and the detection can happen just the way I've
18 explained it.

19 BY MS. DURIE:

20 Q But, again, I'm not -- I'm not asking you about
21 error-free reads.

22 In your view of the world, the presence of errors
23 that get introduced, let's say, in library prep has
24 nothing to do with your ability to detect an SNV, right?

25 MS. SRINIVASAN: Objection; misstates testimony.

1 THE WITNESS: I disagree with that.

2 BY MS. DURIE:

3 Q Well, but if all you need to do in order to
4 detect the SNV is to know the position and to see the
5 signal, you can do that regardless of whether there was an
6 error in library prep or not, right?

7 A I don't understand the question.

8 Q So you're saying all that's required in order to
9 detect the SNV is know the position it should be in and
10 see the signal that corresponds to the SNV, right?

11 A I think I've explained it more broadly than that.
12 Involving identifying where SNVs are present, doing
13 targeted multiplex PCR where you're amplifying specific
14 amplicons. I'm not disagreeing errors can happen, but the
15 processes over billions of sequencing reads -- and so I'm
16 going to detect many reads that have an SNV at the correct
17 location. If I get one wrong, I might figure that out
18 down the road, but initially, I'm going to call it an SNV.

19 Q Right. So --

20 A I'm going to call it that way even though I might
21 later on change that call because I've identified it as an
22 error.

23 Q Right. So I want to focus on just the piece of
24 the process in terms of what is required to detect an SNV.
25 So you've said what is required in sort of layman's terms

1 is you know the position of the SNV, and you make the base
2 call that it is the T at that position, right?

3 A That's part of my testimony, yes.

4 Q Okay. And at that point in time, you have
5 detected the SNV even if that call of a T resulted from an
6 error in the library prep process, right?

7 A Again, so the detection is based on the
8 fluorescent signal that is made during the sequencing
9 process. But we've talked about the wherein clause where
10 you also have to satisfy a percentage, and so you may
11 never get to the percentage of less than or equal to
12 0.015 percent of the claim language.

13 Q But I'm not asking you about that. I'm just
14 saying, your position is that you have detected an SNV as
15 soon as you see the fluorescent signal that says it's a T
16 at the correct position even if there was an error in the
17 library prep process, right?

18 MS. SRINIVASAN: Objection; asked and answered.

19 THE WITNESS: Again, you might initially. You'll --
20 the sequencer is detecting which base has been
21 incorporated, but I think in -- I've explained, for
22 example, the error rate of an Illumina system is about
23 1 percent. And I'll just say that it would not meet the
24 claim language because you have to detect the presence --
25 the SNV mutation that is present in less than or equal to

1 0.015 percent.

2 So errors you might be detecting at 1 percent you
3 wouldn't be reading on the claim language because it's
4 well above that threshold.

5 BY MS. DURIE:

6 Q So, again, I'm just asking your understanding of
7 what it means to detect an SNV. Okay? I think you said
8 that you detect an SNV as soon as you detect the
9 fluorescent signal that tells you it is a T that is
10 present at the correct position, right?

11 A Correct. I'm -- I am -- I'm trying to be as
12 clear as I can, that in the sequencing process, the
13 detection occurs at a particular location where a known
14 SNV mutation is located, and then based on the fluorescent
15 signal --

16 Q Right.

17 A -- a base call is made.

18 Q Right. At that point, the SNV has been detected,
19 right?

20 A Yes.

21 Q Okay. And that's true even if that signal
22 resulted from an error in the library prep process, right?

23 A It is true, but the wherein clause has another
24 limitation, and that error rate would take it above that
25 limitation.

1 Q Well, I haven't told you what the error rate was.

2 I just said that that particular call happened to be a
3 function of an error in the library prep process, right?

4 You would agree that in the patented system, you could
5 have errors in the library prep process, right?

6 A Right. And in the library process that we've
7 been discussing out of my reply report, Illumina has a
8 known error rate of about 1 percent.

9 Q Okay. So I'm not asking about a known error
10 rate. I'm just saying in the patented system, you could
11 have an error in the library prep process, right?

12 MS. SRINIVASAN: Objection; vague.

13 THE WITNESS: And I have not disagreed that you can
14 have an error in the library process.

15 BY MS. DURIE:

16 Q Okay. Right.

17 And if I detect a T in the correct position, I
18 have detected according to you an SNV, even if that T in
19 that one example happens to result from an error in the
20 library prep process, right?

21 MS. SRINIVASAN: Objection; asked and answered.

22 THE WITNESS: As I've explained, the sequencer's doing
23 the detection on a per cycle basis based on the
24 fluorescence that has been detected in the system. Now,
25 error rates are much higher than the limitation after the

1 wherein clause, and I think that can all get resolved
2 out --

3 BY MS. DURIE:

4 Q I'm not asking you about the rate. I'm just
5 saying, it doesn't change your opinion as to whether an
6 SNV has been detected if the reason that there was a T in
7 that position was a function of an error in the library
8 prep process, right?

9 MS. SRINIVASAN: Objection; beyond the scope.

10 THE WITNESS: Well, all I can explain is what I've
11 explained, is in the sequencing process, the detection is
12 happening based on which nucleotide gets incorporated.
13 Now, there are other parts of the claim limitation that
14 will typically resolve errors out of the -- out of the
15 reading on the claim.

16 BY MS. DURIE:

17 Q Okay. But I just want to be clear, the claim
18 doesn't require zero errors, right?

19 A No.

20 Q Okay. So I want to posit this: We have an error
21 in library prep. It results in a T in the relevant
22 position. That T gets read by the sequencer. That T
23 would correspond if correct to an SNV in that position.
24 According to you, an SNV has been detected in that
25 position, true?

1 MS. SRINIVASAN: Objection; incomplete hypothetical,
2 vague.

3 THE WITNESS: So what sequencing process are we
4 referring to? Because in the NGS world, we have millions
5 and millions and millions of reads.

6 BY MS. DURIE:

7 Q I'm asking about just one read --

8 A It sounds like we have one read --

9 Q I'm asking about -- it may be in the context of
10 lots of others, but I'm asking about this one read and the
11 detection of this one SNV. So there's an error in the
12 library prep process that results in a T in that location.
13 The output of the sequencer is fluorescence of a T at that
14 location. The base is called as a T.

15 In your view, the SNV has been detected, correct?

16 A According to the claim language, that would be
17 detecting an SNV mutation, but that's a very isolated
18 scenario that you're painting. In the real world, things
19 don't work that way.

20 MS. SRINIVASAN: Counsel, we've been --

21 BY MS. DURIE:

22 Q Okay. Well, what you're saying is, in the real
23 world, you will detect many, many, many instances of SNV
24 mutations and do back-end processing to determine whether
25 any of them are errors, right?

1 A You -- you might do some downstream analysis to
2 figure out errors from real SNV mutations. You might.
3 You might do that.

4 Q All right. Now, in paragraph 93 of your report,
5 when you said the sequencing workflow exceeded the
6 technique's ability to detect rare genetic DNA variants,
7 that wouldn't be true given what you are saying today
8 about what it means to detect those DNA variants, right?

9 A I'm sorry. What wouldn't be true?

10 Q Well, the errors in sample library preparation
11 and sequencing workflow would not hinder your ability to
12 read the fluorescent signal from the sequencer and detect
13 the presence of an SNV mutation, right?

14 MS. SRINIVASAN: Objection; misstates testimony.

15 THE WITNESS: I'm not following the question.

16 BY MS. DURIE:

17 Q Well, all you need to do to detect a rare genetic
18 DNA variant is to know the correct position and to get the
19 readout of the sequencer, right?

20 A Well, there's a lot that's involved in getting to
21 the performing step of high-throughput sequence analysis.
22 So as I've explained, you have to go through all of the
23 steps of the claim before you actually get to this --

24 Q Sure.

25 A -- this point in the claim.

1 Q Sure. So you go through all these steps. You
2 know the position of the interest. You get the readout of
3 the sequencer. You know it should be a T. The readout of
4 the sequencer tells you it's a T. You've detected,
5 according to you, the rare genetic DNA variant, right?

6 A Well, I don't know it's -- if it's rare or not at
7 that point. I mean, the claim language doesn't have any
8 restriction on rare.

9 Q Fine. You've detected the SNV, right?

10 A I think I've explained this many times. Based on
11 the fluorescence intensity --

12 Q Right.

13 A -- at that cycle, based on the way the
14 multiplex -- targeted multiplex PCR assay has been
15 designed, you will measure the fluorescence intensity and
16 determine whether it's present or absent.

17 Q Okay. And you can do that, you can detect rare
18 SNV variant -- or you can detect SNVs in that way
19 irrespective of the level of error in library prep, right?

20 MS. SRINIVASAN: Objection; misstates testimony.

21 THE WITNESS: I -- I don't understand that. I think
22 the errors make it more difficult to detect SNV mutations,
23 and there are ways of handling that.

24 BY MS. DURIE:

25 Q Why do the errors make it more difficult to

1 detect SNV mutations?

2 A So, for example, SNV -- I'm sorry. Errors are
3 stochastically spread across the amplicon, and if you are
4 in the business of doing de novo detection, you are going
5 to detect many errors which may or may not be mutations.
6 I think it becomes easier when you know the mutation, and
7 there are tricks that you can use to -- once you get a
8 base call, determine whether there's an error or not.

9 Q No, but you said errors make it more difficult to
10 detect SNV mutations.

11 A De novo, that's correct.

12 Q Well, you didn't actually say de novo. You just
13 said errors make it more difficult to detect SNV
14 mutations.

15 Is it your testimony that errors only make it
16 more difficult to detect SNV mutations when you are doing
17 it de novo?

18 A It's more difficult de novo versus knowing what
19 you're looking for, yes.

20 Q Okay. If you know what you're looking for, do
21 errors make it more difficult to detect SNV mutations?

22 A It's not as difficult, but there's still some
23 level of difficulty that you may do downstream to -- to
24 weed out all the errors.

25 Q Well, if you know what you are looking for, how

1 does an error make it more difficult to detect an SNV
2 mutation?

3 A Well, you've given an example. Say in Loci 1 at
4 Position 4, I measure a signal that I know should be an
5 SNV, but it turns out to be an error, I would call it an
6 SNV mutation, but I may sequence the other strand and see
7 that it's wild-type, and say that's an error and discount
8 it as an error.

9 Q And so that error has affected my ability to
10 detect the SNV mutation?

11 A No, it has not.

12 Q Okay. So let's go back to my question. How is
13 it that an error could have an impact on your ability to
14 detect an SNV mutation if you know what you're looking
15 for?

16 A Well, I may detect an error. I'm not disagreeing
17 with that at all. But I'm also going to detect if the
18 patient has SNV mutations in the circulating plasma, I
19 will also detect SNV mutations. I will do both. I mean,
20 I -- you can't get away from detecting errors.

21 Q Okay. Not my question.

22 A But it doesn't affect my ability to detect SNV
23 mutations.

24 Q That's the point. I just want to make sure we're
25 really clear.

1 The presence of errors, in your view, does not
2 affect your ability to detect SNV mutations?

3 A In the presence of errors, I can detect SNV
4 mutations.

5 Q And whether there are errors present or not does
6 not affect my ability to do that?

7 A I don't understand that extreme. I think it's --
8 there are -- it's more challenging de novo. It's less
9 challenging for known mutations, but errors have to be
10 weeded out of the data downstream.

11 Q Okay. I'm not asking about weeding stuff out of
12 the data downstream. Well, maybe I am, but you're going
13 to tell me.

14 We're talking about known loci, okay, so not de
15 novo?

16 A Yes.

17 Q How does an error make it more difficult to
18 detect an SNV?

19 A Initially, the base caller will call it an SNV
20 mutation because if by chance -- and the chances are much
21 lower, but by chance, at that position at that nucleotide
22 it's the same as the mutation I've identified in the
23 patient, I might determine that -- I would detect it as an
24 SNV mutation. Later on, I may reevaluate doing something
25 else and say, no, this is really an error. I'm not going

1 to call it -- I'm going to weed out that error.

2 Q And it is for that reason that errors can make it
3 more difficult to detect SNV mutations?

4 A We have errors in sequencing data. That --
5 getting rid of the errors is always part of the analysis.
6 It's there. It's a problem that -- it's something that is
7 known to be solved, but in the sequencer, it's going to
8 call the base based on the fluorescence. If it matches
9 the SNV in the position of the amplicon, that will be
10 considered an SNV mutation detection step.

11 Q Let me try my question again.

12 Is it your testimony that the difficulties that
13 you have talked about are why errors can be -- can make it
14 more difficult to detect SNV mutations?

15 A Are you talking about in the context of Forshew?

16 Q In the context of the claim.

17 A Well, the claim doesn't have any limitations on
18 errors.

19 Q That's right. So let me ask again. You said
20 errors can make it more difficult to detect -- well,
21 strike that.

22 Is it your -- okay. This is a yes-or-no
23 question: Can errors make it more difficult to detect SNV
24 mutations?

25 A Not in the context of the claim.

1 Q How about in the context of Forshew?

2 A In the real world, we know there are errors, and
3 there are ways of weeding out the errors out of the
4 sequencing data.

5 Q In the real world, can errors make it more
6 difficult to detect SNV mutations?

7 A It really depends on a lot of factors. There are
8 a lot of factors, as you've mentioned, that contribute to
9 the error rate. There are ways of dealing with errors.
10 There are ways of weeding out errors. It depends on the
11 way the experiments are set up.

12 Q Okay. But it is -- strike that.

13 Is weeding out errors relevant to the ability to
14 detect SNV mutations in the real world?

15 A Sorry. I heard the real world, the last of the
16 sentence. Can you read the first part of the sentence,
17 please?

18 Q Sure.

19 Is weeding out errors relevant to the ability to
20 detect SNV mutations in the real world?

21 MS. SRINIVASAN: Objection; vague.

22 THE WITNESS: In the real world, you do not want to
23 report errors as SNV mutations. You want to weed those
24 out.

25 MS. SRINIVASAN: Counsel, I think we've been going

1 about an hour and 20 minutes.

2 BY MS. DURIE:

3 Q And -- and therefore, is the ability to weed out
4 those errors relevant to the ability to detect the SNV
5 mutations?

6 A Not in the context of the claim.

7 Q Well, you say not in the context of the claim,
8 but does detect mean something different in the claim from
9 what it means in the real world?

10 A Well, in the real world, we're doing lots of
11 other things in addition to what's claimed, and I think
12 that's what we're talking about. All the other things
13 that are not claimed you can do in the real world to
14 remove errors in the sequencing process.

15 Q Again, but this is, I think, not that complicated
16 a question, and then once I get an answer to this, we can
17 take a break.

18 But are the existence of errors relevant to the
19 ability to detect SNV mutations in the real world?

20 MS. SRINIVASAN: Objection; asked and answered.

21 THE WITNESS: They're relevant.

22 BY MS. DURIE:

23 Q They are relevant?

24 A They are relevant in the real world.

25 Q Okay.

1 MS. DURIE: Let's take a break.

2 THE VIDEOGRAPHER: We are going off the record. The
3 time is 11:29 a.m.

4 (Recess taken.)

5 THE VIDEOGRAPHER: We are back on the record. The
6 time is 11:37 a.m.

7 BY MS. DURIE:

8 Q So let's continue with the declaration that you
9 submitted in reply in the preliminary injunction
10 proceedings, Exhibit 5, and if you can turn to
11 paragraph 96. So in paragraph 96 --

12 A I'm sorry, Ms. Durie. Can I just get a second to
13 read this paragraph?

14 Q Sure.

15 A Okay. Thank you.

16 Q So in paragraph 96, you're citing a reference
17 that is Kinde 2011.

18 THE STENOGRAPHIC REPORTER: I'm sorry. I didn't hear
19 it.

20 MS. DURIE: Kinde 2011, K-I-N-D-E, 2011.

21 THE WITNESS: I am citing Kinde 2011.

22 BY MS. DURIE:

23 Q And I take it you're citing -- you're citing it
24 because you agree with it. Is that reasonable?

25 A Yes.

1 Q Okay. And the first sentence that you cite that
2 you bold and you italicize says, Massively parallel
3 sequencing cannot generally be used to detect rare
4 variants because of the high error rate associated with
5 the sequencing process.

6 Now, a rare variant can be an SNV, right?

7 A Yes.

8 Q Okay. And so this is saying that massively
9 parallel sequencing cannot generally be used to detect
10 SNVs because of the high error rate associated with the
11 sequencing process, right?

12 A That is what Kinde is saying.

13 Q Okay. Now, massively parallel sequencing can be
14 used to get a fluorescent signal that corresponds to an
15 SNV at a given location, correct?

16 A Well, the way I've defined it in the context of
17 Claim 1 of the '596 patent, yes.

18 Q Okay. Now, the way that you understand the use
19 of the term detect in the context of the patent, is that
20 the same as how you understand persons of skill in the art
21 used the term detect in the context of sequencing
22 generally?

23 A No.

24 Q So you are using a definition of detect that is
25 different from its ordinary meaning in usage by persons of

1 skill in the art?

2 A Not its ordinary meaning because sequencing can
3 do lots of things, and the example I'll give you is whole
4 genome sequencing, and we've heard a lot about that. For
5 whole genome sequencing, we are detecting base calls, but
6 we don't know the position of any of the reads relative to
7 the genome.

8 So we -- we in that instance, and I would agree
9 with Dr. Lennon because this is the way he's explained how
10 you find SNVs, is you sequence, you generate a sequence
11 read, and then you compare it to the reference and you
12 look for differences. So in that context, I don't know
13 the position of the SNV like I would in a targeted
14 multiplex PCR reaction.

15 Q So the word detect -- just take the word detect.
16 What do you understand detect means?

17 A Generally, or in the context --

18 Q Just as persons of skill in the art in sequencing
19 use the word detect, what does the word detect mean?

20 A I would describe it pretty similarly the way I've
21 described it in the context of the claim. So detect is
22 usually measuring the fluorescence that is emitted from a
23 nucleotide that has been incorporated at a given cycle in
24 the SBS method.

25 Q Okay. And that is an example of detecting the

1 presence of a base; is that right?

2 A That's correct. And it makes a base call.

3 Q Right. And in your opinion, that is also
4 detecting the presence of an SNV if you know the location
5 of the SNV in the sequence, right?

6 A If you know what you're looking for, it can also
7 be associated with detecting the presence or the absence
8 of a mutation.

9 Q Right. And is that usage consistent with how you
10 understand persons of skill in the art use the term detect
11 in describing sequencing?

12 A Again, sequencing is a very broad category.
13 There's lots of ways to perform sequencing, and I've given
14 you an example where you wouldn't know the position of
15 any -- you still detect bases --

16 Q Right.

17 A -- but you don't know the importance of that
18 particular base call.

19 Q Right. But does the meaning of the word detect
20 change contextually?

21 A No, I don't think so. I've described it as
22 detecting the fluorescent signal that comes from a given
23 cycle in the SBS method.

24 Q Okay. But, again, I just want to understand.
25 I'm not asking about different ways to do sequencing, just

1 what the word detect means.

2 Are you using the word detect to mean something
3 different from how you think persons of skill in the art
4 use the word detect generally?

5 A In the context of sequencing and in the context
6 of fluorescent sequencing where I'm detecting the
7 fluorescent signal, no.

8 Q Okay.

9 A I'm using it consistently with the claim
10 language. I think there's a little bit difference because
11 we know what we're looking for, or generally in the
12 sequencing process that -- as understood by a person of
13 ordinary skill.

14 Q Okay. And your understanding is that detecting
15 an SNV mutation means that you need to know the location
16 where you would expect to see it, and you need to see or
17 the machine needs to have a sequencing output?

18 A I agree with the location. The person of
19 ordinary skill in the art would also know what the
20 mutation is in advance.

21 Q Right. Right.

22 A And based on the fluorescent signal that is
23 detected would either detect the presence or the absence
24 of the SNV mutation.

25 Q Okay. Now, if we look at the section of Kinde

1 that you quoted, it says, Massively parallel sequencing
2 cannot generally be used to detect rare variants because
3 of the high error rate associated with the sequencing
4 process.

5 Now, the way that you are using the term detect,
6 it is possible to detect rare variants even if there is a
7 very high error rate, is it not?

8 A In the general context of sequencing or in the
9 context of the claim?

10 Q Well, let's say in the general context of
11 sequencing. Where you know a priori what you're looking
12 for. Okay?

13 A Okay.

14 Q In that context, you can detect rare variants
15 regardless of the error rate in your view of the world,
16 right?

17 A Not regardless, and I've never said regardless of
18 the error rate. I've always said it was more difficult.
19 And there's ways -- the whole premise of Kinde is actually
20 a new method to reduce -- to remove all the errors so you
21 can detect rare variants.

22 Q But if I know the position and I know the
23 mutation that I'm looking for at that position, and I get
24 a sequencing output, I have, in your view of the world,
25 detected the rare variant even if there's a really high

1 error rate, right?

2 A No. If we're talking about the claim right now,
3 you've just detected the presence of an SNV mutation. I
4 don't know whether it's rare or not.

5 Q But you would know a priori whether it was rare,
6 right? It's -- the whole point is that you've done an
7 analysis of the patient's tumor in order to identify what
8 you're looking for, right?

9 A No. I disagree with that. You've -- when you've
10 performed Steps 1A and 1B and even 1C, at least the
11 beginning part, you do know what you're looking for. You
12 don't know whether it's rare or not, and it really depends
13 on the status of the patient. I mean, the patient may be
14 going -- undergoing chemotherapy, and there's no
15 detectible ctDNA present. I hope that's the case in all
16 cancer patients, but it may come up as 1 or 2 percent,
17 which is actually by definition not rare.

18 Q Okay. But the claim requires that you be able to
19 detect an SNV mutation that is present in less than or
20 equal to 0.015 percent of the cell-free DNA, right?

21 A That is correct.

22 Q Can we agree that's rare?

23 A I would agree that is rare.

24 Q Okay. And that's what the claim requires, right,
25 that you be able to detect that rare SNV mutation?

1 A It requires that you detect a mutation that's
2 present in less than or equal to 0.015 percent. I would
3 agree that is a rare variant.

4 Q Okay. So the claim requires that you be able to
5 detect a rare variant, and I think we've established that
6 in your opinion, that ability to detect that rare variant
7 is not affected by the error rate, right?

8 A It's not affected by the ability to detect the
9 SNV mutation --

10 Q Right.

11 A -- in the sequencing process.

12 Q So it is your opinion that the ability to detect
13 rare variants is unaffected by the error rate?

14 A No, I didn't -- I haven't said that as well.
15 There are ways of -- for example, in Kinde, there are ways
16 to remove the errors that allow rare variant detection to
17 take place. I've also testified that the error rate is
18 typically 1 percent, and you would find those errors at a
19 much higher frequency than 0.015 percent.

20 Q Right. But if we go back to the claim, the claim
21 requires that I detect an SNV mutation, right?

22 A Yes.

23 Q And it requires that that SNV mutation is present
24 in less than or equal to 0.015 percent of the DNA, right?

25 A That's correct.

1 Q The claim doesn't say anything about an error
2 rate, right?

3 A That's correct.

4 Q So --

5 A There's no reference to errors at all.

6 Q Right. And so the error rate could be super
7 high, right? But I could still practice the claim if I --
8 according to you, if I get a readout that says there is an
9 SNV mutation that is present in a particular position, and
10 I get that readout in less than or equal to 0.015 percent
11 of the cell-free DNA that is being analyzed?

12 A Correct. And I'll give you an example, and I
13 think Dr. Lennon said the same thing: If I sequence 7,000
14 reads from the same loci, and I detect one read that has
15 an SNV mutation that's been detected in the sequencing,
16 I've met the claim language.

17 Q Right. And that's true, according to you, even
18 if the error rate is super high?

19 A Well, I don't think of the error rate as super
20 high. I will have a percentage equal to or less than
21 0.015 percent. I will have an error rate much higher, and
22 it will not read on this claim.

23 Q Well, why not? Let's assume that my error rate
24 is, like, 50 percent. Okay? But I do the things that you
25 just said. I sequence 7,000 times. I get one read that

1 is a read that corresponds to the mutation of interest.

2 Maybe I've got a really high error rate. Why does that
3 affect whether I've practiced the claim?

4 A The error rate does not affect whether you
5 practiced the claim or not.

6 Q Okay. So I think we agree, then, that I could
7 practice the claim, according to you, and detect the
8 presence of an SNV mutation even if there's a really high
9 error rate as long as I get a signal that corresponds to
10 the mutation in the correct position?

11 A I agree with that.

12 Q Okay.

13 A I think based on the way it's designed, if I get
14 a -- the correct base call, not a signal, but the correct
15 base call. Because I know it's either a C will be mutant
16 or, let's say, a T is normal.

17 Q Right.

18 A If I get something else in that position like a
19 G, I wouldn't call it an SNV.

20 Q Fine.

21 A There has to be very specific steps that are
22 followed to get to the point where you're performing
23 high-throughput frequency.

24 Q Well, but -- fine. But I -- according to the
25 claim, I do the analysis. I get a C in the position of

1 interest. C corresponds with the SNV. According to you,
2 I've detected the SNV and I've practiced the method,
3 right?

4 A Repeat that again, please.

5 Q Sure.

6 I do all the steps of the claim. I do the
7 sequencing. I get a C. The C is in the expected
8 position. C corresponds to an SNV. I have practiced the
9 claim, I have detected an SNV in that position, right?

10 A Okay.

11 Q Agreed?

12 A Right. There's other -- I mean, you also have to
13 at least get to the limit of detection of equal to or less
14 than 0.015 percent.

15 Q So the SNV mutation has to be present in less
16 than or equal to that percentage of the cell-free DNA,
17 right? So I do 6,999 other sequence runs -- or I sequence
18 600 -- 6,999 other amplicons, and I have now practiced the
19 claim; is that right?

20 A Well, I don't know. You've said an error rate of
21 50 percent. No one would ever run an experiment at
22 50 percent. But if your hypothetical is my 6,999 reads
23 are error-free, and I have one that has the mutation, then
24 I would read on the claim.

25 Q Well, do I have to make a determination that the

1 other 6,999 reads are error-free in order to practice the
2 claim?

3 MS. SRINIVASAN: Objection; outside the scope.

4 THE WITNESS: You will know at that base position
5 whether it's the normal base or the mutated base, and
6 that's by design.

7 BY MS. DURIE:

8 Q So let me ask my question again. Do I need to
9 know whether the results of the other 6,999 are error-free
10 in order to practice the claim?

11 A No.

12 Q Okay. So returning to my hypothetical, I do my
13 sequencing run. I do 7,000 of them. For one of them, I
14 get a C at the right position where C corresponds to the
15 SNV. I have, according to you, detected the presence of
16 an SNV mutation, right?

17 A Yes.

18 Q And that is true without regard to what the error
19 rate of the assay is, right?

20 A Well, I would disagree with that. Because I
21 don't know how you would get down to 0.015 percent if
22 50 percent of the time, the nucleotide that is in the
23 position where I know my SNV is something other than what
24 I expect.

25 Q So forget 50 percent, but I don't need to know

1 what the error rate is in order to say that I've practiced
2 the claim, right?

3 A My reading of the claim, there's no requirement
4 of an error rate or the use of an error rate.

5 Q Right. Right.

6 So as long as I get C in one position and I don't
7 get C in the other 6,999 reads, I've practiced the claim?

8 MS. SRINIVASAN: Objection; incomplete hypothetical.

9 THE WITNESS: Again, I would disagree with that. I
10 think as you've said before, you can think of it as binary
11 or biolily, we might call it that although they're not
12 inherited, but there's two choices: You either have
13 normal base present, or you have the SNV mutated base
14 present.

15 And so the way I understand this claim, if I do
16 7,000 -- it's just a hypothetical, but because Dr. Lennon
17 has also used this example -- in 6,999 times, I see the
18 normal base --

19 BY MS. DURIE:

20 Q Yeah.

21 A -- and in one time, I detect the SNV mutated
22 base, I've practiced the claim.

23 Q Okay. And so -- got it.

24 And so in order to practice the claim, not only
25 do I need to detect an SNV mutation that is present in

1 less than or equal to 0.015 percent of the cell-free DNA,
2 I also need to detect the expected nonmutated base in the
3 other 6,999 sequences?

4 A I think that's correct.

5 Q Okay.

6 A Yeah.

7 Q And so I have not according to you detected the
8 SNV until I have completed all 7,000 sequencing
9 operations?

10 A No. I disagree with that. So, again, this is
11 massively parallel sequencing. All -- let's just say
12 there are 7,000 amplicons all from the same target loci
13 being sequenced at the same time. At -- and let's say our
14 SNV mutation is at Cycle 4. I will know at Cycle 4 across
15 all seven reads whether it's the normal base or the
16 mutant -- SNV mutant base.

17 Q But according to you, the sequencer needs to look
18 at, if you will, and you need to analyze the output with
19 respect to all 7,000 bases in order to know whether you
20 have detected an SNV mutation in any of them?

21 A Can you repeat that question, please?

22 Q Sure.

23 So one would need to look at and know the output
24 with respect to all 7,000 bases at that location in order
25 to be able to determine whether an SNV has been detected

1 at any of them?

2 MS. SRINIVASAN: Objection; misstates testimony.

3 THE WITNESS: Well, I think in the real world you look
4 at many more than 7,000, but you will know -- for that
5 given target loci at Position 4, which is our example of
6 where our SNV mutation is, you will know whether it's a
7 normal base because the base caller will detect the
8 fluorescence from the normal base, and the detector will
9 detect the fluorescence from the SNV mutated base all in
10 the same step, all in the same cycle, across all of the
11 different amplicons that are being characterized on the
12 sequencer.

13 BY MS. DURIE:

14 Q And do I need to look at all 7,000 in order to
15 know whether an SNV has been detected at any one of them?

16 A No. But you'll need to know whether it's
17 detected equal or less than 0.015 percent. You will need
18 to know that.

19 Q And I need to know that in order to decide
20 whether an SNV has been detected?

21 A No.

22 Q Okay.

23 A Detected at equal or less than 0.015 percent.

24 Q So just to be clear, the claim requirement is an
25 SNV mutation is present in less than or equal to

1 0.015 percent of the cell-free DNA. So if I understand
2 your testimony, the SNV mutation is detected looking at
3 the single instance of the base call at the position where
4 the mutation would be expected and having the base call
5 correspond to the mutation.

6 In order to know that the mutation is present in
7 less than or equal to 0.015 percent of the cell-free DNA,
8 you need to analyze a sufficient amount of cell-free DNA
9 in order to make that determination?

10 MS. SRINIVASAN: Objection; compound.

11 THE WITNESS: No, you wouldn't. You -- in your
12 targeted multiplex PCR, you are amplifying -- for a given
13 loci, you will have a number of amplicons that are derived
14 from the targeted multiplex PCR. In the sequencing,
15 you're sequencing those multiple amplicons from the same
16 target loci. So you are characterizing thousands and --
17 probably 50,000 or more amplicons at the same time at the
18 same cycle, and the detector, based on the incorporation
19 of the nucleotide, what is the fluorescent signal that's
20 being detected, will identify the normal base or the SNV
21 mutated base.

22 BY MS. DURIE:

23 Q Right. But in order to detect the SNV mutated
24 base, does it matter -- just in order to detect it, does
25 it matter what any of the other signals are?

1 A No.

2 Q Okay.

3 A It doesn't matter just for detecting the SNV
4 mutated base.

5 Q Great. So I can detect an SNV mutation without
6 regard to the error rate, right?

7 A I don't understand what that means, without
8 regard to the error rate.

9 Q Well, you said that the error rate might affect
10 your ability to know whether an SNV mutation is present in
11 less than or equal to 0.015 percent of the cell-free DNA.
12 And I think what you're saying is if you have two high an
13 error rate, you're not going to be able to make that
14 determination, right?

15 A That's probably true.

16 Q Okay. But an error rate does not affect your
17 ability to call the base, right, in detecting SNV?

18 A You'll call the base, and based on design, based
19 on the position and knowing what you're looking for, if
20 you get the correct signal, you will call that an SNV
21 mutated base.

22 Q Right. And so if we go back to the Kinde
23 discussion, massively parallel sequencing can be used,
24 according to you, to detect SNVs notwithstanding a high
25 error rate associated with the sequencing process, right?

1 A It can be, but there are ways to resolve the
2 error rate problem. You'll resolve the error rate
3 problem.

4 Q But just to be clear, you can detect rare
5 variants regardless of what the error rate is, right?

6 MS. SRINIVASAN: Objection; vague.

7 THE WITNESS: I've been -- I don't think I said
8 regardless of what the error rate is.

9 BY MS. DURIE:

10 Q But when --

11 A I don't think anybody would -- your example of a
12 50 percent error rate is -- like, no one would do that.

13 Q Well, fine. But, I mean, in principle, right,
14 the ability to call the particular base at a location
15 where you know a mutation is expected and, according to
16 you, detect the presence of that mutation by looking at
17 the fluorescence, that -- you can do that regardless of
18 the error rate associated with the assay, right?

19 A Again, in the context of the claim error rate is
20 not a limitation. In the context of what you would do in
21 the real world, no one would run sequencing at super high
22 error rates. I mean, they just wouldn't do that.

23 Q But -- but that's not my question. I want to
24 understand sort of your view of what the claim requires.

25 So according to you and your understanding of how

1 people use the word detection, right, you can detect a
2 rare variant regardless of what the error rate is because
3 you can look at the base call and see whether it
4 corresponds to the position of interest and the variant of
5 interest?

6 A I disagree with the statement of regardless of
7 what the error rate is. I -- that's just not even
8 reasonable in the real world that anybody would actually
9 just completely ignore or have artificially high error
10 rates and still try to detect rare variants.

11 Q But I just -- again, I'm not asking whether you
12 think this is a thing one might want to do. I'm just
13 saying that in theory, right, according to you, if
14 detecting a rare variant means knowing where it's supposed
15 to be and seeing whether you get a light, whether you get
16 a fluorescent signal, that corresponds to it, I can do
17 that regardless of what the error rate is in my assay,
18 right?

19 A I'm not sure whether you can do that or not. I
20 mean, the error rate may be so high that you just generate
21 a lot of noise. You get no sequencing information
22 whatsoever.

23 Q Assume that you're getting sequencing
24 information. Okay? But you get sequencing information
25 with a high error rate like the error rates that were

1 associated with the sequencing process that was being
2 discussed in Kinde.

3 A Right. Well, Kinde explains this error rate
4 varies from 1 percent to 0.05 percent.

5 Q Right.

6 A That's a big range.

7 Q Okay.

8 A That's a big range.

9 Q Let's talk about that error rate. So we've got
10 an error rate of that range of 1 percent to 0.05 percent.
11 I can in a sequencing setup that has that error rate
12 identify the locus of interest, identify the position of
13 the mutation, know what the mutation is, perform that
14 sequencing operation, get a signal, and, according to you,
15 detect the presence of an SNV, right?

16 MS. SRINIVASAN: Objection; incomplete hypothetical,
17 misstates testimony.

18 THE WITNESS: Well, again, if you follow all the steps
19 of the claim and you know the position and you know the
20 mutated base and you measure the fluorescence, and it
21 corresponds to that mutated base, you would have detected
22 an SNV mutated base.

23 BY MS. DURIE:

24 Q Right. And --

25 A According to the claim. That's what you would

1 do.

2 Q Right. And you would have done that even if the
3 error rate of the sequencing process was from 0.05 percent
4 to 1 percent?

5 A I think you can, that it's possible to do it.
6 It's easier to remove the errors to do rare variant
7 detection, but you can do it. And -- and, again, in the
8 context of the claim, error rate is not even a limitation.

9 Q So I -- that's right. And so in that example, if
10 that SNV is a rare variant, you have, according to you,
11 detected that rare variant notwithstanding the high error
12 rate associated with the sequencing process?

13 A I disagree with that. Because when you talk
14 about rare variant -- and I agree a rare variant can be
15 0.015 percent, meaning that in our example of 7,000 reads,
16 6,999 have to have the normal base. If I have errors that
17 are being injected into the read, I'm never going to get
18 to that level because the errors are impacting my ability
19 to generate -- or to identify -- to detect the rare
20 variant.

21 Q SNVs can be rare variants, right?

22 A I agree with that. I -- I totally agree with
23 that.

24 Q Okay. And so if I make a call that something is
25 an SNV, that SNV might be a rare variant, right?

1 A So in the process I've been describing, I'm
2 describing a process of detecting an SNV mutated base or
3 an SNV mutation. That process doesn't qualify whether
4 it's a rare variant or a common variant at that stage.

5 You have to then look further into the claim
6 limitation of this 0.015 percent to determine whether at
7 the rare variant level or not.

8 Q But you would agree, if you're detecting an SNV,
9 it might or might not be a rare variant, right?

10 A Yeah, I don't know.

11 Q Right. And so when Kinde is talking about the
12 ability to detect rare variants, do you have in mind some
13 threshold for what constitutes rare?

14 A I don't.

15 Q Would 1 in 100 be rare?

16 MS. SRINIVASAN: Objection; outside the scope.

17 THE WITNESS: Probably not.

18 BY MS. DURIE:

19 Q So turn to page 56 of your report, paragraph 103.

20 A Sorry. If I can just have a moment.

21 Q Sure.

22 A Okay. I've read paragraph 103.

23 Q So you say -- you're talking about Forshew 2012,
24 right?

25 A Correct.

1 Q And you say, The consequence of the sequencing
2 workflow errors described above is that following Forshaw
3 2012's approach, rare genetic variants EG SNVs on tumor
4 cfDNA present in the plasma at low levels are not likely
5 to be detectible below the noise of the error rate, even
6 if amplified 50,000 times or more at each locus.

7 Now, those SNVs on tumor DNA present in the
8 plasma at low levels can be detected, according to you, in
9 the sense that you can get a signal at a particular
10 location that corresponds to that SNV, right?

11 A So this description is in the context of the '454
12 patent, and I'm addressing specifically the limitation of
13 a depth of read of 50,000 X, and why it would not have
14 been obvious for Forshaw just to turn the switch on and
15 increase the number of reads to meet the claim limitation
16 of Claim 1 of the '454 patent. That's -- that's what's
17 being discussed here.

18 Q I understand.

19 But what you say is that following Forshaw's
20 approach, rare genetic variants EG SNVs are not likely to
21 be detectible below the noise of the error rate. The
22 noise of the error rate doesn't affect your ability to
23 make a base call at a particular location, right?

24 A Well, in the context of the Forshaw method, it
25 did. It -- Forshaw could only get down to a level of

1 about 2 percent, which was really not considered a rare
2 variant, and I'm making the point that just applying
3 Forshew's method and increasing the depth of read would
4 not improve the sensitivity or read on Claim 1 of the '454
5 patent.

6 Q Well, when you say sensitivity, what do you mean
7 by sensitivity?

8 A So sensitivity -- for example, can I detect an
9 SNV mutation at 0.1 percent, or can I detect it at
10 0.5 percent? So I don't necessarily mean it in the
11 context of clinical specificity whether -- how correct are
12 you at identifying a patient that actually has a disease.
13 I'm talking more about what's the level that I can
14 actually detect an SNV mutation.

15 Q Well, you say here that genetic variants are not
16 likely to be detectible below the noise of the error rate.
17 Now, you can, according to you, detect an SNV even if
18 there is a lot of noise, right?

19 A I don't think I've said you can detect an SNV
20 with a lot of noise. I don't think that's my testimony at
21 all.

22 Q So I want to imagine, then, a situation where
23 you've got a very noisy assay. That means that you're
24 getting a lot of false positives, right?

25 A Or false negatives.

1 Q Fair enough.

2 A Sure.

3 Q But you're getting a lot of errors in the read.

4 And so I have that noisy assay, and I detect a C
5 in Position 4 where a C in Position 4 corresponds to an
6 SNV. According to you, I have detected an SNV, right?

7 A In the real world, no, not at all. No one would
8 run a noisy assay to detect variants associated with
9 cancer. No one would do that.

10 Q Well, but if that happened, if there were a noisy
11 assay, if I ran it for whatever reason and I got a C in
12 that position, according to you, I would have detected an
13 SNV, right?

14 MS. SRINIVASAN: Objection; misstates testimony, asked
15 and answered.

16 THE WITNESS: No. Again, I've said you can detect an
17 SNV mutation at a particular position if you follow the
18 steps of Claim 1 of the '596 patent. You can -- you can
19 do it that way. But just having a noisy system and just
20 knowing -- just looking at a position and saying I've
21 detected an SNV, no, I don't think you can.

22 BY MS. DURIE:

23 Q So I know the position, I know what I expect to
24 see there, and I get the sequencing output that
25 corresponds with the mutation that is at that position.

1 Why have I not detected an SNV?

2 A The question's too broad for me to answer that.
3 It's too general. Like, I would need a little more
4 detail. Maybe a lot more detail.

5 Q Well, what -- so I targeted PCR. I know the
6 position at issue. I know the mutation that I expect to
7 see at that position. I do my sequencing operation. A C
8 in that position means an SNV. I get the fluorescent
9 signal that indicates a C in that position. What more do
10 you need to know in order to know whether I have detected
11 an SNV?

12 A So if we're practicing the steps of Claim 1 of
13 the '596 patent, as I've explained, you will know at a
14 given cycle whether there's a normal base or a mutant
15 base, and based on the fluorescence that's detected, you
16 would detect the presence or the absence of the SNV
17 mutation.

18 Q Okay. But, again, I just want to make sure that
19 we're clear. So I'm just saying in general, I'm just
20 asking about usage in the world. Okay?

21 A Okay.

22 Q It's targeted PCR. I've determined the sequence
23 of interest. I've determined the position that
24 corresponds with the mutation. I know that a C in
25 Position 4 equals an SNV. I do sequencing. I get a

1 fluorescent signal that indicates a C at Position 4.

2 Is there any other information that you need in
3 order to be able to say that I have detected an SNV?

4 MS. SRINIVASAN: Objection; vague, incomplete
5 hypothetical.

6 THE WITNESS: Me, personally? A personal of ordinary
7 skill?

8 BY MS. DURIE:

9 Q A person of ordinary skill.

10 A So I think initially -- and, again, I think a
11 person of ordinary skill in the art would not be silly
12 enough to run a noisy assay. They would have lots of
13 controls and understand the performance of their assay.
14 If they detect something at a particular location, they
15 may want to verify it. They may do something else.

16 For example, they may sequence the other strand
17 and ask the question, does the mutated base occur on both
18 strands? And this is what Kinde does. And when it
19 doesn't -- well, actually, Kinde doesn't do that.
20 Somebody else does that. But if you look at the
21 complementary strand and you get the same result, well,
22 then you might say, I was right. It is a detected mutated
23 base.

24 If I don't, then I may say, well, that really was
25 an error. I'm going to weed that out.

1 Q Okay. But my question is a little bit more
2 specific. If the person of skill in the art knows the
3 sequence of interest, knows the position that corresponds
4 with the mutation, knows that a C in Position 4 equals an
5 SNV, does sequencing, and gets a fluorescent signal that
6 indicates a C at Position 4, is there any other
7 information that is required in order to be able to say
8 that that person has detected an SNV?

9 MS. SRINIVASAN: Objection; incomplete hypothetical.

10 THE WITNESS: Detected the SNV in the read? Which is,
11 I think, what the claim language is that we keep going
12 back to.

13 If we're going to in the general world of
14 determining whether an SNV mutation is in a cancer
15 patient, the person of ordinary skill in the art may do
16 other things as well.

17 BY MS. DURIE:

18 Q So --

19 A With the information that initially they've
20 detected an SNV mutation, they may want to verify it.
21 They may want to quantify it. There may be other things
22 that, in general, a person of ordinary skill in the art
23 would -- may want to do.

24 Q So I understand your testimony that a person
25 might want to do other things, but I just want to be clear

1 that your testimony is that in this example, once you have
2 seen the -- got the fluorescent signal that corresponds to
3 a C in Position 4, you have detected an SNV?

4 A In the read, you would have detected an SNV in
5 the read, the sequence read. I mean, that's even what the
6 claim says. That's -- that's the data that you end up
7 with.

8 Q Is that different from detecting an SNV in the
9 patient?

10 A It might be, yeah. I might initially say I have
11 detected an SNV in my read. I've looked at all the
12 amplicons that are being sequenced, and I can actually
13 quantify that I'm equal or less than 0.015 percent, and
14 my -- and I read on the claim.

15 There may be other analyses that are done to
16 figure out the impact it would be for a patient.

17 Q But just to be clear, when you say the impact,
18 would you -- if you had detected -- if you have, according
19 to you, detected the presence of an SNV by having a
20 fluorescent signal that corresponds to the presence of an
21 SNV, have you detected an SNV in a patient?

22 A If you follow all the steps in Claim 1 of the
23 '596 patent, and you detect at that particular position
24 the correct fluorescent signal, you would have detected an
25 SNV mutation in the read. That's what the claim says.

1 You may do other things to enhance the analysis before
2 it's reported to a patient what is actually present in the
3 sample.

4 Q Have you detected an SNV in the patient?

5 MS. SRINIVASAN: Objection; vague.

6 THE WITNESS: According to the claim or in general?
7 Because we keep switching back and forth.

8 BY MS. DURIE:

9 Q In general, as you understand the meaning of the
10 term detect, have you detected an SNV in the patient?

11 A The initial assessment maybe, yes. There may be
12 some downstream analysis that may verify, may be
13 associated with probabilities, things like that.

14 Q And so --

15 A But the initial assessment would be I have found
16 the mutation that I found previously in a tumor biopsy
17 sample.

18 Q So you would say at that point in time you have
19 detected an SNV in the patient, and then your assessment
20 as to whether you have detected an SNV might change based
21 on further analysis?

22 MS. SRINIVASAN: Objection; misstates testimony.

23 THE WITNESS: My testimony is you detect an SNV
24 mutation in the sequence. That's been my testimony. You
25 may do downstream analysis to then verify, determine -- or

1 figure out whether that mutation is in the patient, you
2 know, actually fluttering around in their circulation.

3 BY MS. DURIE:

4 Q Okay. But my question was about the patient.

5 So at the point in time when you read -- you --
6 strike that.

7 At the point in time when you call the base, and
8 the base is the same as the expected mutation, at that
9 point in time, is it your testimony that you have detected
10 an SNV mutation in the patient?

11 A I have not provided that opinion. That's not my
12 testimony. It would be detecting an SNV mutation in the
13 sequence read.

14 Q Right. But I'm just asking you, as people like
15 you of skill in the art in the field use the word detect,
16 would you say that you have detected an SNV mutation in
17 the patient?

18 MS. SRINIVASAN: Objection; outside the scope.

19 THE WITNESS: I would think you would do a lot more
20 downstream analysis to actually make that determination.

21 BY MS. DURIE:

22 Q Okay. And in your report, in paragraph 103, when
23 you said rare genetic variants are not likely to be
24 detectible below the noise of the error rate, were you
25 talking about detectible in the sequence or detectible in

1 the patient?

2 A Well, I was talking about in the Forshew
3 approach. The way Forshew had designed their experimental
4 method and what they were actually able to find, they
5 could not find variants below 2 percent.

6 Q Well, you could run the Forshew approach, you
7 could figure out that a C in Position 4 is an SNV. And
8 you might be able to see a C in Position 4, right?

9 A For a given target amplicon, sure.

10 Q Sure.

11 A You -- I'm sure you can detect a C in Position 4.

12 Q Okay. And at that point, you would have,
13 according to you, detected that SNV, right?

14 A Well, according to Claim 1 of the '596 patent,
15 that's been my testimony of what is in the claim.

16 Q But I'm not asking -- I'm just saying -- just try
17 focusing on the detection piece. In Forshew, you could
18 determine that a C in Position 4 is an SNV and you could
19 perform sequencing, and you could see a C at Position 4,
20 and you could thereby detect an SNV, right?

21 MS. SRINIVASAN: Objection; incomplete hypothetical.

22 THE WITNESS: So I would have to look. So Forshew did
23 a couple of things in this paper. One is looking for
24 known variants. One was not looking for known variants.
25 So in this context, I'm not sure.

1 But what I have testified, the detection is the
2 same either in the sequencing world or in the realm of
3 Claim 1 of the '596 with respect to calling bases. Now,
4 whether I know that position is going to be a C or not in
5 Forshaw, I don't know.

6 BY MS. DURIE:

7 Q Okay. But you would agree that you can apply the
8 Forshaw technique in a circumstance where you know the
9 base and call the base and identify, according to you, an
10 SNV, right?

11 A I would have to think about the Forshaw method.
12 I haven't -- I haven't thought about Forshaw in a while --

13 Q Well, what is it -- if all you need to do is know
14 the position, know what you expect to see, and do
15 sequencing, and see whether you get a C in that position,
16 why doesn't Forshaw let you do that?

17 A Well, it depends on how Forshaw designed the
18 experiment, whether you can -- it's -- you're able to do
19 that or not. And like I said, Forshaw did it -- several
20 different types of sequencing.

21 Q So you agree, Forshaw did targeted amplification,
22 right?

23 A I think that's one of the methods that they did.

24 Q Okay. So when Forshaw did targeted
25 amplification, isn't it -- if you're doing targeted

1 amplification and you're doing sequencing, isn't it the
2 case that you will be able to perform a sequencing
3 operation, and some percentage of the time you're going to
4 get a C in the position in which C corresponds to a
5 mutation?

6 MS. SRINIVASAN: Objection; incomplete hypothetical.

7 THE WITNESS: I guess if we're thinking about a single
8 amplicon. Because I do know that Forshaw relied on
9 singleton PCR.

10 So if we want to talk about single PCR and you do
11 targeted PCR, you would know the start and stop sites if
12 you know a mutation, where it exists, and I don't quite
13 remember whether they were sequencing amplicons to do de
14 novo detection, or they were actually looking for known --
15 that part, I actually don't remember in Forshaw.

16 BY MS. DURIE:

17 Q Okay. But posit that they were looking for known
18 mutations. You would be able to apply that approach in
19 order to detect SNVs if you got a -- if you saw C where
20 you expected to see a C, right?

21 A Well, I would agree with the premise that an
22 amplicon will have defined start and stop sites. You will
23 sequence it. If you know where the mutation is, the
24 detector should be able to detect at that given cycle
25 whether a normal base has been incorporated or whether a

1 mutant base has been incorporated.

2 Q And therefore should be able to detect whether
3 there's an SNV?

4 A Well, again, I don't know whether Forshew did
5 that or not. I'm just saying if it was set up that way,
6 you should be able to do that.

7 Q So turn to page 58, and I want to ask you about
8 paragraph 105, which starts on page 57.

9 A Okay. If I can have one look.

10 Q Yeah.

11 A Okay. Thank you.

12 Q Okay. Now, the top of page 58, you talk about
13 the fact that SNVs associated with a particular cancer are
14 present at relatively low levels, and then you say,
15 Consequently, the sequencing workflow errors need to be
16 detected and corrected to identify rare genetic variants
17 at the targeted loci.

18 Is there a difference in your mind between
19 identifying rare genetic variants and detecting rare
20 genetic variants?

21 A Well, I don't think I'm expressing an opinion
22 regarding whether identifying and detecting are the same
23 thing or not. This is actually in the context of Claim 1
24 of the '454 patent, and in the context of sequencing a
25 loci 50,000 times or more. And the point I'm making here

1 in the Forshew method, it would just result in detecting
2 more errors and not being able to detect variants in the
3 Forshew method.

4 So I think this is a little bit different than
5 what's described in Claim 1 of the '596 patent.

6 Q You said that the point you are making is that in
7 the Forshew method, it would just result in detecting more
8 errors and not being able to detect variants.

9 What do you mean by not being able to detect
10 variants?

11 A So in the block quote in paragraph 104, Forshew's
12 talking about analyzing hot spot mutations within several
13 cancer genes. And so he doesn't know any of the positions
14 of any of the SNVs that are present, and that would be
15 considered more of a de novo mutation discovery. And in
16 that realm, it is -- the errors really will mask whether
17 hot spot mutations are present or not.

18 Q Okay. If you pull out Forshew, that's Exhibit 6,
19 and turn to page 3. You see at the top of page 3 there
20 are results for targeted deep sequencing?

21 A Yes.

22 Q So that would be the analysis where you know
23 ahead of time what you're looking for, right? That's what
24 makes it targeted?

25 A That's correct. But the block quote I was

1 relying on is actually on page 1 of Forshaw, which is a
2 different sequencing approach that Forshaw applied.

3 Q So what you quoted is from -- because you said
4 page 1, the second paragraph, right?

5 A On the right-hand side.

6 Q And it talks about fragmenting the DNA, and then
7 it says partway down -- you don't have it bolded and
8 italicized in your report, but it says, Various methods
9 have been optimized to detect extremely rare alleles and
10 can assay for predefined or hot spot mutations, right?

11 A That's correct. And those sites are not next
12 generation sequencing methods.

13 Q And then it talks about the limitations of those
14 methods, right?

15 A Correct. Because you look at one or a few loci.

16 Q Right. And then it talks about identifying
17 mutations across sizeable genomic regions has been more
18 challenging, right?

19 A Correct.

20 Q And then if we look at the actual paper from
21 which you pulled this section, it continues immediately
22 below that and it says, In response, we describe a tool
23 for noninvasive mutation analysis on the basis of
24 tagged-amplicon deep sequencing TAm-Seq.

25 And it goes on to talk about the TAm-Seq

1 protocol, right?

2 A Correct.

3 Q And then immediately after that, it sets forth
4 the results and it talks about the results of targeted
5 deep sequencing, right?

6 A That's correct.

7 Q Okay. Now, going back to your discussion on
8 page 58 of your declaration, when you said these
9 sequencing workflow errors need to be detected and
10 corrected to identify rare genetic variants at the
11 targeted loci, does that statement also apply to the
12 targeted deep sequencing that is discussed in Forshaw?

13 A Can you repeat your question, please?

14 Q Sure.

15 Does that sentence at the top of page 58 apply to
16 the targeted deep sequencing that is discussed in Forshaw?

17 A Well, I think it does apply to Forshaw because
18 Forshaw was unable to detect variants below 2 percent
19 using their methods.

20 Q And when you say Forshaw was unable to detect
21 variants at below 2 percent, you are referring to the
22 sensitivity of the assay?

23 A Sensitivity defined as at what level can I detect
24 an SNV mutation.

25 Q Well, when you say at what level can you detect

1 it, let's posit that an SNV mutation is present in 1 out
2 of 1,000 of the target loci. Let's say that the error
3 rate of my assay is 1 in 100.

4 I can still detect the SNV mutation, according to
5 you, right?

6 A You would be able to detect the SNV mutation,
7 yes. According to the claim, which doesn't have an error
8 requirement.

9 Q Right.

10 A But you would detect a lot of -- in the general
11 sequencing world, you would detect a lot of noise as well.

12 Q Right. You would detect a lot of noise, but you
13 would still detect the SNV mutation?

14 A You would detect it.

15 Q Okay.

16 A Yeah.

17 Q And if you take a look at your report,
18 paragraph 106, starting about two-thirds of the way down.

19 A If I can just have a moment.

20 Okay.

21 Q So you say, A substantial increase in the
22 sequencing workflow noise would further obfuscate the
23 detection of rare mutations, making it much harder to
24 identify such mutations.

25 An increase in sequencing workflow noise doesn't

1 necessarily make it more difficult to detect rare
2 mutations, does it?

3 A Just so I understand, so detect in the context of
4 the claim language --

5 Q No. As you --

6 A -- or just generally?

7 Q As you understand the meaning of detect, the
8 ordinary meaning of detect.

9 A Well, again, I -- I've used detect in the
10 sequencing process of identifying which base is present at
11 a given location based on the cycle of the SBS method.
12 That's the way I'm using detect, and if you know what
13 you're looking for, you're able to detect an SNV mutation.

14 Now, in the grand world, and maybe that's what
15 you're asking, I would use detect -- I've used detect as
16 analogous to base calling, but not necessarily being able
17 to detect an SNV mutation because I may not know it's
18 there. So I think it depends on the circumstances.

19 Q So in common -- in common parlance, to detect an
20 SNV mutation would be to know it's there?

21 MS. SRINIVASAN: Objection; misstates testimony.

22 THE WITNESS: By design, by identifying it in advance
23 in a biopsy sample, by defining loci that have my SNV
24 mutation, by designing targeted multiplex PCR primers that
25 target my SNV mutation, I would be able to know where it

1 is under those circumstances.

2 BY MS. DURIE:

3 Q Okay. But, again, I'm not asking about the
4 specifics of how you do it. But just in general, would
5 you agree that to detect an SNV mutation means to know
6 that it's there?

7 MS. SRINIVASAN: Objection; vague.

8 THE WITNESS: No.

9 BY MS. DURIE:

10 Q Okay. And so in your view, you can detect an SNV
11 mutation without knowing that it's there?

12 A No. I guess the way I'm thinking of this, I
13 don't know whether -- I know at a given position I expect
14 to see an SNV mutation. When I take a plasma sample from
15 a patient and I sequence by targeted multiplex PCR, I
16 actually don't know whether it's going to be there or not.
17 If it's there, then I can assess the cancer's coming back.
18 If it's not there, the survival rate's going to be a lot
19 longer.

20 I don't know whether it's there or not, but I do
21 know that I have found it once, and I'm looking for it.

22 Q So I think my question was a little bit
23 different.

24 In order to detect an SNV mutation, at the point
25 in time when I am detecting it, do I need to know it's

1 there?

2 MS. SRINIVASAN: Objection; vague.

3 THE WITNESS: Under the claim, under Claim 1 of the
4 '596 patent designed in that way, I know there's a
5 possibility it can be there. I know that's the location
6 I'm looking for, and I'm using the sequence -- sequencing
7 process to tell me whether the SNV mutation is present or
8 not.

9 BY MS. DURIE:

10 Q But just in general, in terms of ordinary usage
11 by experts like you in the field, if I say I have detected
12 an SNV mutation, does that mean that I know there is an
13 SNV mutation there?

14 MS. SRINIVASAN: Same objection.

15 THE WITNESS: That's too broad to answer, and the
16 reason is, for example, there's lots of SNV mutations that
17 are well characterized and known in the field. There are
18 others that you may think but not necessarily true.

19 BY MS. DURIE:

20 Q So going back to your report, a substantial
21 increase in the sequencing workflow noise would further
22 obfuscate the detection of rare mutations. An increase in
23 sequencing workflow noise doesn't obfuscate detection of
24 rare mutations, does it?

25 A Well, we've used examples where I'm expecting two

1 outcomes. I'm expecting a normal base or I'm expecting an
2 SNV mutated base. And because of sequencing errors, I get
3 something different that could obfuscate the ability to
4 know whether there's an SNV mutation there or not because
5 I'm not getting what I expect.

6 Q All right. Let's take a short break.

7 A Okay.

8 THE VIDEOGRAPHER: Okay. We are going off the record.
9 The time is 12:43 p.m.

10 (Recess taken.)

11 THE VIDEOGRAPHER: We are back on the record. The
12 time is 12:54 p.m.

13 BY MS. DURIE:

14 Q Let me have marked as the next exhibit a copy of
15 Dr. Metzker's deposition transcript dated September 26,
16 2023.

17 (Whereupon Deposition Exhibit 7 was
18 marked for identification.)

19 BY MS. DURIE:

20 Q Dr. Metzker, I'd like to ask you about your prior
21 testimony that appears at the bottom of page 62 and the
22 top of page 63 of your September 2023 deposition. So at
23 the bottom of page 62, you were asked the following
24 question and you gave the following answer:

25 Question: I think I was asking about something

1 different. I was asking about how the variants that are
2 in the sequencing data from the cell-free DNA are
3 identified. Do you know how that's done?

4 And your answer was: Well, my understanding
5 based on the public documents is they used high-throughput
6 sequencing to generate sequencing reads, and then there's
7 a bioinformatic pipeline to identify whether the variants
8 that are in the assays are detected or not.

9 Now, that was a question that you were asked
10 about RaDaR, correct?

11 A I believe that's correct.

12 Q Okay. And you were talking here about a targeted
13 amplification approach, right?

14 A Right. I think I was being asked about TAm-Seq,
15 and my answer is based on whatever public documents I had
16 at the time.

17 Q Okay. And so in your answer, you said
18 high-throughput sequencing was used to generate sequencing
19 reads. That's what gives you that fluorescent signal,
20 right?

21 A Well, it's the process of going through each
22 cycle, building the sequence reads.

23 Q Right. But the sequence reads, that's calling
24 the base, right?

25 A It's calling the bases. So, for example, if

1 Illumina has a 150 base pair cycle, it will have a read
2 length of 150 bases, and we would call that a 150
3 nucleotide read.

4 Q Okay. And at the point in time in TAm-Seq when
5 you have that sequence read, you have a base call as to
6 the base, right?

7 A For each position, you have a base call.

8 Q Right. And so in the TAm-Seq system, this is
9 targeted amplification. You know the position of interest
10 for the variant in question, right?

11 A I believe that's correct for TAm-Seq.

12 Q Okay. You know what the variant would be, right?

13 A I believe that's correct.

14 Q And you have a signal that allows you to
15 determine the base that you have at that position, right?

16 A Depending on the polymerase incorporating a given
17 nucleotide, there would be a fluorescent signal associated
18 with that, and that's what is detected by the sequencer.

19 Q Okay. So at the point that you say they use
20 high-throughput sequencing to generate sequence reads, at
21 that point, you have a sequence read that, according to
22 your testimony today, is sufficient to detect an SNV,
23 right?

24 A And in the TAm-Seq method, yes, it would be
25 sufficient to detect the presence or absence of an SNV

1 mutation at that particular position because that's what
2 they're looking for.

3 Q But in your prior testimony, you said, And then
4 there's a bioinformatic pipeline.

5 That bioinformatic pipeline takes the output of
6 that sequencing process, right?

7 A Well, I explained there's a bioinformatic
8 pipeline to identify whether the variants that are in the
9 assays are detected or not. And I think here, I'm
10 explaining kind of the end result because RaDaR will
11 report ctDNA present or ctDNA not present.

12 Q Okay. That's right. But what you say in your
13 answer -- let's just sort of break it down. You say, And
14 then there's a bioinformatic pipeline.

15 So you're talking about a bioinformatic pipeline
16 that takes the output from the sequencing process, right?

17 A Yes.

18 Q Okay.

19 A It would take the read data that already has SNV
20 mutations called and do a downstream analysis.

21 Q Right. And what you say in your prior testimony
22 is that there's a bioinformatic pipeline to identify.
23 That means that bioinformatic pipeline is being used to
24 identify, right, that's what you meant?

25 A Well, what I meant, and I'm -- again, this is

1 based on -- I think in this time period, I had very little
2 public documents, so I'm only relying on what I had at the
3 present time, but I think what I'm trying to explain is
4 the end result of the RaDaR assay of whether ctDNA is
5 present or not present.

6 Q Well, you say there's a bioinformatic pipeline to
7 identify whether the variants that are in the assays are
8 detected or not.

9 So your testimony today is that those variants
10 are detected from the sequence, as a function of the
11 sequence reads themselves, right?

12 A Well, in the context of Claim 1 of the '596,
13 that's been my testimony. I think here, this is a little
14 different because I'm generally talking about the output
15 of the RaDaR assay and what it would report to a clinician
16 or a patient or things like that.

17 Q And so it is your understanding that in the
18 context of reporting results, the variants are the --
19 strike that.

20 Is it your understanding that in the context of
21 reporting results in the RaDaR assay, variants are
22 detected by the bioinformatic pipeline?

23 A No. The variants are detected in the sequencing
24 process, as I've described -- not -- I think I'm pretty
25 consistent in Claim 1 of the '454 patent as well. I think

1 what I'm explaining here is the end result that would be
2 reported to a patient or a clinician of whether they have
3 been able to -- with some probability -- and, again, I
4 have very limited public documents -- of whether they're
5 able to detect or not the presence of ctDNA.

6 Q Well, but that's not what you said in your
7 answer. In your answer, you talked about whether the
8 variants were detected or not, right? Variants refers to
9 SNVs?

10 A They do, and the RaDaR -- as I understand it,
11 the RaDaR -- just similar to Signatera, they actually use
12 a combination of variants to get to this end result of
13 whether ctDNA is detected or not. So I'm not trying to
14 explain here that variant detection is happening in the
15 bioinformatic pipeline. It's already been detected in the
16 sequencing process.

17 But I don't disagree there's downstream analysis
18 to get to the end result.

19 Q So you said that there's a bioinformatic pipeline
20 to identify whether the variants are detected, and now
21 you're saying the variants already had been detected and
22 you did not need the bioinformatic pipeline to identify
23 that, right?

24 A That's not what it says. It says to identify
25 whether variants that are in the assays are detected or

1 not. I am talking about the end result of what is
2 reported to the patient or the clinician.

3 Q Right. But you said there's a bioinformatic
4 pipeline to identify, right?

5 A Those are my words, but I'm explaining the
6 context of what I meant when I gave that answer.

7 Q So do you stand by the assertion that the
8 bioinformatic pipeline is what identifies whether the
9 variants that are in the assay are detected?

10 A No. That's not what that answer says at all.
11 It's whether the variants that are in the assays are
12 detected or not, meaning the end result of whether ctDNA
13 is present in the sample or not. That's the way I was
14 trying to explain that answer.

15 Q Well, you said a bioinformatic pipeline to
16 identify. You're saying the bioinformatic pipeline
17 identifies something, right?

18 A The end result is the detection or nondetection
19 of ctDNA.

20 Q Not asking about the end result. I'm asking
21 about the bioinformatic pipeline.

22 In your answer, you said there's a bioinformatic
23 pipeline to identify. You were saying that the
24 bioinformatic pipeline identifies something, right?

25 A Yes.

1 Q Okay. And what the bioinformatic pipeline
2 identifies in your answer is whether the variants are
3 detected, right?

4 A No, that's not what it says. You're not reading
5 that correctly. It says whether the variants that are in
6 the assays are detected or not.

7 Q Okay. So the bioinformatic pipeline identifies
8 whether the variants that are in the assays are detected.
9 What is the work that the bioinformatic pipeline is doing
10 to make that identification?

11 A That, I actually -- I don't know the details. I
12 don't think that has ever been disclosed by NeoGenomics.
13 I was basing this on public documents that I had at the
14 time, and I was trying to give a more general answer of
15 what the end result would be from performing the RaDaR
16 test.

17 Q As you sit here today, was the answer that you
18 gave in your deposition at the top of page 63 correct?

19 A Yes. To the best of the -- my ability at the
20 time that I had information in front of me, I think I gave
21 the best answer I could give.

22 Q Different question. As you sit here today,
23 knowing what you know now, was the answer that you gave in
24 your deposition at the top of page 63 correct?

25 A I think it's still correct.

1 Q Okay.

2 A In the context of what I just explained, the end
3 result of whether ctDNA is present or not. I think that's
4 still correct today.

5 Q Okay. But, again, I'm asking specifically with
6 respect to your answer. So as you sit here today, the
7 bioinformatics pipeline to identify, what do you
8 understand that bioinformatic pipeline is doing?

9 A Again, I don't have the details to the
10 bioinformatics pipeline that Neo uses in its assay. Based
11 on what documents I had, I was trying to summarize the
12 best answer I could give.

13 Q Okay. But based on the -- and as you sit here
14 today, based on everything that you know about the
15 NeoGenomics platform, when you said there's a
16 bioinformatic pipeline to identify, what is it that that
17 bioinformatic pipeline is doing?

18 A Again, I don't know the details of the RaDaR
19 bioinformatics pipeline because as far as I know, they
20 haven't been disclosed in this case.

21 Q But do you stand by the proposition that what you
22 understand is that there is a bioinformatic pipeline to
23 identify whether the variants that are in the assays are
24 detected or not?

25 A Yes.

1 Q Okay. And so the bioinformatic pipeline has a
2 role in making the determination as to whether the
3 variants that are in the assays are detected or not?

4 A Insomuch and, again, the way I understood, the
5 way I answered this question is the end result of whether
6 they will report to a patient or clinician the presence or
7 the absence, the detection or no detection of ctDNA, which
8 is kind of the end result of why you would do the RaDaR
9 assay.

10 Q You didn't say whether ctDNA is detected or not.
11 You said whether the variants are detected or not, right?

12 A Well, I -- no. Again, whether the variants that
13 are in the assays are detected or not.

14 Q And that means the SNVs, right?

15 A Yeah, no. I agree that the SNVs need to be
16 detected as part of the bioinformatics pipeline, but they
17 are detected on the sequencing process. There's other
18 analyses that get performed to get down to the final
19 answer.

20 Q The sequencing process and the bioinformatics
21 pipeline are two different things, right?

22 A I would agree with that.

23 Q Okay. And the variants that are in the assays,
24 that's SNVs, right?

25 A I think that's right. I think they only look at

1 SNVs.

2 Q Okay. So there's a bioinformatics pipeline to
3 identify whether SNVs are detected or not. That was your
4 testimony?

5 A There's a bioinformatics pipeline to identify
6 whether variants that are in the assays are detected or
7 not. That's my testimony.

8 Q Okay. And variants that are in the assays,
9 that's SNVs, right?

10 A I would agree the variants in the assays are
11 detected SNVs.

12 Q Okay. So we could say that what you said is,
13 there's a bioinformatics pipeline to identify whether the
14 SNVs are detected or not?

15 MS. SRINIVASAN: Objection; mischaracterizes
16 testimony.

17 THE WITNESS: Well, again, the detected or not, I
18 understood the way I was answering the question and if I
19 omitted ctDNA because this is the end result of the RaDaR
20 assay, this is what you report to the patient or the
21 clinician.

22 BY MS. DURIE:

23 Q What is the role of the bioinformatics pipeline
24 in identifying whether SNVs are detected or not?

25 A Again, I'll say I have not seen detailed

1 documents of the bioinformatics pipeline from NeoGenomics.
2 I can imagine there may be some error correction. There
3 may be some -- there may be other ways of looking at the
4 data to determine whether the SNVs that were detected are
5 actual results of ctDNA being measured in the patient.

6 But I'm speculating because I haven't seen those
7 documents.

8 Q Okay. But what you were referring to in your
9 answer when you said there's a bioinformatic pipeline to
10 identify whether the variants that are in the assays are
11 detected or not was things like error correction that are
12 happening in the bioinformatic pipeline in order to
13 determine whether SNVs are present?

14 MS. SRINIVASAN: Objection; misstates testimony.

15 THE WITNESS: That's not what I testified in
16 September. You asked me -- I said, I don't know what's in
17 the pipeline. I haven't seen any documents. I was
18 speculating. If I had to guess, probably some steps like
19 that may be performed. They may not be performed. I
20 actually don't know.

21 BY MS. DURIE:

22 Q When you referred in your answer to the fact that
23 there was a bioinformatic pipeline to identify whether the
24 variants that are in the assays are detected or not, I
25 understand you didn't know the details of how the

1 bioinformatic pipeline worked, but what was it that you
2 had in your mind as to what that bioinformatic pipeline
3 might be doing?

4 A I don't think I had something in my mind. I -- I
5 know that -- I think Neo has described having a
6 bioinformatics pipeline, and so based on the documents
7 that I've seen, I was answering the question. I've seen
8 reference to a bioinformatic pipeline, but the details, I
9 don't know.

10 Q Okay. You would agree that the bioinformatics
11 pipeline results in a determination as to whether SNVs are
12 present?

13 A No. I think the bioinformatic pipeline end
14 result is characterizing whether ctDNA has been detected
15 or not detected in the plasma sample.

16 Q And is part of that to determine whether SNVs are
17 present?

18 A Well, SNVs are detected in the sequencing
19 process. Then there's some analysis -- downstream
20 analysis in the bioinformatic pipeline. I don't know
21 what's happening in the RaDaR system. I think the end
22 result is what they report to the patient or the
23 clinician.

24 Q Okay. Do you have an understanding as to at what
25 point in the RaDaR process there is a determination as to

1 whether SNVs are present?

2 A I do not know that SNVs are detected on the
3 sequencing -- during the sequencing process. I don't have
4 detailed information of other steps that are part of the
5 downstream analysis for the bioinformatics pipeline.

6 Q Okay. So you don't know where in the process
7 SNVs are determined to be present?

8 A Well, again, that's not even my language. I've
9 said they're detected in the sequencing process.

10 Q Right.

11 A There is a bioinformatics pipeline and there is
12 then a final result, and I was kind of characterizing that
13 in general terms.

14 Q Right. But my question is specifically you
15 understand what it means to determine that an SNV is
16 present, right?

17 A Well, I can imagine what it means. With respect
18 to the NeoGenomics bioinformatics pipeline, I have no
19 opinion on that.

20 Q Okay. And the input to the bioinformatics
21 pipeline is the sequencing reads, right?

22 A I believe that's correct. I think they come in
23 maybe at a FASTQ file level.

24 Q So the determination that is made in the
25 bioinformatics pipeline is a determination that is done

1 from the sequencing reads as an input?

2 A Well, I think they're analyzing the -- so a FASTQ
3 file is where the base calls and the quality scores are in
4 a format that can then be further analyzed. For example,
5 mapped to a reference genome to create a BAM file. Other
6 things can happen, but the actual base calls, including
7 SNV mutations, are already determined in the sequence
8 read.

9 Q Okay. But I -- just to be clear, the output of
10 the bioinformatics pipeline, what you refer to here, that
11 output comes from an analysis of the sequencing reads,
12 right?

13 A I don't understand what you mean an analysis of
14 the sequencing reads. The sequencing process has created
15 the sequence read.

16 Q Right.

17 A So --

18 Q The sequence read is then input into the
19 bioinformatics pipeline, which performs an analysis on it,
20 right?

21 A There -- a sequence read, as I understand it,
22 gets converted into what is called a FASTQ file -- those
23 are all capital letters -- and then it can go into a
24 bioinformatics pipeline, and there's lots of different
25 things that can happen in the bioinformatics pipeline.

1 Q But --

2 A And I don't know the details for the NeoGenomics
3 bioinformatics pipeline.

4 Q But do you agree that the analysis that is done
5 is an analysis -- a determination that is done from the
6 sequencing reads that were generated as part of the
7 sequencing process?

8 A Well, no. I -- I understand that FASTQ files
9 that have all the base calling information and the quality
10 scores are fed into the bioinformatics pipeline. The
11 actual steps that are performed, I don't know. I do know
12 there's an end result, and I think that's what I was
13 trying to explain, that there's a determination of whether
14 ctDNA is detected or not detected.

15 Q Okay. And there's also, as you said in your
16 earlier answer, a determination as to whether the variants
17 that are in the assays are detected or not, right?

18 A Well, here, I'm explaining how they identify
19 which SNVs to go into their RaDaR assays. If you're --
20 if -- I'm sorry. Maybe I misread, but I'm looking at
21 page 62 starting at line 10 to line 21 --

22 Q We're actually on page 63. The answer is at
23 lines 3 through 7.

24 A Oh, so we're on the same question and answer.

25 Q Yeah. And --

1 A I apologize. You said the previous answer.

2 Q And -- right. I think we'll wrap this up in a
3 sec.

4 But in the answer that you gave at your
5 deposition in September, you were indicating that the
6 output of the bioinformatics pipeline includes an
7 identification of whether the variants that were in the
8 assays are detected or not, right?

9 A Well, I mean, I can read my answer. It says,
10 Then there's a bioinformatic pipeline to identify whether
11 the variants that are in the assays are detected or not.

12 And I've tried to give you my best answer of what
13 that meant, and at the time, I had very -- I had only
14 public documents, and that was the best answer I could
15 get.

16 Q Right. And -- but I just -- to be clear, I want
17 to understand, what that means is that, to your
18 understanding as you sit here today because you've adopted
19 this answer, one of the outputs of the bioinformatics
20 pipeline is whether the variants, the SNVs, have been
21 detected?

22 A I disagree with that. If it's the output of the
23 bioinformatics pipeline, the output is whether ctDNA is
24 detected or not. That is the output.

25 Q So you say in your answer variants, right, the

1 variants in the assays?

2 A I do.

3 Q So the bioinformatics pipeline identifies
4 whether -- if that pipeline identifies whether the
5 variants in the assays are detected, right?

6 A I can read what I answered. You asked me what it
7 means to me, and I'm trying to explain what -- the way I
8 thought of it at that time I was giving that answer.

9 Q Okay. Good.

10 MS. DURIE: I don't have any of further questions.

11 MS. SRINIVASAN: Okay. I have a couple of redirect
12 questions.

13 EXAMINATION

14 BY MS. SRINIVASAN:

15 Q Dr. Metzker, do you recall counsel asking you
16 about testimony from your September 26, 2023, deposition
17 on pages 62 and 63 of the transcript?

18 A Yes.

19 Q And I believe you testified that you were relying
20 on publicly available materials; is that correct?

21 A Yes.

22 Q Okay. Can you tell me what public -- what
23 publicly available materials you were relying upon?

24 A That's a good question. It would have been
25 probably papers that were published such as Forsheew 2012,

1 Gayle 2018, and there may have been a few documents from
2 Neo, but I don't think they were very detailed.

3 Q And I believe you testified that you said, I
4 think I was being asked about TAm-Seq.

5 Do you recall that testimony in relation to this
6 line of questioning?

7 A Yes.

8 Q And can you say whether or not RaDaR uses
9 TAm-Seq?

10 A Not fully. It only uses part of it.

11 Q And do you recall at the time when you gave this
12 testimony what version of RaDaR you were being asked
13 about?

14 A This would have been RaDaR 1.0.

15 Q And are you aware of what is the current version
16 of the accused assay in this case?

17 A I have a general idea.

18 Q And have you seen what the bioinformatics
19 pipeline is associated with the version that's currently
20 asserted in this case?

21 A I have not.

22 Q And do you recall counsel asking you today about
23 the difference between Dr. Lennon's construction for the
24 term at issue, which is performing high-throughput
25 sequencing of the amplified DNA comprising the plurality

1 of target loci to obtain sequence reads wherein an SNV
2 mutation that is present in less than or equal to
3 0.015 percent of the cell-free DNA having the SNV locus is
4 detected from the sequence reads?

5 A Generally, yes.

6 Q Do you recall counsel asking you about whether or
7 not you recall the difference between Dr. Lennon's
8 construction for that term and your construction?

9 A Yes.

10 Q And what evidence, if any, did you rely upon in
11 interpreting the meaning of that term?

12 A The claim language and the specification of the
13 '596 patent.

14 Q And did you find that that evidence supported any
15 of Dr. Lennon's opinions for that term?

16 A It did not.

17 MS. SRINIVASAN: No further questions.

18 FURTHER EXAMINATION

19 BY MS. DURIE:

20 Q So you said the evidence didn't support
21 Dr. Lennon's opinions. How do you understand the
22 substance of Dr. Lennon's construction to be different
23 from yours?

24 A Well, he was relying in the specification on
25 embodiments that are not claimed in the '596 patent.

1 Q Not my question.

2 How do you understand the substance of his
3 construction to be different from yours?

4 A Well, I think he's trying to provide a
5 construction that the sequence reads are analyzed outside
6 of the sequencing process. I think that's what he's
7 trying to do, and I don't agree with that. I think the
8 detection is happening within the sequencing processes set
9 forth in my reports.

10 Q So Dr. Lennon's construction is that the SNVs are
11 determined to be present, right?

12 A I think that's correct, yeah.

13 Q Okay. And the construction that you are
14 offering, does that mean that the SNVs have not been
15 determined to be present?

16 MS. SRINIVASAN: Objection; vague.

17 BY MS. DURIE:

18 Q Strike that. Let me ask that slightly
19 differently.

20 Does your construction not require that the SNVs
21 have been determined to be present?

22 A That's a double -- is that a double negative?
23 Can you repeat that again, please? Sorry.

24 Q Sure.

25 So under your construction, have the SNVs -- does

1 the claim require that the SNVs have been determined to be
2 present?

3 A Under my construction?

4 Q Yeah.

5 A No.

6 Q And so what is the difference in your mind --
7 well, strike that.

8 What else would have to be required in your mind
9 for the SNVs to be determined to be present?

10 A So based on what Dr. Lennon has described, it
11 appears he wants to take the read, and then map it to a
12 reference genome, and -- or compare it to something else
13 to make a determination that the SNV is present or not.
14 So he wants to push the analysis downstream before
15 determining the presence of an SNV mutation.

16 Q And so as you understand it, the difference of
17 opinion between yourself and Dr. Lennon is whether the
18 claim requires that there be some analysis in order to
19 make a determination as to whether the SNV is present or
20 not?

21 A I think the claim requires detecting the presence
22 of the SNV mutation in the sequencing process. I think
23 that's what the claim requires.

24 Q I understand. You said that a bunch of times. I
25 want to understand the difference between you and

1 Dr. Lennon.

2 So the thing that you are saying is incorrect
3 about Dr. Lennon's construction is that he is saying some
4 analysis needs to be done in order to make a determination
5 about whether there is or isn't an SNV that is present,
6 right?

7 A Correct.

8 Q Okay.

9 A So my understanding is Dr. Lennon wants to
10 rewrite the claim language, such as the detection or the
11 determination of the presence of an SNV mutation happens
12 downstream and outside of the sequencing process. I think
13 he wants to rewrite the claim so that construction can
14 hold, and I disagree with that.

15 Q Well, you say --

16 MS. SRINIVASAN: Counsel, I think we're out of time.

17 MS. DURIE: Well, I'm following up on the questions
18 that you asked on your redirect.

19 MS. SRINIVASAN: But I think it's still four hours
20 notwithstanding the redirect that I did.

21 MS. DURIE: Well, I don't agree that your time counts
22 against me, and I think I can follow up on it.

23 MS. SRINIVASAN: I started it when you started asking.
24 I didn't count my time.

25 MS. DURIE: That's fine. We can be done. We can be

1 done. It's fine.

2 MS. SRINIVASAN: Okay.

3 THE VIDEOGRAPHER: Okay to go off the record?

4 MS. DURIE: Yes.

5 THE VIDEOGRAPHER: We are going off the record. The
6 time is 1:26 p.m.

7 (WHEREUPON THE DEPOSITION WAS
8 CONCLUDED AT 1:26 P.M.)

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1 Please be advised I have read the
 2 foregoing deposition, pages 1 through
 3 173, inclusive.

4 I hereby state there are:

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(Check one) _____ no corrections

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DR. MICHAEL METZKER

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1 WITNESS'S CHANGES OR CORRECTIONS

2

3 NOTE: If you are adding to your testimony, print
4 the exact words you want to add. If you are
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6 words you want to delete. Specify with "Add"
7 or "Delete" and sign this form.

8

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9

Case Title: NATERA V. NEOGENOMICS

Date of Deposition: FEBRUARY 11, 2025

10

I, _____ have
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11 Page Line Change/Add/Delete

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REPORTER'S CERTIFICATE

I, Christa Yan, CSR No. 14316, do hereby declare:

That, prior to being examined, the witness named in the foregoing proceeding was by me duly sworn pursuant to Section 30(f)(1) of the Federal Rules of Civil Procedure, and the proceeding is a true record of the testimony given by the witness as accurately as possible. That said proceeding was taken down by me stenographically at the time therein named and thereafter reduced to text under my direction.

--- That said witness was requested to review the transcript and make any changes to the transcript as a result of that review pursuant to Section 30(e) of the Federal Rules of Civil Procedure.

--- No changes have been provided by the witness during the period allowed.

--- The changes made by the witness are appended to the transcript.

--- No request was made that the transcript be reviewed pursuant to Section 30(e) of the Federal Rules of Civil Procedure.

I further declare that I have no interest in the event of the action. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

WITNESS my hand this 12th day of February 2025.

Christa Yan

Christa Yan, CSR NO. 14316



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