

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,
v.
Personalis, Inc.,
Patent Owner.

IPR2023-00224 U.S. Patent No. 11,384,394
IPR2023-00317 U.S. Patent No. 11,408,033

DEPOSITION OF DR. JOHN QUACKENBUSH
APPEARING REMOTELY
February 1, 2024
10:00 a.m.

Reported by: Eileen Mulvenna, CSR/RMR/CRR

DIGITAL EVIDENCE GROUP
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Washington, D.C. 20036
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1 REMOTE DEPOSITION of DR. JOHN QUACKENBUSH,
2 a witness on behalf of Foresight Diagnostics in the
3 above-titled action, held on Thursday, February 1,
4 2024, commencing at approximately 10:00 a.m., before
5 Eileen Mulvenna, CSR/RMR/CRR/RDR, Certified
6 Shorthand Reporter, Registered Merit Reporter,
7 Certified Realtime Reporter, Registered Diplomate
8 Reporter, and Notary Public of the State of New
9 York.

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1 A P P E A R A N C E S:

2

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19 ALSO PRESENT:

20 Stephen Moore, Esquire (Personalis)

21 Henry Marte, Exhibit Technician

22

1 I N D E X

2 WITNESS EXAMINATION BY PAGE

3 DR. JOHN QUACKENBUSH

4 MR. LUMAN 12

5 MR. KRAUSE 292

6

7 E X H I B I T S

8 PAGE

9 Exhibit 1002 No Bates Numbers, 149

10 Development of Personalized

11 Tumor Biomarkers Using

12 Massively Parallel

13 Sequencing, Cancer

14 Genetics, 2010, Leary et

15 al.

16 Exhibit 1006 No Bates Numbers, Targeted 62

17 enrichment of genomic DNA

18 regions for next-generation

19 sequencing, Briefings in

20 Functional Genomics, Vol.

21 10, No. 6, 2011, Mertes et

22 al.

1 (Continued)

2 E X H I B I T S PAGE

3 Exhibit 1008 No Bates Numbers, Cancer 273

4 Genome Scanning in Plasma:

5 Detection of

6 Tumor-Associated Copy

7 Number Aberrations,

8 Single-Nucleotide Variants,

9 and Tumoral Heterogeneity

10 by Massively Parallel

11 Sequencing, Clinical

12 Chemistry 59:1, 2013, Chan

13 et al.

14 Exhibit 1020 No Bates Numbers, 82

15 Declaration of John

16 Quackenbush, Ph.D. in

17 Support of Petition for

18 Inter Partes Review,

19 IPR2023-00317

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22

1 (Continued)

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3

E X H I B I T S

PAGE

4

Exhibit 1030

No Bates Numbers,

16

5

Noninvasive Identification

6

and Monitoring of Cancer

7

Mutations by Targeted Deep

8

Sequencing of Plasma DNA,

9

Tim Forshew et al., Science

10

Translational Medicine 4,

11

2012, Tim Forshew et al.

12

Exhibit 1033

No Bates Numbers,

90

13

High-Throughput Detection

14

of Actionable Genomic

15

Alterations in Clinical

16

Tumor Samples by Targeted,

17

Massively Parallel

18

Sequencing, Research

19

Article, Wagle et al.

20

Exhibit 1216

No Bates Numbers, Amplicon

22

21

NGS battles begin in

22

earnest - Enseqlopedia

1 (Continued)

E X H I B I T S

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2 Exhibit 1223 No Bates Numbers, 180

3 Deposition of Henry Morrice

4 Furneaux, Ph.D.

5 Exhibit 1225 No Bates Numbers, 15

6 Declaration of John

7 Quackenbush, Ph.D. in

8 Support of Petitioner's

9 Reply to Patent Owner

10 Response, IPR2023-0024 and

11 IPR2023-00317

12 Exhibit 2031 No Bates Numbers, 145

13 Declaration of Henry

14 Morrice Furneaux, Ph.D.

15 Exhibit 2157 No Bates Numbers, 113

16 Gender-Specific Molecular

17 and Clinical Features

18 Underlie Malignant Pleural

19 Mesothelioma, Molecular and

20 Cellular Pathobiology,

21 2015, DeRienzo and

22 Quackenbush et al.

1 (Continued)

2 E X H I B I T S PAGE

3 Exhibit 2158 No Bates Numbers, Exome 124

4 sequencing-based

5 copy-number variation and

6 loss of heterozygosity

7 detection: Exome CNV,

8 Bioinformatics, Vol. 27,

9 No. 19, 2011,

10 Sathirapongsasuti and

11 Quackenbush et al.

12 Exhibit 2166 No Bates Numbers, Detection 141

13 and Diagnostic Utilization

14 of Cellular and Cell-Free

15 Tumor DNA, Annual Review of

16 Pathology: Mechanisms of

17 Disease, 2021, Jonathan C.

18 Dudley and Maximilian Diehn

19 Exhibit 2178 No Bates Numbers, The 31

20 Chicago Manual of Style,

21 Sixteenth Edition, The

22 University of Chicago Press

1 (Continued)

2 E X H I B I T S PAGE

3 Exhibit 2179 No Bates Numbers, The 38

4 American Heritage

5 Dictionary of the English

6 Language Fourth Edition

7 Exhibit 2180 No Bates Numbers, 82

8 Declaration of John

9 Quackenbush, Ph.D. in

10 Support of Petition for

11 Inter Partes Review,

12 IPR2023-002247, U.S. Patent

13 No. 11,408,033

14 Exhibit 2182 No Exhibit Numbers, 170

15 Declaration of John

16 Quackenbush, Ph.D. in

17 Support of Petition for

18 Inter Partes Review,

19 IPR2023-00546, U.S. Patent

20 No. 10,450,611

21

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1 (Continued)

2 E X H I B I T S PAGE

3 Exhibit 2183 No Bates Numbers, Detection 211

4 of Chromosomal Alterations

5 in the Circulation of

6 Cancer Patients with

7 Whole-Genome Sequencing,

8 Diagnostics,

9 www.ScienceTranslationalMed

10 icine.org 28 November 2012

11 Exhibit 2184 No Bates Numbers, Cancer 218

12 detection using

13 whole-genome sequencing of

14 cell free DNA, Oncotarget,

15 August, Vol. 4, No. 8, 2013

16 Exhibit 2185 No Bates Numbers, 255

17 Predicting Radiotherapy

18 Responses and Treatment

19 Outcomes Through Analysis

20 of Circulating Tumor DNA,

21 Seminars in Radiation

22 Oncology, 2015

1 (Continued)

2 E X H I B I T S PAGE

3 Exhibit 2186 No Bates Numbers, Potential 259

4 clinical utility of

5 ultrasensitive circulating

6 tumor DNA detection withx

7 CAPP-Seq, Expert Reviews

8 Mol. Diagn., 2015

9 Exhibit 2187 No Bates Numbers, Accurate 277

10 whole human genome

11 sequencing using reversible

12 terminator chemistry,

13 Nature, 2008, David Bentley

14 et al.

15 Exhibit 2022 No Bates Numbers, Sequencing 174

16 depth and coverage: key

17 considerations in genomic

18 analyses, Nature Reviews |

19 Genetics, 2014, Sims et al.

20

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1 (Witness sworn.)

2 MR. LUMAN: The time is 7:01 Pacific.

3 Good morning. My name is Nate Luman, and I'm
4 going to be taking the deposition today.

5 DR. JOHN QUACKENBUSH,
6 having been duly sworn by Eileen Mulvenna,
7 a Notary Public of the State of New York,
8 was examined and testified as follows:

9 EXAMINATION

10 BY MR. LUMAN:

11 Q. Dr. Quackenbush, can you hear me okay?

12 A. Yes, I can. Can you hear me well?

13 Q. I can.

14 A. Thank you.

15 Q. Would you please state your full name
16 and home address for the record?

17 A. Sure. My name is John, J-O-H-N,
18 Quackenbush, Q-U-A-C-K-E-N-B-U-S-H. And I live at
19 86 Walpole, W-A-L-P-O-L-E, Street in Dover,
20 Massachusetts. The ZIP is 02030.

21 Q. Do you understand that you're under
22 oath today?

1 A. Yes, sir.

2 Q. Is there any reason that you would be
3 unable to give truthful and accurate testimony
4 today?

5 A. No, there is not.

6 Q. So I'll just do the ground rules
7 quickly. I'm going to be asking questions, and the
8 court reporter is taking down my questions and your
9 answers.

10 Do you agree to give verbal responses
11 today?

12 A. Yes, I do. And if I fail to, please
13 remind me.

14 Q. Will do.

15 And I'm going to try to refrain from
16 speaking over you, and I would ask that you would
17 try to refrain from speaking over me.

18 Is that okay?

19 A. I love those ground rules. So yes.

20 Q. Thank you.

21 And if you don't understand a
22 question, please let me know. Otherwise, I'll

1 assume that you've understood my question; is that
2 fair?

3 A. That's fair.

4 Q. Your attorney may object to my
5 questions from time to time, but you'll still need
6 to answer the questions unless you're specifically
7 instructed not to.

8 Do you understand that?

9 A. Yes, that's my understanding.

10 Q. And I'll probably take a break every
11 hour or so, but if you ever need to take a break,
12 please let me know, but just first answer any
13 pending question before we take a break.

14 Is that okay?

15 A. That will be fine with me, yes.

16 MR. LUMAN: So what I'd like to do is
17 make Exhibit 1225 available to
18 Dr. Quackenbush.

19 Henry, can you handle that for us?

20 THE DOCUMENT TECH: No problem.

21 MR. LUMAN: Thank you.

22

1 (Exhibit 1225 , No Bates Numbers,
2 Declaration of John Quackenbush, Ph.D. in
3 Support of Petitioner's Reply to Patent Owner
4 Response, IPR2023-0024 and IPR2023-00317,
5 received and marked.)

6 MR. LUMAN: So let's see. If I
7 understand right, that will go in the Box?

8 THE DOCUMENT TECH: And it is. All
9 you need to do is just refresh, and you
10 should see 1225 up.

11 THE WITNESS: All right.

12 BY MR. LUMAN:

13 Q. Dr. Quackenbush, if you can give me a
14 verbal queue once you've had a chance to download
15 that document, I'd appreciate it.

16 A. I have it downloaded, and it is open.

17 Q. Okay. So, Dr. Quackenbush, is this a
18 copy of the declaration that you submitted in
19 IPR 2023-00224 and 00317?

20 A. Yes, December 22, 2023, in response to
21 Dr. Furneaux's declaration.

22 Q. Thank you.

1 Let's see, would you turn with me to
2 paragraph 56? If you could let me know when you
3 arrive there.

4 A. All right, I'm there.

5 Q. And there's a block quote from the
6 Encyclopedia blog from James Hadfield.

7 Do you see that?

8 A. Yes, Enseqlopedia.

9 Q. Thank you.

10 Now, James Hadfield was one of the
11 coauthors of the Forshaw reference; is that right?

12 A. I don't have the Forshaw reference in
13 front of me, but I will take your word for it.

14 Q. We don't mind looking at the Forshaw
15 reference to verify that.

16 MR. LUMAN: Would you mind making
17 Exhibit 1030 available to Dr. Quackenbush,
18 please.

19 (Exhibit 1030, No Bates Numbers,
20 Noninvasive Identification and Monitoring of
21 Cancer Mutations by Targeted Deep Sequencing
22 of Plasma DNA, Tim Forshaw et al., Science

1 Translational Medicine 4, 2012, Tim Forshaw
2 et al., marked for identification.)

3 THE DOCUMENT TECH: It's coming up.

4 THE WITNESS: All right. It hasn't
5 appeared yet.

6 THE DOCUMENT TECH: Try again.

7 MR. LUMAN: There it is. If you could
8 go to the next page, please.

9 BY MR. LUMAN:

10 Q. And, Dr. Quackenbush, is the James
11 Hadfield who put the Enseqlopedia blog that you
12 quoted in paragraph 56 one of the coauthors of
13 Forshaw, Exhibit 1030 in this case?

14 A. Yes, he is.

15 Q. If you could turn back to paragraph 56
16 of your declaration, please.

17 A. All right.

18 Q. And I'm looking at the -- I mean, the
19 block quote starts with the "Fluidigm Access Array,"
20 and then there's the bold italicized sentences. I
21 want to look at the second bolded italicized
22 sentence that starts with "Microfluidics."

1 Do you see that?

2 A. Yes, I do.

3 Q. So it says, "Microfluidics, emulsion
4 PCR probes and oligo-probes are the different
5 'capture' mechanisms."

6 Do you see that?

7 A. Yes, I do.

8 Q. I wanted to know what the
9 microfluidics refers to. Is that something from the
10 Fluidign Access Array, the RainDance? What is that
11 microfluidics referring to?

12 A. So I don't have the entire
13 Enseqlopedia blog entry here in front of me. So the
14 top of the block quote, he talks about "Fluidigm's
15 Access Array, RainDance's new ThunderStorm, Halo
16 Genomics, MIPs, traditional multiplex PCR are all
17 competition from the in-house kits of Illumina and
18 Life Technologies. The major differences with all
19 the platforms are the way in which multiple loci are
20 captured and amplified."

21 And then I believe when he's talking
22 about microfluidics, emulsion PCR -- so

1 microfluidics, I believe he's referring to
2 Fluidigm's Access Array, possibly RainDance's
3 ThunderStorm. So I'm not sure about Halo Genomics.

4 Emulsion PCR, he might be referring to
5 RainDance. I don't know. I'd have to look more
6 fully at the blog to fully answer that.

7 But he's talking about different
8 PCR-based assays. As he says in the next sentence,
9 "All rely on PCR for amplification and to add to the
10 sequencing platform adapters and bar codes [sic]."

11 Q. And I'm interested in the next part
12 where there's oligo-probes. Are those oligo-probes
13 referring to solution-based hybridization capture
14 probes, or is that referring to something else?

15 A. So I'm not sure I understand your
16 question. It says, "Microfluidics, emulsion PCR and
17 oligo-probes are the different 'capture'
18 mechanisms." So I would believe here that he's
19 referring in general to all the nucleotidic probes
20 like those in PCR, PCR primers, where those are
21 capture probes. He's also referring back to MIPS,
22 which are molecular inversion probes.

1 I'm not sure what Halo Genomics does,
2 but -- and then they're in-house kits from Illumina,
3 Life Technologies. Life Technologies at the time
4 was definitely doing emulsion PCR.

5 So he's trying to distinguish between
6 the three. But, you know, as he states in the next
7 sentence, there is reliance to all of these on PCR.
8 So my interpretation is that the oligo-probes are
9 oligonucleotides that are used to capture the
10 different individual molecules, and that would
11 include PCR probes.

12 Q. So in the context of this blog post
13 and referring to PCR, the oligo-probes would refer
14 to the PCR primers and not solution-based
15 hybridization capture probes; is that fair?

16 MR. KRAUSE: Objection,
17 mischaracterizes testimony.

18 THE WITNESS: So I don't think that's
19 fair. I don't think that's what I would say.

20 As we've discussed previously, capture
21 probes, especially in the context of the '394
22 and '033 patents, have pretty broad

1 definitions, and those broad definitions are
2 consistent with actually what appears in the
3 contemporaneous literature and actually with
4 Dr. West's testimony and Dr. Furneaux's
5 testimony in deposition.

6 So the oligonucleotide probes are
7 simply the oligonucleotides that are used in
8 different capture moieties, which would
9 include, based on the PTAB's claim
10 construction, techniques such as solution or
11 solid phase hybridization, but also the use
12 of PCR capture probes.

13 BY MR. LUMAN:

14 Q. I'm interested in what the
15 oligo-probes in this blog refer to. And I was
16 wondering if your interpretation is that the
17 oligo-probes here include both PCR primers and
18 solution-based hybridization capture probes?

19 A. So would it be possible to provide me
20 with the full blog so that I can review it?

21 Q. Yes.

22 MR. LUMAN: That's Exhibit 1216. Can

1 we make that available to Dr. Quackenbush,
2 please.

3 (Exhibit 1216, No Bates Numbers,
4 Amplicon NGS battles begin in earnest -
5 Enseqlopedia, received and marked.)

6 THE DOCUMENT TECH: It's up.

7 MR. LUMAN: Thank you.

8 THE WITNESS: All right. It's
9 appeared.

10 BY MR. LUMAN:

11 Q. When you've had a chance to review it,
12 can you give me a verbal cue?

13 A. I just have it open now.

14 (Document review.)

15 BY MR. LUMAN:

16 Q. Are you waiting for me, or are you
17 still reviewing, Dr. Quackenbush?

18 A. Oh, I'm still looking at it, just a
19 second. I was just about to ask you to repeat the
20 question, please. Okay.

21 (Document review.)

22 THE WITNESS: So please repeat the

1 question.

2 BY MR. LUMAN:

3 Q. In this blog post, when the author
4 refers to oligo-probes, is he referring to just PCR
5 primers, or is he also referring to solution-based
6 hybridization capture probes?

7 A. So based on what's presented here,
8 it's hard for me to fully conclude the breadth of
9 what he's referring to. He talks about doing PCR
10 and sequencing.

11 I believe Fluidigms Access -- I'd have
12 to -- I don't recall these technologies fully. I
13 think Fluidigms Access Array was a solid state
14 capture assay or maybe -- I don't recall. I don't
15 recall exactly what it was. I did some work with
16 that, but it was a long time ago.

17 We did look at RainDance's technology,
18 and that prepared basically emulsion PCR.

19 Halo Genomics, I'm not familiar with,
20 but I believe he was trying to be -- to the best of
21 my knowledge to understand what he's presenting
22 here, to be inclusive.

1 And since he mentions microfluidics,
2 emulsion PCR, and oligo-probes, I think he's talking
3 about these oligo-probes generally. And that would
4 include not only the solution phase capture that you
5 were referring to, but also potentially solid-phase
6 capture and then varieties or different variations
7 on PCR.

8 MR. LUMAN: If we could take down the
9 exhibit and have paragraph 56 back on the
10 screen, please.

11 BY MR. LUMAN:

12 Q. And so my question is -- well, I'm
13 looking at the sentence that says they have
14 different "capture" mechanisms. And my question
15 would be, what is the different capture mechanism
16 between microfluidics and oligo-probes?

17 A. So saying that they're different
18 doesn't necessarily mean that there aren't shared
19 similarities too, right. So I'd have to look at the
20 individual microfluidics. He may be -- so there are
21 microfluidics techniques that are similar to digital
22 droplet PCR in which you take nucleic acids and

1 solution and then you take PCR-based reagents and
2 you fuse them together in microfluidic channels
3 through which an oil -- oil is flowing, and what you
4 end up doing is creating little droplets that are
5 individual reaction vessels.

6 So it's a technique in which one could
7 do PCR by flowing in PCR reagents. And so the
8 difference is rather than doing it as a multiplex
9 PCR in a single tube, what one is doing is creating
10 little reaction vessels which are often then
11 amplified together in emulsion PCR.

12 Emulsion PCR, as implemented by Life
13 Technologies, used a different approach to create
14 emulsions. But, again, the goal was to try to get
15 single DNA molecules with the appropriate PCR
16 reagents to perform amplification. And I think he's
17 talking about a variety of different oligo-probes.

18 So every single mechanism he refers
19 to, to the best of my understanding -- again, I'm
20 really not familiar with Halo Genomics -- relies on
21 the binding between complementary strands of DNA
22 that could be hybridization capture probes that you

1 were referring to earlier either in liquid -- I
2 guess in this case it would all be liquid phase,
3 unless Access Array had a solid phase component, or
4 PCR capture probes where the PCR primers are serving
5 to capture individual molecules as Dr. West
6 testified they can be used for.

7 Q. And so what are the different capture
8 mechanisms between emulsion PCR and oligo-probes?

9 A. So emulsion PCR is PCR that's
10 performed typically in droplets. The droplets are
11 often in a single tube, but the capture probes in
12 that case would be the PCR primers that are used to
13 amplify the individual molecules.

14 So, you know, the difference might be
15 a multiplex PCR versus an emulsion PCR. I would
16 describe those as different mechanisms, but they're
17 all based on the same underlying base-pair between
18 one or more capture probes and the target molecule,
19 where those capture probes can be hybridization
20 capture probes or PCR capture probes; right?

21 MIPS is a different technology in
22 which essentially two PCR primers are linked

1 together -- or the two PCR probes are linked
2 together, and they bind around a target region.
3 They're all based on complementary base-pairing.

4 So, you know, I guess the differences
5 here, again, are sort of in the details, but the
6 underlying mechanism of all nucleic acid-based
7 capture is this complementary base-pairing.

8 Q. And I see that the word "capture" has
9 quotes around it. What would a person of ordinary
10 skill in the art understand about the meaning of the
11 word "capture" being in quotes?

12 A. So I can't speculate on what
13 Dr. Hadfield was trying to present here, what he was
14 trying to represent by putting quotes around
15 "capture." I can tell you that a person of ordinary
16 skill in the art reading this entire paragraph is
17 that he's simply talking about the growing number of
18 ways that were available to one skilled in the
19 art -- available as commercial platforms to use
20 complementary base-pairing. And, again, there are a
21 variety of different techniques one can use, but to
22 use this complementary base-pairing biological

1 mechanism as a way of targeting specific regions of
2 the genome.

3 And, you know, as we've discussed
4 previously, this is not limited. This could include
5 hybridization-based capture either in liquid phase
6 or solid phase, but could also include the use of
7 PCR capture probes.

8 So, yeah, I'm not sure what
9 Dr. Hadfield was trying to imply here, but as a
10 person of ordinary skill in the art, I see this as
11 something that would be inclusive rather than
12 exclusive.

13 Q. Do you think that -- well, let me ask
14 it this way: Do the quotes inform the reader that
15 Dr. Hadfield is using the word "capture" in a way
16 that's unusual or not usually complied?

17 MR. KRAUSE: Objection, vague. Form,
18 as well.

19 THE WITNESS: I can't really speak to
20 what Dr. Hadfield was -- what his intent was.
21 In rereading this entire paragraph, my
22 interpretation of this, at least as a person

1 of ordinary skill in the art, is that what
2 Dr. Hadfield is -- would most likely be
3 trying to imply is that capture is pretty
4 broad, right, that it's not something which
5 is just narrowly defined; but, again, as
6 we've discussed in the past, that capture
7 could include a variety of different methods.

8 And he lists a number of them here,
9 and I think what he's trying to say is that
10 despite what one might perceive as
11 differences between these platforms, that
12 ultimately each one of them is providing a
13 capture mechanism that is based on
14 complementary base-pairing, and that capture
15 process would include PCR and other steps,
16 right.

17 So the very next sentence says all of
18 the methods he discusses, rely on PCR for the
19 amplification and to add sequencing platform
20 adapters and bar codes. So I don't think
21 he's trying to exclude things. I think he's
22 trying to be more inclusive and really to

1 reflect the state of the art, that "capture"
2 was defined in a pretty broad manner.

3 BY MR. LUMAN:

4 Q. And during that answer, you made a
5 gesture with your hands like a pair of quotes; is
6 that correct?

7 A. Yes, I was trying to say,
8 quote-unquote, capture, since we referred to the
9 quotation -- single quotation marks, since he's
10 British, around the word "capture."

11 Q. Did you consider any treatise on
12 grammar regarding the use of quotation marks when
13 you were considering how a person of ordinary skill
14 in the art would interpret the word "capture" being
15 in quotes here?

16 A. I don't know what Dr. Hadfield would
17 refer to. I can tell you that having written and
18 edited many, many papers and published some in
19 journals like Nature, which are published in the UK,
20 that standard utility in the UK is for single
21 quotes, where we would typically use double quotes.
22 But, you know, you would have to ask Dr. Hadfield

1 what he was referring to here -- or what he was
2 trying to -- what he was trying to encompass.

3 I can tell you that as a person of
4 ordinary skill in the art thinking about this and
5 now really rereading this paragraph is that he was
6 trying to talk about "capture" being sort of
7 inclusive not trying to limit it to one form of
8 "capture," right. Because he says "different
9 'capture' mechanisms." So he's really trying to
10 talk about this in an inclusive way.

11 MR. LUMAN: I'd like to mark an
12 exhibit. This will be Exhibit 2178 and the
13 exhibit I'd like marked is the one called The
14 Chicago Manual of Style.

15 (Exhibit 2178, No Bates Numbers, The
16 Chicago Manual of Style, Sixteenth Edition,
17 The University of Chicago Press, received and
18 marked.)

19 THE WITNESS: Okay.

20 MR. KRAUSE: And I'd just lodge an
21 objection to timeliness, authenticity, and
22 completeness.

1 BY MR. LUMAN:

2 Q. Dr. Quackenbush, will you let me know
3 when you've had a chance to access The Chicago
4 Manual of Style excerpts?

5 A. I have it. There's actually a copy
6 here since my wife is a professional editor. So I
7 can go and grab it, although I don't know if she has
8 the Sixteenth Edition or not.

9 Q. Okay. In Exhibit 2178, I'd like to
10 turn to page 365.

11 A. All right. I'm there.

12 Q. And do you see there's a header called
13 "Highlighting Key Terms and Expressions"?

14 A. On 36 -- yes, I see that.

15 Q. And then there's Item 7.55, the one
16 that starts with "Scare quotes," do you see that?

17 A. I see that, yes.

18 Q. And it says, "Quotation marks are
19 often used to alert readers that a term is used in a
20 nonstandard (or slang), ironic, or other special
21 sense."

22 Do you see that?

1 A. Yes, I do.

2 Q. If you'll turn to the next page,
3 page 366, do you see the entry for 7.57?

4 A. Yes, I do.

5 Q. And that one says, "Quotation marks
6 are rarely needed for common expressions or figures
7 of speech (including slang)"?

8 A. I see where it says that, yes.

9 Q. So in view of the recommendations in
10 The Chicago Manual of Style, a person of ordinary
11 skill would understand that Dr. Hadfield is using
12 "capture" in a nonstandard sense rather than in a
13 commonly accepted use of the term "capture"; is that
14 fair?

15 MR. KRAUSE: Objection, lacks
16 foundation, calls for speculation.

17 THE WITNESS: So I'm not sure I would
18 conclude that. First, Dr. Hadfield is in the
19 UK. I'm not sure if he's a student of The
20 Chicago Manual of Style.

21 Second, Dr. Hadfield is a biologist.
22 I don't know what his liberal arts training

1 and background is. I can tell you from
2 having worked with many, many scientists, if
3 you show them these passages, it would be the
4 first time they would see this, you know.
5 And I'm not sure they would know immediately
6 how to interpret it.

7 So I don't think it's fair to try to
8 use the Chicago Manual of Style. I can read
9 a lot more here in this section about
10 highlighting key terms and expressions to try
11 to get a more complete understanding.

12 But, you know, if we look at the way
13 Dr. Hadfield describes this, the exact
14 language he used, I believe, was that there
15 are different "capture" mechanisms, and what
16 he was trying to do was likely alert the
17 reader to the fact that he's using "capture"
18 the way it was commonly applied as a broad
19 term, not something that was limited to one
20 technique or another.

21 BY MR. LUMAN:

22 Q. And, again, Dr. Hadfield goes on in

1 the very next sentence to say that all of the
2 capture mechanisms rely on PCR. So PCR was
3 definitely one of the mechanisms that was used at
4 the time of Dr. Hadfield's blog post as a capture
5 mechanism.

6 BY MR. LUMAN:

7 Q. If we can turn back to paragraph 56 in
8 your declaration.

9 A. All right. I'm there.

10 Q. And still focused on that "capture"
11 being in quotes, would you agree that there's
12 several different definitions of the word "capture"
13 that a person of ordinary skill in the art could
14 apply here?

15 MR. KRAUSE: Objection, form.

16 THE WITNESS: So, no, I'm not really
17 sure what you're asking. I think a person of
18 ordinary skill in the art would understand
19 that the way Dr. Hadfield is using the term
20 "capture," in quotes, is to really underscore
21 the fact, maybe alert them, since you
22 referred to scare quotes, to alert them to

1 the fact that these different capture
2 mechanisms really represent something which
3 is inclusive and relies on complementary
4 base-pairing and that these complementary
5 techniques would encompass things that would
6 include solid phase hybridization, liquid
7 phase hybridization, PCR-based capture, and
8 then capture using sort of variations on PCR,
9 like molecular inversion probes, the MIPs,
10 M-I-P-S.

11 He also refers to multiplex PCR, and
12 that's one of the capture mechanisms that
13 he's referring to earlier. And, you know, I
14 think really the thing that's important here
15 is right before "capture," right, he calls
16 that microfluidics, emulsion PCR and
17 oligo-probes. And one skilled in the art
18 would understand that oligo-probes could
19 encompass both the hybridization-based
20 capture, but also PCR, which fundamentally is
21 a hybridization-based capture method.

22 So, again, I think he's -- my best

1 interpretation is that what he's trying to do
2 is alert the reader to that these capture
3 mechanisms are fundamentally the same in
4 their molecular mechanism but may differ in
5 the details of how they're implemented.

6 BY MR. LUMAN:

7 Q. You mentioned in your last answer that
8 he was trying to alert the reader that the capture
9 mechanisms are fundamentally the same.

10 Why did you say they were
11 fundamentally the same? What was the word
12 "fundamentally" meant to express?

13 A. So I'm sorry if you missed this.
14 Looking at all of the techniques that are here --
15 and again, I'm not -- I don't recall what Halo
16 Genomics did, but every single mechanism that he
17 refers to here at a molecular level requires
18 complementary base-pairing between one or more
19 oligonucleotide probes and a target nucleic acid
20 molecule.

21 And I don't recall the exact language
22 of the claims in the '033 or the '394 patent, but

1 the capture -- in the written description, but the
2 capture probes, whether PCR or hybridization-based,
3 are going to rely on that complementary base-pairing
4 between one or more probes and a target DNA
5 molecule.

6 And I guess in the context of these
7 patents, they would be target DNA molecules where
8 one would expect a polymorphism to exist.

9 Q. So what I'd like to do is look at a
10 dictionary definition of the word "capture" and then
11 see if we can identify what use of "capture" a
12 person of ordinary skill in the art would understand
13 from reading this Enseqlopedia blog.

14 MR. LUMAN: So what I'd like to do is
15 mark as Exhibit 2179 The American Heritage
16 dictionary.

17 (Exhibit 2179, No Bates Numbers, The
18 American Heritage Dictionary of the English
19 Language Fourth Edition, received and
20 marked.)

21 BY MR. LUMAN:

22 Q. And, Dr. Quackenbush, can you give me

1 a verbal cue when you've had a chance to download
2 that?

3 A. I'm downloading it now, and I'll tell
4 you as soon as I have it open. And I have it open.

5 MR. KRAUSE: Give me one second. I
6 haven't gotten it yet.

7 And I'll just object to relevance,
8 authenticity, timeliness, completeness, and
9 under 403.

10 BY MR. LUMAN:

11 Q. If you'll turn to page 278 of
12 Exhibit 2179.

13 Do you see that definition of
14 "capture"?

15 A. Yes, I have that.

16 Q. And then in the dictionary definition
17 of "capture," there's four different definitions of
18 the word "capture" as a verb.

19 Do you see that?

20 A. Yes.

21 Q. Which one of those definitions would a
22 person of ordinary skill in the art apply when

1 reading Dr. Hadfield's Enseqlopedia blog that you've
2 quoted in paragraph 56 of your declaration, or would
3 they apply all of those definitions?

4 MR. KRAUSE: Objection to form.

5 Objection to relevance.

6 THE WITNESS: So, first, Dr. Hadfield
7 is from the UK. I'm not sure he is an avid
8 user of The American Heritage Dictionary. He
9 might use the Oxford English Dictionary or
10 the compact Oxford English Dictionary or some
11 online dictionary. I don't know.

12 Second, this is a standard usage
13 dictionary, and I'm not sure the authors of
14 this dictionary considered applications in
15 molecular biology. I'm not sure any of the
16 definitions are perfect. The first is to
17 take captive, as by force or craft, seize.

18 So I could construct a potential way
19 of being crafty and using complementary
20 phase-pairing as a way of seizing molecules,
21 right, to gain possession or control of, as
22 in a game or contest.

1 You know, I'm not sure sequencing
2 tumors would be considered a game or contest,
3 but, you know, what one would like to be able
4 to do is to gain possession of these
5 molecules from solution.

6 To attract or hold. You want to hold
7 on to these and capture them.

8 To succeed in preserving in a lasting
9 form. I'm not sure -- it says capture a
10 likeness as in a painting. I guess because
11 we're sequencing these eventually, maybe that
12 is a way, but I really don't think this is
13 appropriate.

14 You know, what would one really has to
15 do is ask what a person of ordinary skill in
16 the art would mean by "capture," and that
17 interpretation, particularly given
18 Dr. Hadfield's description here, would imply
19 that he's discussing ways of going into a
20 complex mixture of DNA molecules and then
21 capturing specific regions, so extracting,
22 purifying, amplifying, preparing them for

1 downstream sequencing reactions.

2 So I notice "purify" isn't a synonym
3 that's listed here. One could credibly argue
4 that purification is a capture mechanism. So
5 what I'm trying to say is I don't think the
6 American Heritage Dictionary definition is
7 necessarily relevant for interpreting
8 "capture."

9 A person of ordinary skill in the art
10 would understand very clearly that
11 Dr. Hadfield is referring to mechanisms that
12 rely on complementary base-pairing that would
13 include both hybridization probes and PCR
14 capture probes among other fundamental
15 techniques for preparing DNA for sequencing.

16 BY MR. LUMAN:

17 Q. One of the ways that PCR captures is
18 by copying and generating amplicons; is that fair?

19 A. Yes, part of the way that PCR -- part
20 of the way that PCR captures is by generating
21 amplicons of specific regions. And as Dr. West
22 testified, the PCR primers perform the function of

1 capturing DNA loci for sequencing. So I think
2 that's a fair characterization, maybe not a full
3 characterization.

4 Q. Which, if any, of the four definitions
5 of "capture" in Exhibit 2179 best fit with a copy
6 capture mechanism?

7 MR. KRAUSE: Objection, foundation,
8 relevance, 403.

9 THE WITNESS: So, again, you're
10 pointing me to The American Heritage
11 Dictionary, referring to something written by
12 someone in the UK. And in the field of
13 molecular biology, this dictionary is from --
14 the copyright page you gave me is from 2000.
15 Dr. Hadfield's Enseqlopedia blog entry was --
16 let me go back to that -- 2011.

17 So, you know, I'm not sure if the
18 American Heritage Dictionary kept up to date
19 with -- this definitely wouldn't be up to
20 date with common usage of molecular biology
21 in 2011. And, again, I don't think it's a
22 perfect fit. We're not looking for a single

1 definition here.

2 What a person of ordinary skill in the
3 art would understand "capture" to mean in
4 this context would be to use the
5 complementary hybridization between DNA
6 strands either through what we've referred to
7 earlier as hybridization capture probes or
8 what we've been referring to as PCR capture
9 probes as a way of creating DNA mixtures --
10 or preparations that could then subsequently
11 be used for sequencing. And I don't see any
12 reference in the American Heritage Dictionary
13 to DNA or sequencing.

14 BY MR. LUMAN:

15 Q. You had mentioned that Dr. Hadfield
16 was writing in the UK. Do you think a person of
17 ordinary skill in the art in interpreting what
18 Dr. Hadfield was writing would need to turn to a UK
19 dictionary to understand what he's saying?

20 A. I don't think a person of ordinary
21 skill in the art would need to turn to a dictionary.
22 A person of ordinary skill in the art would

1 understand in the context of what Dr. Hadfield is
2 writing that there are a variety of different ways
3 of isolating and purifying DNA and preparing it for
4 sequencing and that encompassed within that
5 definition is the use of PCR as a capture
6 technology, right.

7 So if you look at the opening of
8 paragraph 56, which you referred to, Dr. Furneaux
9 testified that the cancer research UK Cambridge
10 Institute was one of the most sophisticated
11 sequencing labs in the world, and in this
12 definition -- in this excerpt paragraph from his
13 blog, it clearly lays out that capture is not
14 limited to hybridize capture but that PCR is a
15 capture technology.

16 And, again, this is consistent with
17 some of Dr. Furneaux's own testimony and testimony
18 from Dr. West, who is, I believe, one of the listed
19 inventors on these patents.

20 MR. LUMAN: If we could keep
21 Exhibit 2179, the dictionary definition of
22 "capture" on the screen, please.

1 BY MR. LUMAN:

2 Q. And I heard you speak a little bit
3 about the first definition. Let's look at the
4 second one, "To gain possession or control of, as in
5 a game of contest." And then it's got something
6 about capturing the queen in chess.

7 Could the copy capture mechanism of
8 PCR have anything to do with the second definition?

9 MR. KRAUSE: Objection, form,
10 relevance, 403, foundation.

11 THE WITNESS: So it's very
12 interesting. As we're trying to parse these
13 definitions -- and for something from
14 molecular biology and what a person of
15 ordinary skill in the art would understand --
16 into a dictionary definition.

17 So my background is in theoretical
18 physics. When I started working in biology,
19 I had heard about vectors being things like
20 mosquitoes for transmitting disease. But
21 once I stepped into a molecular biology lab,
22 it didn't mean a vector is an arrow, a

1 quantity with a magnitude direction. It
2 didn't mean a mechanism of transmitting
3 disease.

4 In that context, it had a very
5 specific meaning, which in the case of the
6 work we were doing, was a plasmid as a way of
7 transmitting DNA into a bacterial cell,
8 right.

9 So try to force something into a
10 dictionary definition of common usage doesn't
11 necessarily make perfect sense. There are
12 elements of each of these definitions that
13 reflect the use of "capture" in some way.

14 So I don't consider DNA purification
15 either a game or contest or DNA sequencing a
16 game or contest. But, you know, to the
17 extent that one could say, Yeah, I'm going to
18 gain possession of these molecules for
19 sequencing, you know, you could see shades of
20 that, just like taking captive, one could see
21 shades of that or to attract and hold, the
22 third definition.

1 You know, what one of ordinary skill
2 in the art would understand is that
3 Dr. Hadfield is discussing mechanisms of
4 preparing DNA for sequencing that involve
5 targeting specific molecules for sequencing
6 and that these capture mechanisms use
7 complementary base-pairing either through
8 hybridization-based capture, solid phase or
9 liquid phase or PCR-based capture, and then
10 other techniques like MIPs, which kind of
11 fall -- you know, fall into their own unique
12 category. But there are many different
13 capture mechanisms. They all rely on
14 complementary base-pairing.

15 BY MR. LUMAN:

16 Q. Let's look at definition 3, to attract
17 and hold, and definition 4, to succeed in preserving
18 in a lasting form, capture a likeness in a painting.

19 Does the PCR copy capture mechanism,
20 is that reflected in either definition 3 or 4?

21 MR. KRAUSE: Same objections as to the
22 previous line of questions.

1 THE WITNESS: So, again, I don't think
2 this is the right question to answer -- to
3 ask. I don't think any one of these
4 perfectly reflects how one of ordinary skill
5 in the art would interpret "capture" in the
6 context of a molecular biology assay.

7 There are elements of 1, 2, 3, and 4
8 that -- that include aspects of capturing
9 here. One of ordinary skill in the art
10 reading Dr. Hadfield's blog would recognize
11 that the capture process he's talking about,
12 whether PCR or hybridization-based capture,
13 PCR-based capture, that these are ways of
14 taking DNA molecules from a biological sample
15 and preparing these for subsequent sequencing
16 assays. And that's really the entire
17 description he has in this paragraph, right.

18 After the use of "capture," he says,
19 all these different mechanisms he's referred
20 to -- and I would imply -- or I would infer
21 "others" all rely on PCR for the
22 amplification and to add sequencing platform

1 adapters and bar codes, right.

2 So he's really talking about "capture"
3 sort of broadly as a way of preparing these
4 DNA molecules for subsequent sequence and
5 analysis. And his definition with the scare
6 quotes that you referred to earlier are a way
7 of alerting us to the fact that this is a
8 broad definition, but one that one of skill
9 in the art would recognize and understand.

10 BY MR. LUMAN:

11 Q. Would you turn in your declaration
12 that's Exhibit 1225 to paragraph 52 with me?

13 A. Sure.

14 Q. And do you see the first sentence,
15 "Dr. Furneaux points to certain pros and cons of
16 'enrichment by PCR' and 'enrichment by hybrid
17 capture'..."?

18 A. Yes, I see that.

19 Q. So what are some of the pros of
20 enrichment by PCR?

21 A. So I'm not sure what Dr. Furneaux was
22 pointing to. I don't have his declaration in front

1 of me. He's discussing pros and cons as presented
2 in Mertes. And I'm not sure -- again, I don't have
3 Mertes sitting in front of me. So I'm not sure what
4 Mertes was referring to. Every technique has pros
5 and cons, and one would have to look at it in the
6 context of a particular assay.

7 So -- if you're asking me for a pro of
8 PCR as of 2010, 2011, I would say simply PCR was a
9 transformational technology in molecular biology
10 invented by Kary Mullis in 1985, for which he won
11 the Nobel Prize in 1997.

12 So one of the pros is that it was a
13 well-understood technique that could be modified in
14 a variety of different ways. But, you know, to ask
15 me about the pros in a particular context, we'd have
16 to look at that context. And, again, I'm not sure
17 what either Furneaux or Mertes specifically was
18 referring to based on this passage.

19 Q. And what are some of the cons of
20 enrichment by PCR in the 2011 time frame?

21 A. It would depend on the application.
22 As I state later on in the paragraph, "As I

1 explained in my initial declaration, a person of
2 skill in the art [sic] would readily be able to
3 evaluate the pros and cons of these (and other)
4 enrichment techniques depending on the needs of
5 their experiment."

6 So the choice of enrichment technique
7 would largely depend on the experiment -- the
8 particular experiment one was doing. So, you know,
9 we have to look at a particular example to talk
10 about pros and cons relative to something else,
11 right, because advantages and disadvantages are
12 always relevant to some other technique.

13 Q. In the last sentence of paragraph 52,
14 you say a person of skill in the art would readily
15 be available to evaluate the pros and cons of these
16 and other enrichment techniques.

17 Do you see that?

18 A. Yes, I do.

19 Q. What are some of the cons of
20 enrichment by PCR as compared to enrichment by
21 hybrid capture?

22 A. It would depend on the particular

1 application. I'm not sure what either Furneaux or
2 Mertes was referring to. Again, depending on the
3 application, I would want to look and evaluate the
4 different -- the different pros and cons in that
5 particular assay as compared to the other techniques
6 I would consider using.

7 And that's really what I'm referring
8 to here, is that one has to perform that analysis in
9 context of both the particular experiment, but also
10 the particular alternatives one would be
11 considering.

12 You know, in the next paragraph, I
13 also refer to Dr. Furneaux's misquoting of -- or
14 misinterpreting of both Mertes and Mamanova. We've
15 discussed both of these references previously, and I
16 recall we discussed in detail one of the figures in
17 Mamanova that showed that areas that Mamanova
18 interpreted as being maybe best -- I wouldn't say
19 ideal -- but being -- where PCR and other capture
20 technologies, such as hybridization capture probes
21 might be chosen, actually overlap substantially.

22 So, again, there are lots of things

1 that go into making decisions like that and you'd
2 really want to look at them in the context of the
3 particular assay you were trying to perform.

4 Q. So it's important to look at the
5 particular context of an assay someone's trying to
6 perform in order to determine which pros and cons of
7 enrichment by PCR would apply versus enrichment by
8 hybrid capture; is that fair?

9 MR. KRAUSE: Objection to form.

10 THE WITNESS: So what Dr. Furneaux is
11 arguing and what I'm responding to is his
12 assertion that hybridization capture probes
13 and PCR primers -- the use of PCR primers are
14 very different techniques, but while they are
15 different, they -- and I state this in
16 paragraph 53, they both involve capture
17 probes, they both perform the function of
18 enrichment.

19 And so, you know, you often have many
20 choices in performing molecular biology
21 assay, but Dr. Furneaux is somehow trying to
22 draw a hard-line distinction between

1 PCR-based capture and the use of
2 hybridization probes.

3 And, you know, Dr. Furneaux even
4 considers and acknowledges that both PCR and
5 hybridization-based capture use capture
6 probes. So the pros and cons, there might
7 not even be a significant difference between
8 them in many applications, and it would be a
9 choice.

10 The important thing is that in the
11 context of the patents, the patents clearly
12 disclose capture techniques that are
13 inclusive of PCR that don't exclude PCR. And
14 Mr. West actually confirmed this in his
15 deposition testimony.

16 BY MR. LUMAN:

17 Q. In the second sentence of
18 paragraph 52, you reference the -- it says, "the
19 techniques are different approaches of achieving the
20 same goal."

21 How is enrichment by PCR a different
22 approach than enrichment by hybrid capture?

1 A. So as Dr. Hadfield points out in his
2 blog post, the use of PCR in preparing molecules for
3 sequencing invariably involves the use of PCR,
4 right. And so at some point PCR is going to be
5 performed.

6 Typically -- and I believe this is
7 discussed in part in both Mertes and Mamanova.
8 Typically, the use of hybridization capture would
9 use one oligonucleotide probe for target, and PCR
10 would use two oligonucleotide probes per target in
11 the initial contact between probes and target
12 molecules.

13 Beyond that, there are a variety of
14 differences you can point to. But, again, the
15 important thing in the context of the two patents at
16 issue here is that capture includes both
17 hybridization-based capture, solid phase or liquid
18 phase, and PCR, as well as other techniques and that
19 this is consistent with the broad definition the
20 PTAB has provided in its claim construction
21 arguments.

22 Q. And I want to look at the last bit of

1 that second sentence, the "enrichment of target loci
2 or sequencing." So the enrichment of loci target
3 for sequencing -- the "target loci for sequencing"
4 refers to the location of the target DNA that's
5 intended for sequencing; is that right?

6 I guess what does the "target loci for
7 sequencing" refer to?

8 A. So, again, I don't have Dr. Furneaux's
9 declaration in front of me. I'd have to look back
10 to see exactly what he's referring to. I also don't
11 have the patents in front of me. But in general,
12 the patents involve steps in which particular loci
13 are identified for sequencing.

14 And the '394 arrives at those through
15 an initial whole genome sequencing followed by what
16 we'd refer to as targeting sequencing. And the '033
17 starts with designing capture probes, PCR primers
18 based on prior knowledge databases, other sources,
19 including potentially sequencing, but the whole
20 genome sequencing.

21 But both of these have as their goal
22 their analysis of particular loci. So loci is from

1 a Latin root. It's actually plural of locus. Locus
2 is a singular loci, and it -- I believe it simply
3 means location.

4 So the target loci are target
5 locations in the genome, and these are locations
6 that have been selected based on criteria, such as
7 their known mutations involved in the development
8 and progression of cancer, potentially known
9 mutations associated with drug resistance or drug --
10 drug -- "susceptibility" probably isn't the right
11 word, but drug efficacy.

12 And the patents cite to examples like
13 the cosmic database, or it could also be locations
14 identified through sequencing where the tumor
15 differs from a reference genome as possible
16 examples.

17 So what one would like to do is
18 after -- in the '394, after doing the whole genome
19 sequencing in analyzing subsequent samples, one
20 would like to look at those particular locations.
21 So those are the target loci. One would like to
22 enrich for those with the goal of sequencing those

1 repeatedly rather than using real estate on the
2 Illumina flow cells to sequence things that are
3 going to be less informative.

4 So it's really directed toward this
5 goal of identifying locations for further sequencing
6 and analysis. And as we've discussed previously,
7 this is discussed extensively in the prior art, this
8 idea of finding informative loci and then
9 subsequently sequencing them and analyzing them to
10 look at cancer development and progression.

11 Q. I think that was helpful, because I
12 was getting slightly hung up on loci. And so the
13 target loci for sequencing is just the location of
14 target DNA that's intended for sequencing; is that
15 right?

16 A. I don't -- so the location, you could
17 actually identify as locations in the genome. I
18 could provide coordinates given a particular genome
19 build. I think the way you would want to interpret
20 this is that the loci represent those elements, for
21 example, in the '394 patent -- and, again, I don't
22 have it in front of me -- but after the initial

1 whole gene sequencing step, those elements that I've
2 chosen for follow-up later.

3 So those would be the elements that I
4 would like to analyze later, for example, to look
5 for polymorphisms.

6 MR. LUMAN: So we've been going for
7 about an hour. I'm happy to keep going, but
8 if you'd like a break, let me know.

9 Would you like a break or keep going?

10 THE WITNESS: I'll defer to the court
11 reporter. If you'd like to take a break, we
12 can do that.

13 THE REPORTER: I could use a break.

14 THE WITNESS: All right. Why don't we
15 do that then.

16 MR. KRAUSE: All right. We were on at
17 7:01, and we're going off at 8:11 Pacific
18 Time.

19 (Recess from the record.)

20 MR. LUMAN: We are back on the record
21 at 8:20.

22

1 BY MR. LUMAN:

2 Q. I would still like to stay in
3 paragraph 52 of your declaration.

4 MR. LUMAN: Can we have that brought
5 up on the screen, please.

6 THE WITNESS: Thank you.

7 BY MR. LUMAN:

8 Q. And I'm still looking at the last
9 sentence, and it refers to a person of ordinary
10 skill in the art being readily able to evaluate pros
11 and cons depending on the needs of their experiment.

12 And so, Dr. Quackenbush, what are some
13 of the pros and cons that a person of skill in the
14 art would evaluate when selecting between enrichment
15 by PCR or enrichment by hybrid capture, depending on
16 the needs of their experiment?

17 MR. KRAUSE: Objection --

18 THE WITNESS: Well --

19 MR. KRAUSE: -- assumes facts,
20 foundation.

21 THE WITNESS: So I'm referring to a
22 discussion here that I had in -- that I

1 presented in my declaration on the '394
2 patent, paragraph 66 to 69. I don't have
3 that front of me. I don't recall what I laid
4 out there.

5 Again, the pros and cons would be
6 evaluated depending on the needs of the
7 particular experiment. So...

8 BY MR. LUMAN:

9 Q. Are you familiar with the Mertes
10 publication, Exhibit 1006?

11 A. I've read it, but I haven't looked at
12 it recently.

13 MR. LUMAN: Can we make Exhibit 1006
14 available to Dr. Quackenbush, please.

15 (Exhibit 1006, No Bates Numbers,
16 Targeted enrichment of genomic DNA regions
17 for next-generation sequencing, Briefings in
18 Functional Genomics, Vol. 10, No. 6, 2011,
19 Mertes et al., received and marked.)

20 BY MR. LUMAN:

21 Q. Dr. Quackenbush, can you give me a
22 verbal cue when you've got it?

1 A. All right. It is downloaded and open.

2 Q. So we're looking at Exhibit 1006, the
3 Mertes reference.

4 A. Yes.

5 Q. Would you turn with me to page 380?

6 And I'm looking on the right-hand side
7 under the heading "Descriptive metrics" --

8 A. All right, I'm there.

9 Q. Do you see a list of seven metrics
10 provided by Mertes on page 380?

11 A. So I see where Mertes is listing a
12 proposed set of metrics, yes.

13 Q. I guess let me back up. This is a --
14 the Mertes publication is a publication that
15 compares and discusses different enrichment
16 techniques, including hybrid capture and PCR; right?

17 A. So I'm reading the abstract.

18 (Document review.)

19 THE WITNESS: So I'm sorry, Mr. Luman.

20 Would you repeat the question, please?

21 BY MR. LUMAN:

22 Q. Yeah.

1 Why don't we put page 375 up on the
2 screen, and then I'll repeat the question.

3 A. All right.

4 Q. And so there's a heading "Enrichment
5 Techniques." My question is that the Mertes
6 publication discusses different enrichment
7 techniques, including hybrid capture and PCR; right?

8 A. So Mertes discusses enrichment
9 techniques in general, and he characterizes these to
10 include hybrid capture, selective circularization,
11 and PCR-based methods, yes.

12 Q. So with that background in mind, let's
13 go over to page 380 and the seven metrics that are
14 listed there.

15 My question is: Would the seven
16 metrics provided by Mertes be a good starting point
17 for a person of ordinary skill in the art to
18 evaluate pros and cons of using PCR versus hybrid
19 capture as enrichment technique for a given
20 experiment?

21 MR. KRAUSE: Objection to form.

22 THE WITNESS: So I haven't analyzed

1 this proposal. So this is a proposal that's
2 actually made by Nilsson in a manuscript that
3 had not been published at the time Mertes
4 referenced it. So I'm not sure what Nilsson
5 and colleagues were referring to.

6 These are some things that one might
7 want to consider, but there's some things
8 that one might want to consider. One might
9 consider some of these, eliminate some of
10 these, might add others.

11 Again, considering the pros and cons
12 of any application would depend on -- or of
13 any enrichment method would depend on the
14 enrich- -- on the particular experiment one
15 chose to do.

16 BY MR. LUMAN:

17 Q. Would these seven metrics steer a
18 person of ordinary skill in the art towards PCR or
19 in a divergent direction of selecting hybrid capture
20 for a given experiment?

21 MR. KRAUSE: Objection, vague, lacks
22 foundation, calls for speculation.

1 THE WITNESS: So I haven't performed
2 this analysis for any particular application.
3 As I pointed out earlier, there are many
4 instances in which there are overlapping
5 areas of utility for different enrichment
6 methods.

7 Those methods would include -- but, I
8 would say wouldn't be limited to necessarily,
9 Dr. Mertes' suggestion -- suggested
10 classification which would include what he
11 refers to hybrid capture, selective
12 circularization and PCR.

13 You know, I think the important thing
14 about the Mertes publication is that what
15 Mertes is really alluding to here is that
16 capture-based methodologies at the 2011
17 publication date of this paper were pretty
18 broadly defined and that a person of ordinary
19 skill in the art would understand that there
20 were many choices one could make, and those
21 choices would include both hybrid-based
22 approaches and PCR, which I would

1 characterize as a hybrid-based approach since
2 fundamentally the binding of the primers to
3 the target is through the process of
4 hybridization.

5 BY MR. LUMAN:

6 Q. When a person of skill in the art
7 looks at these seven metrics, would that steer them
8 in a direction towards selecting PCR or hybrid
9 capture for -- based on the various needs of any
10 given experiment?

11 A. So Mertes here, again, is referring to
12 proposal in a publication by Nilsson. I'm not sure
13 what Nilsson's analysis was in preparing this.
14 Mertes actually says below this list, the
15 "theoretical examination of how a method's innate
16 enrichment capability and the size of the targeted
17 region work together to determine other
18 parameters" -- and he lists some -- "can be very
19 instructive when choosing an enrichment method for a
20 particular application."

21 So, you know, my interpretation of
22 this is that Mertes isn't necessarily teaching away

1 from one method or another, but instructing a person
2 of ordinary skill in the art that one should look at
3 the various hybridization-based methods, right --
4 hybridization capture probes, PCR-based capture
5 probes, I believe he refers to these as
6 circularization methods -- one should evaluate those
7 given a particular -- one's particular application.

8 So this is sort of a theoretical
9 exercise, and I wouldn't say it would necessarily
10 teach away from one or the other. It provides some
11 guidance, right.

12 He also talks about in the next
13 paragraph, you know, the cost per sample that one --
14 that different methods would have and that that's
15 something else that should be considered which isn't
16 in the list. So -- and then points out the cost
17 change over time as technology's improved.

18 So my interpretation of this is that
19 Mertes is trying to lay out -- trying to provide
20 some view of the landscape, but not being
21 prescriptive for the choice of any of these
22 hybridization-based approaches, PCR or others.

1 Q. Yeah, and so he's not being
2 prescriptive, but he is providing guidance on how a
3 person of skill in the art should go about selecting
4 the enrichment technique; correct?

5 MR. KRAUSE: Objection,
6 mischaracterizes the document.

7 THE WITNESS: So Mertes here is
8 referring to, as of then, and I don't know if
9 it has been published, but unpublished set of
10 recommendations from someone named Nilsson.
11 And there's a list but then other things like
12 cost and doing -- adding some additional
13 things like specificity and redepth.

14 You know, what I think Mertes is
15 saying is that there are many factors one of
16 ordinary skill in the art would consider in a
17 particular application in choosing the
18 techniques one would use.

19 You know, I can make the same argument
20 that if I were doing PCR for a particular
21 application, I would consider which fumarase
22 enzyme I was using and whether or not I would

1 use one that has exonuclease activity or not.
2 I would consider the length of my primers. I
3 would consider the annealing temperature.

4 So I think my best read of this is
5 that what Mertes is doing is really calling
6 out the fact that there are a variety of
7 competing techniques and that the important
8 thing is to think about a particular
9 application in the context of these
10 techniques, all of which rely on
11 hybridization.

12 BY MR. LUMAN:

13 Q. Okay. Are any one of the seven
14 metrics that are listed by Mertes of greater
15 importance in selecting hybrid capture over PCR as
16 an enrichment technique?

17 MR. KRAUSE: Objection, vague, 403.

18 THE WITNESS: So Mertes -- so Mertes
19 himself actually says, "A series of metrics
20 need to be considered, and the importance of
21 each can be weighted according to the
22 specific needs and objectives of any

1 experiment."

2 So Mertes himself is acknowledging
3 that, you know, even in this list from
4 Nilsson, that Mertes' interpretation is that
5 it's not a definitive list, right. Mertes
6 also adds other criteria below, but that the
7 relative importance of these is going to
8 depend on the application.

9 BY MR. LUMAN:

10 Q. Would you turn with me to page 375 of
11 this document?

12 A. Sure.

13 All right. Oh, sorry. I'm there.

14 Q. Looking under the "Enrichment
15 Techniques" heading on the left column, and the
16 first sentence talks about -- it says, "Current
17 techniques for targeted enrichment can be
18 categorized according to the nature of their core
19 reaction principle."

20 And then it lists number 1, hybrid
21 capture; number 2, selective circularization; then
22 number 3, PCR amplification.

1 Do you see that?

2 A. I see where it says that, yes.

3 Q. What would a person of ordinary skill
4 in the art understand to be the core reaction
5 principle of hybrid capture?

6 A. So I'm not sure what Mertes is
7 referring to here specifically. This is Mertes'
8 characterization of different techniques. I would
9 say that a person of ordinary skill in the art would
10 understand that the core reaction principle of
11 hybrid capture, selective circularization, and PCR
12 amplification is going to be complementary
13 base-pairing between one or more nucleic acid probes
14 and a target locus.

15 So I can't speak to Mertes'
16 characterization here, what he considers the core
17 reaction principle that necessarily differentiates
18 these.

19 I would say a person of skill in the
20 art would understand that at their core, all are
21 based on complementary base-pairing between nucleic
22 acid molecules. Right.

1 And Mertes even later says that -- he
2 doesn't talk about core reaction principles in the
3 paragraph immediately following the list. He says,
4 Given the operational characteristics of these
5 different enrichment methods, they naturally vary in
6 their suitability for different fields of
7 application, right.

8 So I don't see a core difference in
9 the principle. I actually -- I would put more
10 weight on his next statement that there are
11 operational differences, right.

12 The way you perform PCR is going to
13 require a thermocycler for the capture.
14 Hybridization is not. MIPS, the way it's typically
15 practiced, would.

16 So, again, there are overlaps between
17 them operationally, but I think of these more as
18 having operational differences rather than core
19 reaction principle differences.

20 Q. So the differences that he's referring
21 to are the differences in operational principles
22 between hybrid capture, MIPS, and PCR amplification.

1 Is that a fair summary?

2 A. So, again, you would have to ask
3 Mertes why these particular classifications were
4 made and what he considers encompassed in these. I
5 think what's important is that Mertes recognizes
6 that as of 2011, these are all enrichment
7 techniques, and they're all techniques which are
8 based on complementary pairing between nucleic acid
9 molecules and that as laid out in the '394 and '033
10 patents, that capture -- which Mertes refers to as
11 enrichment here, that capture is really a term that
12 was broadly -- that was recognized to include a
13 broad set of different techniques, including
14 PCR-based approaches.

15 Q. Mertes -- Mertes does not use the word
16 "capture" in the context of PCR amplification.
17 That's incorrect. It only uses "capture" with
18 respect to hybrid capture.

19 MR. KRAUSE: Objection, form.

20 THE WITNESS: Again, you know -- well,
21 I don't -- is there a question there?

22

1 BY MR. LUMAN:

2 Q. Do you agree that Mertes doesn't use
3 the word "capture" -- no, I don't want to -- I don't
4 want to ask that question.

5 Let's do -- on the right-hand side,
6 given the operational characteristics, do you see
7 that one underneath --

8 A. Yes, I do. Sorry, I talked over you.

9 Q. It talks about the operational
10 characteristics of these different enrichment
11 methods.

12 And what's the different principle of
13 operation between hybrid capture and PCR
14 amplification?

15 A. Again, there are many operational
16 differences, at least in the way Mertes is referring
17 to this. So, you know, he talks about hybrid
18 capture being performed in solution or on a solid
19 support, but doesn't give all of the details of how
20 that's done.

21 He talks about selective
22 circularization and refers to MIPS but then padlock

1 probes and other techniques. And, again, doesn't
2 talk about all of what that encompasses. And then
3 he discusses PCR directed toward targeted regions of
4 interest.

5 And all of these enrich or capture
6 elements of DNA for downstream analysis. And, you
7 know, Mertes actually teaches to the use of PCR as a
8 capture technique in applications like those laid
9 out in the '394 and '033 patent, when Mertes says in
10 the last paragraph in the sentence you pointed to,
11 "PCR-based approaches may be preferable as they
12 enable a deep and even coverage over the region of
13 interest, suitable for genetics analysis."

14 So in finding and analyzing genetic
15 variance, that PCR is a capture or enrichment
16 technique that Mertes actually tells us is suitable
17 for the kinds of applications envisioned in the two
18 patents in question.

19 Q. So Mertes does not refer to PCR
20 amplification as a capture technique. It refers to
21 it as an enrichment technique.

22 My question to you was specific to

1 what is the different principle of operation between
2 hybrid capture and PCR amplification?

3 A. Well, there are many different
4 operational characteristics that the principle of
5 operation, I would say, is the same. It's nucleic
6 acid complementary base-pairing. But, you know, we
7 talked about one of these that PCR amplification as
8 a direct capture technique involves the use of a
9 thermocycler, which typically isn't used in the
10 initial phase of solution-based hybridization or
11 solid-phase hybridization.

12 But in the previous reference we were
13 looking at, I believe it was the blog post, I think
14 Dr. Hadfield referred to the fact that in no matter
15 what initial step is used, all of the different
16 methods rely on PCR for sequencing.

17 So the starting point for capture
18 enrichment might be slightly different, but
19 ultimately, the -- yeah, the use of PCR is an
20 important role. And as Dr. Mertes points out, in
21 doing genetics variance analysis, PCR-based
22 approaches may actually be preferable to some of

1 these others.

2 Q. Is it fair to say that a difference in
3 the principle of operation between hybrid capture
4 and PCR amplification is that hybrid capture
5 physically removes the target DNA, whereas PCR
6 amplification captures the target DNA?

7 I'm sorry, let me ask that again.

8 All right. Is it fair to say that a
9 difference in the principle of operation between
10 hybrid capture and PCR amplification is that hybrid
11 capture physically removes the target DNA, whereas
12 PCR amplification copies the target DNA?

13 MR. KRAUSE: Objection, incomplete
14 hypothetical.

15 THE WITNESS: So, again, how one would
16 actually practice this method would depend on
17 the situation. And I believe that
18 Dr. Furneaux may have made arguments to that
19 effect, but I responded to those arguments
20 and, in fact, cited some of Dr. Furneaux's
21 deposition testimony.

22 And I believe this is in my

1 declaration, which you provided to me earlier
2 starting in paragraph 86, in which
3 Dr. Furneaux himself indicated that one --
4 again, you do PCR in a variety of different
5 ways, but that PCR can actually be used to
6 physically isolate DNA molecules.

7 And I cite to a figure from Leary in
8 which we can see -- I believe it's an agarose
9 gel with different DNA fragments. And as
10 Dr. Furneaux testified in deposition -- this
11 is in paragraph 86, and I'm quoting
12 Dr. Furneaux now -- "If you can find and
13 visualize the fragment of a particular size
14 on a gel, then you can physically remove it
15 from the gel."

16 So PCR can encompass physical removal
17 of these DNA fragments. So, you know, again,
18 hypothetically, you can draw distinctions
19 depending on the application, but one can
20 also see situations where PCR can physically
21 remove samples, and it's -- I can think of
22 lots of different scenarios in which one can

1 physically remove DNA fragments using
2 hybridization -- or using PCR, including
3 specific modifications of the primers which
4 would allow you to explicitly remove those --
5 those fragments from the original sample.

6 BY MR. LUMAN:

7 Q. So how does -- you were talking about
8 Dr. Furneaux's testimony. How does Dr. Furneaux's
9 testimony on PCR -- let me ask it this way: How
10 does PCR equate to what Dr. Furneaux was talking
11 about?

12 MR. KRAUSE: Objection, vague,
13 fortunately.

14 THE WITNESS: If you'd like call up
15 Dr. Furneaux's declaration, we can go through
16 and discuss that. If you'd like to refer to
17 specific areas of my report, we can discuss
18 that. I believe the question you had asked
19 me previously was whether or not PCR -- I
20 believe you stated that hybridization-based
21 capture physically removes molecules from the
22 solution, while PCR amplifies them.

1 When I responded, I pointed out that
2 Dr. Furneaux pointed to examples in his
3 deposition testimony where one could
4 separate -- one could visualize DNA fragments
5 amplified by PCR in a gel and then physically
6 remove them. A person of ordinary skill in
7 the art as of 2011 would also know that one
8 could, for example, use biotinylated primers
9 in PCR and then use those biotinylated
10 primers to physically remove the captured
11 molecules from solution.

12 So, you know, hypothetically, one
13 could do a lot of different things, and
14 simply referring to Dr. Furneaux's testimony
15 is a way of validating the fact that there's
16 not a clear separation between PCR and hybrid
17 capture, that they're part of a larger family
18 of techniques, all of which are based on
19 complementary base-pairing between nucleic
20 acid molecules, and all of which can be used
21 to physically remove -- or which include many
22 different techniques which should be used to

1 physically removal DNA fragments from a
2 sample.

3 MR. LUMAN: So what I'd like to do is
4 pull up Exhibit 1020 from the '317 IPR. So
5 this will be Exhibit 1020 in -- from IPR
6 2023-00317.

7 (Exhibit 1020, No Bates Numbers,
8 Declaration of John Quackenbush, Ph.D. in
9 Support of Petition for Inter Partes Review,
10 IPR2023-00317, received and marked.)

11 THE WITNESS: All right. I see that's
12 loaded into Box. I'm going to download it
13 now.

14 MR. LUMAN: And we'll also mark that
15 as Exhibit 2180 in IPR 2023-00224.

16 (Exhibit 2180, No Bates Numbers,
17 Declaration of John Quackenbush, Ph.D. in
18 Support of Petition for Inter Partes Review,
19 IPR2023-002247, U.S. Patent No. 11,408,033,
20 received and marked.)

21 THE DOCUMENT TECH: Okay. 2180;
22 right?

1 MR. LUMAN: Yes.

2 MR. KRAUSE: I object on timeliness
3 grounds.

4 BY MR. LUMAN:

5 Q. Dr. Quackenbush, can you let me know
6 when you get the document?

7 A. Yes, I have it.

8 Q. And this is the declaration that you
9 submitted in IPR 2023-00317; correct?

10 A. I believe that's correct. And it's
11 dated December 6th, 2022.

12 Q. Would you turn with me to
13 paragraph 183, and let me know when you arrive.

14 A. At 170 --

15 Q. Oh, paragraph 183, sorry.

16 A. Well, yeah, I'm there, 183.

17 MR. LUMAN: And, yeah, this one's --
18 very good. Thank you.

19 BY MR. LUMAN:

20 Q. I'm looking at the screen how the IT
21 person has spliced the two together so we can see it
22 at the same time.

1 MR. LUMAN: Thank you for that.

2 BY MR. LUMAN:

3 Q. Okay. So looking at paragraph 183,
4 I'm looking at the third sentence where it says,
5 "Wagle's approach."

6 Do you see that one?

7 A. Yes, I do.

8 Q. So "Wagle's approach enriches by
9 isolating the targets and removing them from
10 non-targeted nucleic acids in the sample."

11 The targets there, that is the target
12 DNA; right?

13 A. I'd have to fully review -- I'd refer
14 to it as Wagle instead of Wagle. But I'd have to
15 fully review Wagle to understand, but if I look at
16 paragraph 182, Wagle suggested in certain
17 circumstances PCR-capture based techniques may be
18 less optimal (although not ineffective), and thus
19 proposes its exon capture approach as a related
20 technique suitable for the capture portion of the
21 general workflow.

22 So I am not certain what exact method

1 Wagle is using, but in paragraph 184 refers to an
2 RNA bait-based probes -- set of bait-based probes,
3 and that would allow one to do -- as I wrote here,
4 enriches by isolating the targets, so removing the
5 targets. Plus, the way these techniques work, some
6 additional DNA from nontargeted molecules in the
7 sample.

8 So this would be through Wagle's
9 approach, again, if I recall it, physically
10 isolating them as opposed -- and then doing PCR
11 amplification as opposed to doing PCR amplification
12 directly. As I wrote, "Forsheew's approach," which
13 is direct PCR, "captures the targets through
14 base-pairing hybridization and copies the targets
15 and thereby enriching them over nontargeted nucleic
16 acids."

17 So they're both enrichment techniques,
18 but both ultimately involve PCR steps. And in this
19 section, I'm simply arguing -- so this is an
20 obviousness argument that I make that if one doesn't
21 accept PCR as a capture-based -- as an appropriate
22 capture technique, that one of skill in the art

1 would understand one could use others, such as
2 hybridization -- I believe -- I believe Wagle uses
3 solution-based hybridization capture.

4 Q. And my question is a little more
5 basic. I was looking at just the sentence that
6 starts with "Wagle's approach enriches." And it
7 says "isolating the targets," and it doesn't specify
8 what those targets are.

9 The targets are nucleic acids; right?

10 A. So up above it talks about -- and,
11 again, I don't have the Wagle reference in front of
12 me, but up above, it refers to Wagle using an exon
13 capture approach. So Wagle may be using a
14 commercial -- commercially available product, like
15 an Agilent SureSelect. I don't recall.

16 And this would involve hybridization
17 with probes that I believe had biotin attached and
18 then hybridizing them to beads -- magnetic beads and
19 physically separating those and -- those molecules,
20 but along with some contaminating molecules, as
21 well, from the vast amount of DNA as a first step,
22 then to be followed by PCR as opposed to what

1 Forshew does, which is doing the PCR directly.

2 And then I don't recall in Forshew the
3 purification techniques that were used with the PCR.
4 I believe Forshew also includes physical removal of
5 the molecules at a later step through the
6 introduct- -- I don't know which step, but at some
7 point Forshew also does physical removal of the
8 molecules by attaching sequencing adapters.

9 So I guess the easiest way to
10 understand this is that Wagle does a physical
11 separation earlier, while Forshew is describing a
12 physical separation that would be done later.

13 Q. And still in that same sentence, can
14 you explain what you meant here about isolating the
15 target DNA, as Wagle's approach isolate the target
16 DNA?

17 A. So it says, "Wagle's approach enriches
18 by isolating the targets and removing them from the
19 nontargeted nucleic acids in the sample."

20 And as I explained, this then is going
21 to be followed by PCR amplification and sequencing.
22 Forshew's approach does the PCR amplification

1 upfront. But, again, understanding the workflow,
2 there would be an attachment of sequencing adapters
3 and physical isolation through -- attaching the
4 sequencing adapters to the targeted PCR and then a
5 physical isolation later.

6 So both of these are enrichment
7 techniques. I think the easiest way to understand
8 what's happening is they're all based on
9 complementary base-pairing, and I point that out
10 here. And it's simply that -- the major difference
11 is the order in which the physical separation
12 happens, but they're all based on the similar
13 principle. And as I point out here, a person of
14 skill in the art would know that one could replace
15 one with the other with a reasonable expectation of
16 success.

17 Q. So the Wagle approach, using the RNA
18 base probes, that's a version of solution-phase
19 hybridization capture; right?

20 A. So if I recall what's in Wagle, it's
21 an RNA-based approach. And as I point out, that
22 would be a solution hybridization, but these

1 techniques are not mutually exclusive and could
2 be -- a person of skill in the art would be
3 motivated to use hybridization followed by PCR or
4 vice versa.

5 If you really think about this in
6 detail, PCR is also happening in solution. So it's
7 also going to be a solution-based hybridization
8 approach to capture the target molecules.

9 I guess the biggest difference is
10 where the physical separation happens and where the
11 amplification occurs. But, in fact, if one were to
12 perform the solution-based capture, one would then
13 have to do additional modifications, and that would
14 ultimately involve attaching sequencing adapters for
15 the molecules so they could be sequenced so they
16 would again physically be captured.

17 And I don't recall how Wagle does
18 that. I don't have the reference in front of me.
19 But I can imagine a variety of different ways,
20 including targeted PCR being used by Wagle, too.

21 Q. Let's make the Wagle reference
22 available to you.

1 A. All right.

2 Q. That one is Exhibit 1033.

3 MR. LUMAN: Can you put that in the
4 Box available for Dr. Quackenbush, please.

5 THE DOCUMENT TECH: It's up.

6 (Exhibit 1033, No Bates Numbers,
7 High-Throughput Detection of Actionable
8 Genomic Alterations in Clinical Tumor Samples
9 by Targeted, Massively Parallel Sequencing,
10 Research Article, Wagle et al., received and
11 marked.)

12 BY MR. LUMAN:

13 Q. All right.

14 A. I'm downloading it now.

15 Q. Will you let me know when you have it
16 in hand?

17 A. So I do. I thought Wagle was a
18 journal article, and this appears to be something
19 different.

20 Q. Let's see what's in that Dropbox.

21 A. This says petitioner's reply to Patent
22 Owner's response.

1 THE DOCUMENT TECH: So 1033 is exactly
2 what's on the screen right now. That's
3 Exhibit 1033.

4 MR. LUMAN: Oh. Well, let's get a
5 different -- that's not Exhibit 1033. So
6 let's get the right one. So --

7 THE DOCUMENT TECH: So let me go ahead
8 and delete what's in the Box. So just give
9 me one second.

10 MR. LUMAN: All right. Thank you,
11 Henry.

12 I haven't had a chance to drop it in,
13 but I'll let you know when it's there.

14 Can we off the record for a minute?

15 MR. KRAUSE: Sure.

16 MR. LUMAN: Off the record at 9:08.

17 (Pause.)

18 MR. LUMAN: Let's go back on the
19 record at 9:10.

20 BY MR. LUMAN:

21 Q. So, Dr. Quackenbush, we have a new
22 version of 1033 available to you which should be the

1 correct Wagle document.

2 Do you have that in hand?

3 A. Yes, I do.

4 Q. Thank you.

5 So I wanted to let you have Wagle

6 available, but my question stills relate to

7 Exhibit 1020 from IPR 2023-00337, paragraph 183.

8 MR. LUMAN: So we can put 183 --

9 paragraph 183 back up to the screen, please.

10 BY MR. LUMAN:

11 Q. Now, Wagle's RNA bait-based approach
12 is an example of a solution-phased hybridization
13 capture probe approach; right?

14 A. It's an approach one could
15 characterize as a solution-based hybridization
16 capture approach, yes.

17 Q. And solution-based hybridization
18 capture probes, like those used by Wagle, may
19 physically capture the target DNA; is that true?

20 A. So I'm reading what Wagle's
21 describing.

22 (Document review.)

1 BY MR. LUMAN:

2 Q. Is that a yes or a no?

3 A. Sorry, I'm taking a look at Wagle's
4 method section.

5 Q. Okay.

6 (Document review.)

7 THE WITNESS: So I'm sorry, Mr. Luman.
8 Repeat the question, please.

9 BY MR. LUMAN:

10 Q. Solution-based hybridization capture
11 probes, like those used by Wagle, physically capture
12 the target DNA; is that true?

13 MR. KRAUSE: Objection, incomplete
14 hypothetical.

15 THE WITNESS: So if I turn to Wagle's
16 method section, and this is on page 91, and
17 this is often a challenge with reading the
18 literature, but it says, Solution-based [sic]
19 hybrid capture was performed as described
20 previously, and refers to reference 51 with
21 three modifications.

22 So we don't have all the details of

1 what happens. I can speculate as to what
2 likely happens, which is these
3 oligonucleotides are defined to be RNA
4 molecules. They're described as being
5 biotinylated.

6 I would assume, based on that from the
7 perspective of a person of ordinary skill in
8 the art, that those would then be bound to
9 streptavidin-encoded magnetic beads, and the
10 majority of nonbound DNA would be washed
11 away, but not all.

12 But the important thing to recognize
13 here is that this approach described by Wagle
14 also incorporates PCR. And in the very next
15 paragraph in the "Pooling and Hybrid Capture"
16 section of Wagle, on page 91, it says, "The
17 final volume of the hybridization reaction
18 consisted of a variety of different things."

19 And it says, "During PCR enrichment of
20 the captured DNA" -- and he uses surprise
21 quotes, the catch -- "PCR was performed with
22 primers" -- and it describes the primers at

1 one micromolar. Instead of primers, I guess,
2 PE1 and PE2, which he had described
3 previously.

4 So reading Wagle's description, the
5 hybridization -- the pooling and hybrid
6 capture, in the way Wagle implements it
7 explicitly in this section, includes a PCR
8 amplification. So there's some physical
9 removal based on my interpretation, but then
10 also a PCR amplification.

11 BY MR. LUMAN:

12 Q. So let's focus just on the
13 solution-phase hybridization -- hybrid capture
14 that's referenced on page 91 of Wagle.

15 A. Okay.

16 Q. Let's leave out the PCR step.

17 The solution-phase hybrid capture
18 physically captures the target DNA; right?

19 MR. KRAUSE: Objection, incomplete
20 hypothetical.

21 THE WITNESS: So I think Wagle is
22 considering all of this as being part of the

1 hybrid capture, right. So the section
2 doesn't say -- the section heading, and
3 they're only two paragraphs in this section,
4 it says "Pooling and Hybrid Capture." So my
5 interpretation is these two steps are
6 describing the pooling and hybrid capture
7 approach.

8 The discussion here, right, in the
9 second paragraph, which includes the PCR
10 step, says, "The final volume of the
11 hybridization reaction was 19 microliters,
12 consisting of the following components" --
13 and I'm not going to read all of those
14 components.

15 And then the very next sentence goes
16 into, during PCR enrichment of the captured
17 DNA, right, the catch, in quotes, PCR was
18 performed.

19 So Wagle's own description is that the
20 hybrid capture involves what you might refer
21 to as the physical removal of these
22 molecules, but also PCR as the necessary

1 condition for the next step, which he
2 describes as sequencing and analysis.

3 And, again, we don't have all of the
4 steps provided here because he refers back to
5 another reference where he previously
6 described this approach, which was reference
7 51.

8 BY MR. LUMAN:

9 Q. Right. And then let's just talk about
10 the solution-phase hybrid capture portion. There,
11 the solution-phase hybrid capture physically
12 captures the target DNA; right?

13 MR. KRAUSE: Objection, incomplete
14 hypothetical, asked and answered.

15 THE WITNESS: So a read of this, based
16 on Wagle's own disclosure, is that pooling
17 and hybrid capture involves the use of these
18 RNA biotinylated RNA probes referred to
19 previously. One of ordinary skill in the art
20 would understand that that would capture
21 largely the targets but then some other
22 regions and then that there -- that inherent

1 in this hybrid capture is a PCR-based step.
2 That's explicitly what Wagle tells us, that
3 it involves hybridization of these probes and
4 then a subsequent PCR.

5 BY MR. LUMAN:

6 Q. And it's possible to use
7 solution-phase hybrid capture probes to physically
8 capture target DNA without doing PCR; right?

9 MR. KRAUSE: Objection, incomplete
10 hypothetical.

11 THE WITNESS: One could do a lot of
12 different things, right. One has to ask the
13 purpose of Wagle doing this pooling and
14 hybrid capture, and it's actually to
15 subsequently do sequencing and analysis,
16 right.

17 So, you know, Wagle could
18 hypothetically add capture probes and then
19 throw everything away, right. But that's not
20 the purpose of doing this hybrid capture.

21 The purpose of doing hybrid capture is
22 to do sequencing and analysis. And Wagle

1 himself tells us that the hybrid capture was
2 performed in conjunction with PCR to
3 facilitate sequencing.

4 So the hybrid capture includes this
5 PCR-based step which attaches the sequencing
6 adapters. So the hybrid capture is a
7 multi-step process, including PCR.

8 BY MR. LUMAN:

9 Q. Sure. So let's set aside Wagle for a
10 minute and a person of ordinary skill in the art can
11 use solution-phase hybrid capture probes to
12 physically capture target DNA; isn't that true?

13 MR. KRAUSE: Objection, form.

14 THE WITNESS: So, hypothetically, one
15 could do a variety of different things,
16 right. And I wouldn't want to speculate on
17 all the different things one could do.
18 Remember we're talking about two patents,
19 each of which discusses the design -- I don't
20 have the patents in front of me. So I
21 apologize if I'm not quoting the language
22 exactly -- but each of which involves

1 designing capture probes, and those could be
2 PCR capture probes, hybridization-based
3 capture probes, other types of capture
4 probes, I believe there's a long list that
5 are disclosed in the written description of
6 each patent, each of which relies on
7 complementary base-pairing between nucleic
8 acids and that one is doing this capture or
9 enrichment specifically for doing sequencing.

10 So as Wagle himself discloses, the PCR
11 step is inherently necessary to attach what
12 are referred to as primers with P5 and P7,
13 one skilled in the art would understand that
14 those are actually part of the sequencing
15 adapters that are necessary for doing
16 Illumina sequencing, which is what's
17 described in the very next section, right.

18 So, hypothetically, one could do lots
19 of things in the context of what the patents
20 are claiming and in the context of what Wagle
21 is disclosing is part of a process. The
22 hybridization with these RNA-based baits and

1 the PCR are all part of the hybrid capture
2 process.

3 BY MR. LUMAN:

4 Q. And I'm looking at paragraph 183 of
5 your declaration in that third sentence, "Wagle's
6 approach enriches by isolating the targets and
7 removing them from non-targeted nucleic acids in the
8 sample."

9 And that was true when you wrote it;
10 right?

11 A. That's true and --

12 MR. KRAUSE: Objection,
13 mischaracterizes.

14 BY MR. LUMAN:

15 Q. And it's still true today?

16 A. I'm sorry.

17 THE WITNESS: I'm sorry, Mr. Krause.

18 MR. KRAUSE: I was just lodging an
19 objection to the extent he's
20 mischaracterizing what's in the declaration
21 in the question.

22 MR. LUMAN: I mean, I read it

1 verbatim.

2 THE WITNESS: If I can answer the
3 question --

4 BY MR. LUMAN:

5 Q. So that --

6 (Cross talk.)

7 THE WITNESS: If I could answer the
8 question that you posed, please.

9 You asked me if that's true. And yes,
10 it is true. It enriches by isolating the
11 targets and removing them, but that isn't the
12 only thing it does. And we just looked at
13 Wagle and the hybrid capture approach Wagle
14 describes includes also doing PCR.

15 So yes, it does involve a step -- that
16 PCR-based approaches and the solution-based
17 hybrid capture approaches described by Wagle
18 has different steps in different orders,
19 right. But one skilled in the art would
20 understand that these are both techniques for
21 enriching target loci for subsequent
22 sequencing. And that's really the point.

1 What I'm trying to -- if you look at
2 this entire section, I'm not distinguishing
3 solution-based hybridization from PCR as
4 performing a different, a fundamentally
5 different method, right.

6 If you look at paragraph 182, I write,
7 "A person of skill in the art [sic] would
8 have been motivated to combine Forshew and
9 Wagle by using Wagle's solution-based
10 hybridization RNA baits as capture probes,
11 either in place of, or in addition to,
12 Forshew's PCR primer capture probes," right.

13 So the argument really here is that
14 these are methods that were known to be
15 complementary to each other, all directed
16 toward isolating target loci for subsequent
17 analysis.

18 BY MR. LUMAN:

19 Q. The target loci -- I just don't want
20 to get hung up on -- the target loci is the -- the
21 target location of DNA; is that fair?

22 A. The target loci are the regions of the

1 genome that one wants to subsequently analyze.

2 Q. And the last sentence of paragraph 183
3 says, "ForsheW's approach captures the targets
4 through base-pairing hybridization and copies the
5 targeted and thereby enriches them over non-targeted
6 nucleic acids."

7 That was true when you wrote it;
8 right?

9 A. That's true. And looking at Wagle,
10 too, we understand that Wagle also does PCR to --
11 using base-pairing hybridization and copies the
12 targets thereby enriching them over the nontargeted
13 nucleic acids. So it's true of both ForsheW and
14 Wagle.

15 Q. Do you have any edits you'd like to
16 make to paragraph 183?

17 A. No, paragraph 183 is true as written.
18 And, again, we have to interpret this in the context
19 of what I wrote.

20 Q. And Wagle's approach uses
21 solution-phase hybrid capture probes, and that
22 process involves physically capturing the target

1 DNA; right?

2 A. In the same way that PCR involves
3 physically capturing target DNA, there's a process
4 of hybridization and amplification.

5 Q. If we can turn back to Mertes. That's
6 Exhibit 1006.

7 A. Sure. I have that up.

8 THE DOCUMENT TECH: And you want that
9 on the screen or --

10 MR. LUMAN: Yes, please. And I'd like
11 to go to page 375.

12 THE WITNESS: All right. I'm there.

13 BY MR. LUMAN:

14 Q. And I want -- do you see the
15 sentence -- it's on the right-hand side. It says,
16 "Given the operational characteristics."

17 Do you see that one?

18 A. Yes, I do.

19 Q. Okay. So Mertes says, "Given the
20 operational characteristics of these different
21 target [sic] enrichment methods, they naturally vary
22 in their suitability for different fields of

1 application."

2 Do you agree with Mertes at this -- do
3 you agree with Mertes' statement?

4 MR. KRAUSE: Objection, 403.

5 THE WITNESS: So I'm not sure all of
6 what Mertes is trying to imply. In general,
7 there are differences between these
8 techniques. There are different variations
9 on these techniques.

10 Wagle, for example, is using RNA-based
11 solution hybridization probes. I can tell
12 you that because subsequently Wagle, I'm
13 sure, uses an RNase to degrade the RNA.
14 There are other approaches that use DNA-based
15 hybridization capture probes, followed by
16 PCR, just like Wagle follows his by PCR,
17 right.

18 So there are different applications.
19 And we talked about Mertes previously. And
20 Mertes called out a list of criteria that he
21 believed were important -- I believe this was
22 on page 380. There were, I think, eight or

1 nine criteria he had called out that he would
2 consider in addition to others in making a
3 right choice, right.

4 But an important aspect here is that
5 PCR-based approaches in this very same
6 paragraph may be preferable as they enable a
7 deep and even coverage over the region of
8 interest, right. That is what I would call a
9 locus suitable for genetic variance analysis,
10 right.

11 So, you know, Mertes is actually
12 teaching, I think, here to some of the
13 advantages of PCR, like Leary's approach.
14 But, you know, I think Mertes I think would
15 also recognize that there's significant
16 overlap between many of these different
17 methods. And, again, each one is going to
18 have advantages and disadvantages, depending
19 on the particular application.

20 So I don't disagree with Mertes, but I
21 think we shouldn't overinterpret what Mertes
22 is saying, because it's being presented in a

1 much broader context.

2 MR. LUMAN: So I realize it's about
3 12:30 your time. Would you like a lunch
4 break? Now would be a good time.

5 THE WITNESS: I mean, we can take a
6 short break.

7 Ellen, I -- or, I'm sorry, Eileen, are
8 you located on the East Coast or West Coast?

9 THE REPORTER: East Coast.

10 THE WITNESS: Oh, okay. Then for our
11 court reporter, why don't we take a lunch
12 break.

13 MR. LUMAN: Okay. Let's go off the
14 record at 9:32 Pacific Time.

15 (Luncheon recess from the record.)

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1 A F T E R N O O N S E S S I O N

2 MR. LUMAN: We're back on the record
3 at 10:04 Pacific.

4 BY MR. LUMAN:

5 Q. I would like to go back to
6 Exhibit 1033, that's Wagle, and look at page 91.

7 MR. LUMAN: Can we have page 91
8 brought up on the screen, please.

9 And specifically in the "Pooling and
10 Hybrid Capture," can we zoom in on that section?
11 That's the right-hand column.

12 BY MR. LUMAN:

13 Q. Dr. Quackenbush, I'm looking at the
14 second paragraph. Do you see the one that says,
15 "The final volume"?

16 A. Yes.

17 Q. And then there's a sentence that
18 begins, "Third, during PCR enrichment."

19 Do you see that one?

20 A. Yes, I do.

21 Q. It says, "Third, during PCR enrichment
22 of the captured DNA" -- and it's got "the catch."

1 Okay. It's referring to capture DNA,
2 right, in that sentence?

3 A. The sentence refers to captured DNA,
4 which they call "the catch," yes.

5 Q. And at that point, the solution-phase
6 hybrid capture probes have physically captured the
7 target DNA; right?

8 MR. KRAUSE: Objection, incomplete
9 hypothetical.

10 THE WITNESS: So, you know, I'm not
11 sure what you mean here by "the target DNA,"
12 right. The general principle of hybrid
13 capture is that if you think about hybrid
14 capture probes, they're -- they're really --
15 they're designed to capture -- and I think
16 Mertes uses this phrase -- the sequences of
17 interest, right.

18 So there's a locus in the genome that
19 in the context of these patents that includes
20 some polymorphism that we believe is going to
21 be informative for some reason, right. And
22 so the probes capture these sequences of

1 interest, right.

2 They can capture the native DNA. They
3 can capture amplified DNA, right. They're
4 not necessarily built for -- it's not
5 necessarily the target DNA. Again, this
6 capture protocol here that you're referring
7 to refers back to reference 51, right.
8 Capture -- the hybrid capture is performed as
9 previously described, reference 51.

10 I don't know what the molecules are.
11 I don't know if the DNA has been amplified,
12 pre-amplified. I don't know what's happened.
13 The important thing here is the catch, are
14 these sequences of interest that are then
15 going to be used downstream in the sequencing
16 and analysis step.

17 So, you know, if they're amplified
18 there's still DNA, and that's what's
19 captured. So I guess I don't fully
20 understand the question you're trying to ask.

21 BY MR. LUMAN:

22 Q. So solution-phase hybridization

1 capture probes, they can capture the target DNA by
2 physically isolating it from solution; right?

3 MR. KRAUSE: Objection, incomplete
4 hypothetical.

5 THE WITNESS: So, hypothetically, they
6 can do lots of different things, right. The
7 key thing about them is that they're designed
8 to enrich for sequences at loci of interest,
9 at -- yeah, sequences of interest which
10 appear at a particular locus of interest.

11 And, you know, at least the way that
12 Wagle is describing this, it's -- the hybrid
13 capture involves some steps which I don't
14 know because they're previously described in
15 reference 51. It's hybridization with
16 biotinylated RNA baits, which would imply
17 that they're doing some streptavidin
18 enrichment, but then the entire capture
19 process involves doing this PCR, too, right.

20 So the captured DNA is going to be
21 enriched for particular loci but, you know, I
22 don't know the nature of that DNA. It's

1 really an emphasis on capturing these -- the
2 sequences of interest by which I would infer
3 these are the loci of interest that one wants
4 to analyze.

5 BY MR. LUMAN:

6 Q. So what I'd like to do now is look at
7 Exhibit 2157.

8 MR. LUMAN: Could we make Exhibit 2157
9 available to Dr. Quackenbush.

10 (Exhibit 2157, No Bates Numbers,
11 Gender-Specific Molecular and Clinical
12 Features Underlie Malignant Pleural
13 Mesothelioma, Molecular and Cellular
14 Pathobiology, 2015, DeRienzo and Quackenbush
15 et al., received and marked.)

16 THE DOCUMENT TECH: It's up.

17 MR. LUMAN: Thank you.

18 BY MR. LUMAN:

19 Q. Dr. Quackenbush, can you let me know
20 when you've got it?

21 A. I've got it, yes.

22 Q. Do you recognize this document?

1 A. It's a paper on which I was a coauthor
2 about eight years ago.

3 Q. Can you turn to page 320 with me. And
4 I'd like to look --

5 A. All right. I'm there.

6 Q. -- at the section called "Validation
7 of SNV."

8 MR. LUMAN: That's the upper right.

9 Yeah, up there.

10 THE WITNESS: Okay.

11 BY MR. LUMAN:

12 Q. So the first sentence says, "Selected
13 candidate SNVs were further characterized using
14 PCR."

15 Do you see that?

16 A. Yes, I do. Excuse me. Yes, I do.

17 Q. You did not use solution-based
18 hybridization capture probes for that step; right?

19 MR. KRAUSE: Objection, relevance.

20 (Document review.)

21 THE WITNESS: So this work that I
22 published over eight years ago. There are

1 some candidate SNVs that were sequence -- so
2 SNV here means single nucleotide variant. If
3 I look previously, there was whole genome
4 sequencing that was performed to identify
5 these SNVs. And they were characterized
6 using PCR and conventional Sanger sequencing.
7 So this would be isolating each individual
8 SNV and sequencing it separately, not using
9 the next-generation sequencing techniques.

10 And it says, Gene-specific primer
11 pairs were use to amp- -- to PCR amplify
12 genomic DNA from tumor and normal samples
13 (Supplementary Table) -- and then, again, as
14 previously described.

15 So this would be PCR using
16 solution-based hybridization of capture PCR
17 primers to genomic DNA to capture those
18 specific regions with the SNVs. I don't
19 believe we used biotinylated probes and
20 streptavidin beads here.

21 So this is distinct from what you're
22 been calling capture probe analysis, but it

1 does use solution-based hybridization of
2 nucleic acids to target regions in PCR in
3 ways consistent with what was described in
4 Wagle -- we could do what was described in
5 Wagle here.

6 BY MR. LUMAN:

7 Q. And do you see at the bottom of that
8 page, there's -- on the right-hand side there's a
9 "Target capture, sequencing and data analysis"
10 heading? And it splits the page.

11 A. Yes.

12 Q. And once it splits the page, the first
13 full sentence starts with "Library construction."

14 Do you see that one?

15 A. Yes.

16 Q. "Library construction and custom exome
17 capture were performed using SureSelect XT2 for
18 Illumina protocol (Agilent)..."?

19 A. Yes.

20 Q. So here you did use solution-phase
21 hybridization capture probes; right?

22 A. In a protocol that also involved PCR

1 amplification, because that's what's necessary for
2 Illumina sequencing, just as described in Wagle.
3 So, yes, we used Agilent SureSelect XT2 protocol.

4 Q. Why didn't you use PCR for this step
5 of your paper?

6 A. So PCR was used here in doing the
7 library preparation. I don't recall why we chose
8 the SureSelect exome capture. I think it was just
9 the availability of reagents rather than trying to
10 get a whole exome set of PCR primers. I don't
11 recall the exact reason why we chose this one over
12 the other.

13 As we discussed earlier, there are a
14 lot of factors that play into that choice, and this
15 is a choice we made over eight years ago. I think
16 it was really the availability of this commercial
17 product, SureSelect XT2, from Agilent.

18 Q. What advantages did using the
19 solution-phase hybridization capture probes for this
20 step provide over PCR?

21 A. Again, this method involves PCR. I
22 think our selection of the Agilent SureSelect XT2

1 protocol was just that it was a commercially
2 available set of reagents that we had used.

3 There are also other differences
4 between this and what we discussed with the SNV
5 sequencing. The SNV sequencing was done using
6 Sanger sequencing, where each individual molecule
7 was amplified in sequence -- or each independent
8 target locus was amplified in sequence independently
9 on a single lane on a Sanger sequencing -- I guess
10 it would be a capillary at that point. So in a
11 single capillary in a Sanger sequencing instrument,
12 while here there was a multiplex analysis using the
13 Illumina HiSeq 2000, so a next-generation sequencing
14 instrument.

15 So there were a lot of different
16 factors that went into the choice at which
17 particular step as to why we chose one over the
18 other, but the important thing is that both of these
19 are hybridization-based enrichment techniques.

20 Q. If we can go back to the previous
21 page, which is page 320, and look back at the
22 "Validation of SNV by Sanger sequencing" section.

1 MR. LUMAN: Yeah, that section there.

2 BY MR. LUMAN:

3 Q. For the validation of SNV by Sanger
4 sequencing, what would you have to change to your
5 protocol here to use solution-phase hybridization
6 capture probes instead of PCR?

7 A. I don't recall all the details. The
8 important thing is that to a person of ordinary
9 skill in the art, and this was 2016, one would have
10 recognized that one could use, either depending on
11 the circumstances, and this simply happened to be a
12 choice that we had made in one case because we were
13 doing Sanger sequencing, in another case because we
14 were using Illumina sequencing and looking at at
15 least a significant fraction of the exome.

16 So these both fall into the broad set
17 and did as of 2006, as well as prior to 2010, as
18 hybridization-based approaches that rely on
19 hybridization of nucleic acid molecules to
20 complementary base-pairing of those molecules to
21 target loci that were then used for subsequent
22 analysis.

1 Q. What would you have to change to
2 what's described in the section "Validation of SNV
3 by Sanger sequencing" in order to use solution-phase
4 hybridization capture probes instead of PCR?

5 MR. KRAUSE: Objection, incomplete
6 hypothetical, relevance, outside the scope.

7 THE WITNESS: So I don't have the
8 detailed protocol here. It referred -- so
9 the PCR step that you're referring to with
10 the SNV analysis refers to reference 16.

11 Reference 16 is a 2010 paper and from
12 some of the same authors. I don't believe I
13 was a coauthor on that paper.

14 So I don't know the exact protocol,
15 but one skilled in the art would understand
16 that one could use PCR, one could also use
17 MIPS, one could use solution or
18 solid-phase-based hybridization capture
19 followed by PCR all to do sequencing.

20 If I were to use -- actually, there
21 are a lot of reasons why in this case PCR was
22 probably the most reliable technique, not the

1 least of which would be for Sanger sequencing
2 precisely defining the sequence of interest
3 that one would want to determine.

4 So one could use hybridization-based
5 capture, but one would certainly for Sanger
6 sequencing want to follow it up with a
7 targeted PCR, and those would be the
8 molecules that one would analyze.

9 BY MR. LUMAN:

10 Q. What is it about the Sanger sequencing
11 that would make PCR the most reliable technique?

12 A. So I don't know if I would call it the
13 most reliable. I would say it's preferable. So if
14 you look at next-generation sequencing, alter
15 high-throughput sequencing, Illumina sequencing,
16 whatever you'd like to call it, following the
17 amplification step, right, which is inherent in each
18 one of the methods that we've discussed, the
19 amplified biological molecules, which are enriched
20 for the loci of interest are introduced into
21 something called a flow cell at low enough
22 concentration that they bind at locations that are

1 physically separated from each other.

2 Following the binding, the P5 and P7
3 regions that Wagle referred to are used in a process
4 called bridge amplification that takes each
5 individual molecule and copies it thousands --
6 hundreds of thousands, I don't know, millions of
7 times in -- it's a process called clonal
8 amplification. So in a little region or spot on the
9 slide, you get millions of copies of that individual
10 molecule.

11 So in some sense after the
12 amplification step, each molecule is sequenced
13 individually. In Sanger sequencing, a collection of
14 molecules -- and that sequencing process is an
15 enzymatic process.

16 In Sanger sequencing, a collection of
17 molecules is processed through the Sanger sequencing
18 reaction. Next-generation sequencing, Illumina
19 sequencing does sequencing by synthesis. So each
20 base is added and then detected in each one of these
21 little spots on the flow cell.

22 In Sanger sequencing -- Sanger

1 sequencing relies on something called di-deoxy
2 terminator chemistry. So you have a family of
3 amplified molecules. And I have to carry out in
4 principle four separate sequencing reactions, each
5 which of terminates the synthesis of a new strand of
6 DNA at a particular base. Those are pooled
7 together. It's actually typically pulled together
8 all at one using different chemistry, but
9 conceptually it's four reactions. And then each
10 individual molecule is used to determine only one
11 base in contrast to Illumina sequencing, where each
12 molecule is used to determine multiple bases.

13 So they're fundamentally different
14 ways in which a sequencing works that requires
15 different preparation techniques. And the good
16 thing about having PCR amplified molecules for
17 Sanger sequencing is, first, you also have to attach
18 a primer sequence just like you do with Illumina,
19 but all of the molecules start at the same place,
20 and that allows the sequencing to come out -- the
21 sequencing data to emerge in phase.

22 Q. So if you had chosen to use

1 solution-phase hybridization capture probes for the
2 process described under the validation of SNV by
3 Sanger sequencing, how would you go about doing
4 that?

5 A. Again, there are a variety of
6 different ways one could hypothetically do that.
7 Ultimately, whatever one did one would have to do
8 targeted PCR on whatever was captured to allow the
9 Sanger sequencing reactions all to start at the same
10 place because all would have to have primer
11 sequences introduced at the same location.

12 So it would be an additional step,
13 after which one would have to do targeted PCR with
14 specific primers, but all the methods would rely on
15 nucleic acid hybridization through complementary
16 base-pairing.

17 MR. LUMAN: Okay. I'd like to make
18 Exhibit 2158 available to Dr. Quackenbush.

19 (Exhibit 2158, No Bates Numbers, Exome
20 sequencing-based copy-number variation and
21 loss of heterozygosity detection: Exome CNV,
22 Bioinformatics, Vol. 27, No. 19, 2011,

1 Sathirapongsasuti and Quackenbush et al.,
2 received and marked.)

3 THE WITNESS: All right. I have it up
4 and open.

5 BY MR. LUMAN:

6 Q. All right. Do you recognize this
7 document?

8 A. Yes, it's a paper published in 2011
9 with my student Fah as the first author, and this
10 was a collaborative project that he did working one
11 summer with Stan Nelson at UCLA -- sorry, Columbia
12 University. I'm sorry.

13 Q. Thanks.

14 Would you turn to page 2651, and look
15 at Figure 2 with me, please.

16 A. I'm sorry, it was UCLA. Stan is at
17 UCLA.

18 What page, please?

19 Q. Page 2651 Figure 2.

20 A. All right.

21 Q. I'm looking at -- there's a sentence
22 that says, "All 6 samples."

1 Do you see that one under there?

2 A. Yes.

3 Q. "All 6 samples were captured using the
4 Agilent SureSelect Human All Exon G3362."

5 Do you see that?

6 A. Yes.

7 Q. So those Agilent SureSelect are
8 solution-phase hybridization capture probes; right?

9 A. So there's a description on page 2650
10 of the document, and the -- in the "Methods"
11 section. This says, "The libraries were generated
12 following the Agilent SureSelect Human All Exon Kit
13 version 1.01 protocol, and the Illumina Genome
14 Analyzer (GAIIx) flowcell prepared according to the
15 manufacturer's protocol."

16 So the selection that Agilent
17 SureSelect does, if I recall, involves both the use
18 of biotinylated probes and then a specific PCR
19 amplification, as I believe Wagle discloses, to then
20 allow for Illumina sequencing.

21 Q. So the Agilent SureSelect probes are
22 solution-phase hybridization capture probes; right?

1 A. One could call them solution-phased
2 hybridization capture probes. But, again, recall,
3 they operate on the same basic process of
4 complementary base-pairing between nucleic acids to
5 enrich target sequences, and that PCR is a natural
6 consequence -- or natural component of that capture
7 process as directed towards sequencing.

8 Q. Still on page 2651, I want to look on
9 the right-hand column. In the right-hand column,
10 the very top paragraph, there's a sentence that
11 says, "We note that the -- that the power of the
12 method."

13 Do you see that one, about halfway
14 down?

15 A. Okay. Yeah, I found it.

16 Q. Okay. And do you see that it refers
17 to capture probe design, at the end of that
18 sentence?

19 A. Okay. I see where the capture probe
20 design appears, yeah.

21 Q. So the capture probe design is
22 referencing the Agilent SureSelect capture probes;

1 correct?

2 A. So I forget all the details of the
3 Agilent SureSelect protocol that we used 13 years
4 ago. What it -- what this is saying is that in this
5 case, the capture probes were designed specifically
6 to the exons. They or PCR primers could be designed
7 to the flanking intronic sequences in case an exon
8 were deleted.

9 So the probe design, whether PCR or
10 biotinylated oligonucleotides were captured, right,
11 all of which operated in the same procedure, should
12 just target the flanking intronic sequencing in case
13 an exon happens to be deleted.

14 (Discussion off the record.)

15 BY MR. LUMAN:

16 Q. All right. If we could go back to
17 your declaration, Exhibit 1225, please.

18 A. All right. I have that open.

19 Q. I'd like to go to paragraph 37.

20 MR. LUMAN: And we'll need this one to
21 split the page, if we can do that. So that
22 we can see the text that's -- yeah, thank

1 you, Henry.

2 THE WITNESS: All right. I'm there.

3 BY MR. LUMAN:

4 Q. So the last sentence -- I mean, you've
5 got a quote here from John West, but the last
6 sentence of the paragraph says, "This is consistent
7 with the contemporaneous literature."

8 Do you see that?

9 A. Oh, sorry, down below the page break,
10 yeah. Yes.

11 Q. So you say the contemporaneous
12 literature consistently referred to PCR as a
13 technique for capturing genomic loci for sequencing.

14 And my question is: If a technique
15 captures genomic loci for sequencing, does it
16 necessarily use capture probes?

17 MR. KRAUSE: Objection, incomplete
18 hypothetical, calls for a legal conclusion.

19 (Document review.)

20 THE WITNESS: I'm sorry, would you
21 repeat the question, please, Mr. Luman?

22

1 BY MR. LUMAN:

2 Q. If a technique captures genomic loci
3 for sequencing, does it necessarily use capture
4 probes?

5 MR. KRAUSE: Same objections.

6 THE WITNESS: So I think this would
7 depend on how you define "capture probes."
8 In the context of the decision by the PTAB --
9 let's see. I'm looking for the section in my
10 report.

11 The board construed the term to
12 encompass at a -- capture probes to
13 include -- to encompass at a minimum PCR
14 primer capture probes in solution-based
15 hybridization capture probes.

16 So based on the board's construction,
17 that would be consistent that PCR capture
18 probes are, in fact, the type of capture
19 probe.

20 And then I refer in the passage that
21 you pulled out to Section 2.D.3. And there,
22 among other pieces of evidence and arguments

1 that are presented in paragraph 55, it says,
2 "This understanding was reflected in the
3 contemporaneous knowledge of a POSA as well.
4 For example, Forshew expressly described its
5 use of PCR as a capture technique" -- and now
6 I'm quoting -- "All primer sets were used
7 together to capture the starting molecules
8 present in the template." And then I have a
9 citation to Forshew on page 3.

10 So the board has construed capture
11 probes to include PCR primers. In that
12 context, PCR primers and biotinylated
13 oligonucleotides would both fall within the
14 definition of "capture probes."

15 And so I believe you're asking about
16 PCR. This is also reflected in what Forshew
17 describes.

18 BY MR. LUMAN:

19 Q. So I'd actually like to ask a question
20 that's broader than that. There's just a technique
21 for capturing genomic loci for sequencing. It could
22 include PCR. It could include other things.

1 If there's just a technique for
2 capturing genomic loci for sequencing, would that
3 necessarily involve using capture probes under the
4 board's construction of that term?

5 MR. KRAUSE: Objection, incomplete
6 hypothetical.

7 THE WITNESS: I could conceive of many
8 other ways of preparing DNA for sequencing.
9 One could extract DNA -- I have to think
10 about that. I could conceive of many
11 different things one could do with DNA.
12 People might use language in different ways
13 to refer to different things.

14 In the context of the exercise I was
15 asked to carry out here, the analysis I'm
16 performing is based on the board's
17 construction of what a capture probe is, and
18 that is the construction which I believe is
19 consistent with the contemporaneous
20 literature demonstrating that references such
21 as Leary and Forshew represent invalidating
22 prior art.

1 BY MR. LUMAN:

2 Q. I understand that's your opinion. I
3 want to get a sense of the scope of the court's
4 claim construction of capture probe and how that
5 would be applied.

6 So understand the board's construction
7 of capture probe, does any technique for capturing
8 genomic loci for sequencing necessarily use a
9 capture probe?

10 A. So I don't have the patents in front
11 of me. I know the patents refer to a wide variety
12 of different methods that clue PCR, but I don't know
13 if each and every one of them would include what one
14 might construe as a capture probe.

15 The board's construction is actually
16 fairly broad and they've construed capture probes to
17 encompass at a minimum PCR primer capture probes in
18 solution-based hybridization probes, which are
19 biotinylated oligonucleotide baits.

20 Q. Do you think that the board's
21 construction of capture probes being fairly broad is
22 an appropriate construction?

1 A. The construction is consistent with
2 what I recall being presented in the written
3 description of the patents -- and I'll remind you I
4 don't have the patents in front of me now, but is
5 consistent with the written description in the
6 patents and also with the contemporaneous
7 literature.

8 There's a fairly significant portion
9 of this report which refutes Dr. Furneaux's attempt
10 to twist the meaning of capture probes. And I'd be
11 happy to turn to those and review them with you, if
12 that would be helpful.

13 Q. We had looked at two of your journal
14 articles. We had looked at Exhibit -- let me get
15 the exhibit number correct -- Exhibit 2157.

16 A. All right.

17 Q. Do you remember that?

18 A. Yes. And 2158, I believe.

19 Q. 2157 was published in the year 2016.
20 Is that considered contemporaneous literature to the
21 patent at issue?

22 A. So I believe the priority dates for

1 the patents -- and, again, I don't have them in
2 front of me, but they're 2013 and 2012. I don't
3 believe I cited to the paper from 2015 in any of the
4 arguments that I made.

5 Q. So I'd like to go back to your
6 declaration, Exhibit -- I'm sorry, Exhibit 1225.
7 And I'd like to go to paragraph 53, please.

8 A. All right. All right, I'm there.

9 Q. In this paragraph there's a sentence
10 that starts with the word "curiously."

11 Do you see "curiously"?

12 A. Yes.

13 Q. What is curious to you about capture
14 probes including array-based hybrid capture on a
15 solid support?

16 A. So I talk about -- I actually refer
17 back -- again, I don't have the patents in front of
18 me to review them, but in paragraph 43 of my report,
19 I point to the claim limitation -- claim limitations
20 in the '394 patent where -- I read, "The claim
21 language and specification does not require the
22 'capture probe' structure to 'physically capture'

1 DNA. The relevant claim limitations only
2 'contacting' a nucleic acid sample with 'capture
3 probes.'" "

4 And then I quote language from -- oh,
5 from both the '394 and '033 patents in which -- the
6 language says, "contacting," in the '394, "said
7 second nucleic acid sample with a plurality of
8 capture probes"; or in the '033, "contacting said
9 nucleic acid sample with a plurality of capture
10 probes."

11 One of the things I think I found
12 curious was that Dr. Furneaux seems to limit all of
13 his arguments to what he perceives as differences
14 between hybridization-based capture probes and PCR
15 which captures the DNA through hybridization in
16 solution, but his construction also includes
17 array-based hybrid capture in a solid support. And
18 this is something that he seems to discount and
19 doesn't really discuss at all.

20 So the arguments he presents simply
21 don't make a clear -- don't clearly distinguish any
22 features that would cause me to question the board's

1 determination that capture probes could encompass
2 both -- both solution-based hybridization, as well
3 as PCR.

4 And if we, if we accept Dr. Furneaux's
5 arguments, it would also encompass array-based
6 capture. And I think probably -- and now I'm
7 speculating, but one of the reasons might be that
8 using array-based capture probes would actually
9 identify even more significant prior art that would
10 render the '033 and '394 patents obvious.

11 So I don't know why Dr. Furneaux
12 doesn't include those in his arguments, and I think
13 that's what I found curious when I wrote this.

14 Q. In your opinion, is it okay for
15 capture probes to include array-based hybridization
16 capture probes?

17 A. Well --

18 Q. Let me ask that a different way.

19 A. Okay.

20 Q. Is it okay with you for the board's
21 construction of capture probes to include
22 array-based hybrid capture in solid support?

1 A. So the board told us that capture
2 probes encompass at a minimum PCR primer capture
3 probes in solution-based hybridization capture
4 probes. So they're setting a floor. They could
5 incorporate other things. I would put MIPS probes
6 in here, padlock probes. Depending on the
7 application, I would also potentially include
8 solid-phase hybridization probes, right.

9 What they're telling us is that --
10 that the plain language of the claims doesn't
11 exclude PCR-based primer capture probes, which Leary
12 clearly uses as a way of -- and I quoted from Leary
13 earlier -- of capturing, I think it said, the
14 relevant DNA.

15 Yeah, the important thing here is that
16 Dr. Furneaux is trying to narrow the language in
17 ways that aren't consistent with one what -- one of
18 ordinary skill in the art would interpret or what's
19 represented in the literature or even in the patent
20 itself.

21 Q. And I want to be clear about -- you
22 mentioned MIPS. You believe that the board's

1 construction of capture probes encompasses MIPS;
2 correct?

3 A. We would have to look at the
4 application, but it encompasses at a minimum PCR
5 primer capture probes in solution-based capture
6 probes. What that means is that since the capture
7 probes can include PCR capture probes, those are
8 disclosed in Leary, and Leary represents
9 invalidating prior art. And we can go to Leary and
10 discuss that in detail.

11 But the board is telling us not to
12 just limit it to solution-based capture probes.
13 We'd have to look at other references to see how
14 they're used whether or not they meet the board's
15 construction.

16 Q. MIPS are molecular inversion probes;
17 right?

18 A. Yes, they are. And that appears, I
19 believe, in the Mertes reference we were looking at
20 or -- I think it was Mertes who discussed MIPS as a
21 third variation of enrichment techniques, as he
22 referred to them.

1 MR. LUMAN: I'd like to mark as
2 Exhibit 2181 the exhibit that that was
3 previously proposals marked at Exhibit 2177
4 in IPR 2023-00545.

5 Henry, that's -- the exhibit I'd like
6 you to pull up as Exhibit 2177.

7 THE WITNESS: All right. So it's come
8 up in Box.

9 MR. KRAUSE: Object to relevance,
10 foundation, timeliness.

11 THE WITNESS: And I have it open.

12 BY MR. LUMAN:

13 Q. Have you reviewed this article before
14 today?

15 A. I don't recall.

16 Q. Do you see that the author list,
17 there's an author with the last name D-I-E-H-N?

18 A. Sorry, I don't see that.

19 Q. Oh, apologies. We have the wrong
20 exhibit pulled up.

21 MR. LUMAN: All right. So let's do
22 this again. The exhibit I'd like to look at

1 Exhibit 2166 from IPR 2023-00545.

2 (Exhibit 2166, No Bates Numbers,

3 Detection and Diagnostic Utilization of

4 Cellular and Cell-Free Tumor DNA, Annual

5 Review of Pathology: Mechanisms of Disease,

6 2021, Jonathan C. Dudley and Maximilian

7 Diehn, received and marked.)

8 THE DOCUMENT TECH: Okay. And I am

9 just deleting the other one from Box. And

10 2166 is going to be available.

11 BY MR. LUMAN:

12 Q. All right. We are going to have this

13 one be Exhibit 2181, not the -- not Exhibit 2177

14 from --

15 MR. KRAUSE: I object on timeliness

16 grounds, relevance grounds, and outside the

17 scope.

18 BY MR. LUMAN:

19 Q. All right. So Exhibit 2166 from

20 IPR 2023-00545 has been marked as Exhibit 2181

21 during this deposition.

22 A. All right.

1 Q. Do you see on the first page there is
2 an author having the last name D-I-E-H-N?

3 A. Yes, I do.

4 Q. Are you aware of that author?

5 A. I'm bad with names. So I don't recall
6 Dr. Diehn. I can't say that I'm familiar with him.

7 Q. Do you know that he's one of the
8 founders of the company Foresight?

9 A. I haven't met him. I will take your
10 word for it.

11 Q. Would you turn to page 203 with me.
12 And at the top, there's a -- the very first
13 paragraph -- yeah.

14 A. All right.

15 Q. Do you see the paragraph that says --
16 I'm sorry, it's the sentence that says, "An
17 additional limitation is that hybrid capture-based
18 workflows."

19 Do you see that?

20 A. Yes.

21 Q. It says they "typically have longer
22 turnaround times, since the target enrichment

1 process often takes days (instead of hours with
2 PCR), and are more expensive, since they involve
3 sequencing on a larger genomic space."

4 Do you see that?

5 A. Yes, I do.

6 Q. And do you see at the beginning of
7 that paragraph, it says, "A challenge with hybrid
8 capture approaches is that a larger genomic space
9 provides more opportunities for artificial [sic]
10 mutations to arise."

11 A. I see that, yes.

12 Q. Do you agree with this author's
13 discussion of a challenge and an additional
14 limitation of hybrid capture probes?

15 MR. KRAUSE: Objection, foundation,
16 relevance, calls for speculation.

17 THE WITNESS: So I don't believe I
18 have seen this paper before. I have nothing
19 but the out-of-context paragraph you're
20 pointing to in a set of sentences that you're
21 pointing to in this paragraph.

22 And I don't know in what context these

1 authors are actually talking about the
2 relevant advantages they see in a 2021 paper,
3 which is nine years after the priority
4 date -- eight to nine years after the
5 priority dates for the two patents-in-suit.

6 But, you know, I will point out that
7 this analysis on its face appears consistent
8 with some of the discussions we had earlier
9 about the Mertes article in which Mertes was
10 saying that there are a variety of different
11 factors that one might consider in choosing
12 among a variety of different capture
13 techniques and that in certain applications
14 PCR has advantages and certain applications
15 solution-based hybridization capture has
16 advantages.

17 So not knowing the context, I can't
18 render much of a judgment. I'd be happy to
19 take -- it's a 26-page paper. I'd be happy
20 to take the next few hours and read it if
21 you'd like.

22

1 MR. LUMAN: I'd like to bring up
2 Exhibit 2031, which is the Furneaux
3 declaration.

4 (Exhibit 2031, No Bates Numbers,
5 Declaration of Henry Morrice Furneaux, Ph.D.,
6 received and marked.)

7 BY MR. LUMAN:

8 Q. Dr. Quackenbush, have you reviewed
9 this declaration by Dr. Furneaux?

10 A. Sorry, do I have that yet?

11 Q. Oh, sorry. Yeah, let me get -- why
12 don't you get it, and then I'll ask the question.

13 THE DOCUMENT TECH: Give me one
14 second. Okay. You should see 2031 up.

15 THE WITNESS: All right. It has
16 appeared. And I have it here, yes.

17 BY MR. LUMAN:

18 Q. Did you review Exhibit 2031 in
19 preparing your declaration in this case?

20 A. I believe this was the Furneaux
21 declaration that I was responding to in what I think
22 is marked as Exhibit 1225.

1 Q. That's my understanding, too.

2 A. Okay. Good.

3 So the answer is yes, I've reviewed
4 it.

5 Q. Would you turn with me to
6 paragraph 141?

7 A. All right. I'm there. Oh, wait --
8 yes, I'm there now.

9 Q. And do you see the first sentence, it
10 says, "It is unclear to me how Foresight and
11 Dr. Quackenbush propose to change the workflow of
12 Leary's PARE," P-A-R-E, "assay and what such a
13 changed workflow would look like..."?

14 Do you see that?

15 A. Yes, I do.

16 Q. What part of Leary's workflow do you
17 contend a person of ordinary skill in the art would
18 have modified to use hybridization capture probes?

19 A. I have to look back at my report to
20 see what Dr. Furneaux -- how I address
21 Dr. Furneaux's concerns.

22 (Document review.)

1 THE WITNESS: So I don't have Leary in
2 front of me. It's not been provided as an
3 exhibit for today's deposition. And I don't
4 have my original report in which I outlined
5 how one might adapt Leary's method to use
6 solution-based hybridization capture probes.

7 I did refer to some references that
8 were contemporaneous with Leary that disclose
9 the use of those hybridization-based capture
10 probes. My recollection of Leary is that
11 PARE was a paired-end analysis of large DNA
12 molecules using whole genome sequencing as a
13 first step and that the paired-end analysis
14 in Leary allowed Leary to identify
15 translocation breakpoints, which are a type
16 of polymorphism.

17 Leary then describes having isolated
18 those translocation break points designing
19 PCR capture probes to capture the relevant
20 regions of the genome where those
21 polymorphisms exist and then subsequently
22 analyze those in additional biological

1 samples.

2 So there's a whole genome sequencing
3 step -- and, again, I'm working from memory.
4 There's a whole genome sequencing step that
5 would not involve any type of capture probes,
6 identification of polymorphisms, design of
7 capture probes, application of those through
8 hybridization and subsequent sequencing and
9 analysis.

10 So without looking back at the other
11 documents and what Dr. Furneaux is referring
12 to, the ways for this substitution would make
13 sense would be if one doesn't see Leary on
14 its own, and given the board's description of
15 PCR primers as capture probes, if one were to
16 not see that as invalidating prior art, one
17 of the arguments I made was that one could
18 combine Leary with another reference -- and I
19 forget which one I cited to, but Leary and
20 another reference that does discuss the use
21 of hybridization capture one and that one in
22 steps 2 and 3, the subsequent analysis of --

1 the subsequent analysis of biological samples
2 after the whole genome sequencing and
3 identification of polymorphisms, that one
4 could use capture probes -- solution-based
5 hybridization capture probes in place of PCR
6 capture probes as the first step in those
7 subsequent analyses.

8 Does that make sense?

9 BY MR. LUMAN:

10 Q. Why don't I let you have Leary and
11 your declaration and see how that --

12 A. Okay.

13 MR. LUMAN: Can we make Exhibit 1002
14 available to Dr. Quackenbush and Exhibit 1020
15 from IPR 2023-00224.

16 (Exhibit 1002, No Bates Numbers,
17 Development of Personalized Tumor Biomarkers
18 Using Massively Parallel Sequencing, Cancer
19 Genetics, 2010, Leary et al., received and .)

20 THE WITNESS: So Leary is up.

21 BY MR. LUMAN:

22 Q. Can you let me know when you have

1 those two documents downloaded on your end?

2 A. Sure.

3 And the declaration has appeared, as
4 well. So I don't have them open yet.

5 I have the declaration open. Let me
6 get Leary. Whoops, sorry, I don't have Leary yet.
7 Hold on.

8 All right. Now, I have both of them
9 open, yes.

10 Q. So let's have Leary up. I see Leary
11 has got on page 1 the description of the approach
12 header, but it also has Figure 1, and it's got a
13 whole "Materials and Methods" section.

14 So which part of Leary's workflow
15 would you intend that a person of ordinary skill in
16 the art would remove from Leary and substitute in
17 solution-phase hybridization capture probes?

18 MR. KRAUSE: Object to the timeliness
19 and outside the scope.

20 MR. LUMAN: Why is that outside the
21 scope?

22 MR. KRAUSE: Can you point me where

1 this is discussed in the reply declaration?

2 You had seven hours in September to ask about

3 this.

4 BY MR. LUMAN:

5 Q. Dr. Quackenbush, can you answer the

6 question?

7 A. Sorry. Would you repeat the question,

8 please?

9 Q. What part of Leary's workflow would

10 you contend that a person of ordinary skill in the

11 art would remove from Leary and substitute with

12 solution-based hybridization capture probes?

13 MR. KRAUSE: Same objections. And for

14 conciseness, I'll just make this a standing

15 objection to this line of questioning.

16 (Document review.)

17 THE WITNESS: Can you point me to the

18 section of my report that Dr. Furneaux is

19 referring to here? I want to speed this up

20 for you.

21 BY MR. LUMAN:

22 Q. Let's see. We're looking in

1 paragraph 141 of Exhibit 2031, and you can see that
2 there is not a citation back to your original
3 report?

4 A. So you're asking me to respond to
5 Dr. Furneaux, who's not citing back to the original
6 report?

7 Q. Right. I don't think there was an
8 explanation from you in your original report on how
9 Leary's workflow would be modified to accommodate a
10 switch from PCR primers to solution-based
11 hybridization capture probes. So I want to see if
12 you have an opinion on that today.

13 MR. KRAUSE: Same objections and
14 mischaracterizes the declaration.

15 THE WITNESS: So I believe that you're
16 incorrect actually that saying that Foresight
17 Diagnostics doesn't point back to any section
18 of my report.

19 So on page 94 of Dr. Furneaux's
20 report, it says Leary does not -- the heading
21 says, "Leary does not teach or suggest
22 'capture probes.'" And Dr. Furneaux refers

1 to this IPR declaration that you put in front
2 of me from -- that you had a deposition, I
3 believe, back in September and refers to
4 paragraphs 128 to 134.

5 So now looking back at those
6 paragraphs, right, there's a lot here. Okay.
7 So in paragraph 128, which is short, "Leary
8 discloses a step of 'generating a second
9 subset of nucleic acid molecules from a
10 second nucleic acid sample by contacting
11 said" sample -- said -- excuse me, "said
12 second nucleic acid sample with a plurality
13 of capture probes,'" right.

14 So that's actually quoting the
15 language -- the claim language in, I believe,
16 the '394 patent, right. So one has to
17 contact the second nucleic acid sample with a
18 plurality of capture probes.

19 In paragraph 129, and I'm not going to
20 read the whole thing because it goes on for a
21 long time, but it says, "Using the results of
22 Leary's hole genome sequencing steps," right,

1 which is reflected earlier in the claims of
2 the '394 patent, "the authors analyze the
3 sequencing results using two approaches to
4 identify somatic rearrangements in the
5 tumor's genome," right. So now they've
6 identified these rearrangements, and these
7 are polymorphisms.

8 It then goes on in paragraph 130, "By
9 analyzing the whole-genome sequence data,
10 Leary 'identified 57 regions containing
11 putative somatic rearrangements, with an
12 average of 14 rearrangements per sample.'"
13 So now he's found these.

14 And Leary then tells us that he
15 "Designed primers to 42 of the paired-end
16 regions and used them for PCR spanning the
17 putative break points." Okay.

18 So Leary has done a whole genome
19 sequencing, identified polymorphisms. Now
20 Leary has designed PCR primers. Within the
21 context of the board's definition of "capture
22 probes," capture probes encompass PCR

1 primers, right.

2 So if we look at this, right,
3 paragraph 131, I discuss Leary's use of
4 capture probes, the PCR primers that
5 hybridize to the polymorphisms of interest.

6 And then Step 1(c), paragraph 132,
7 Leary discloses that the PCR primer capture
8 probes utilized in 1(c)(i) -- this is
9 Step 1(c)(ii) -- hybridize to one or more
10 polymorphisms which are based on or extracted
11 from one or more databases of polymorphisms
12 observed in a population of one or more
13 samples or a combination thereof, right.

14 And then I go on to talk about how
15 Leary applies these PCR capture probes to
16 hybridize specific regions, right. And in
17 133 and 134, right, I talk about the analysis
18 of these polymorphisms that include
19 insertions, deletions, or rearrangements, and
20 discuss how Leary applies these capture
21 probes to perform the analysis that's
22 disclosed in her paper, right.

1 So Leary has done a whole genome
2 sequencing, identified polymorphisms,
3 identified capture probes and used them in a
4 subsequent analysis through hybridization of
5 complementary base-pairs to these targeted
6 regions, these loci of interest, right.

7 So I then said there are many more
8 pages of presenting this analysis, right. So
9 Leary uses capture probes when she describes
10 steps analyzing a second sample -- again, I
11 don't have the patent in front of me -- I
12 believe analyzing a third sample, and this
13 may also include generating the report.

14 I can point you to Figure 1 in the
15 Leary paper where Leary has a schematic of
16 the analysis, and the use of those PCR
17 capture probes is the place where one skilled
18 in the art -- remember we viewed Mertes and
19 Mamanova and all these other references that
20 indicated that it was well-known in the art
21 at the time that PCR was just one capture
22 technique using capture probes that could be

1 used to enrich DNA samples for loci of
2 interest.

3 So I haven't reviewed this document in
4 preparation for today. I may have had
5 disclosed other applications or other places
6 where I explicitly tell you that other
7 references used capture probes, and I believe
8 there are some of them. I don't believe I
9 discuss this in my reply -- in my reply to
10 Dr. Furneaux.

11 But clearly, in that reply report, I
12 point out that a person of ordinary skill in
13 the art would understand that these
14 techniques could be substituted for each
15 other. This is consistent with the extant
16 literature, and the place where that
17 substitution would naturally occur would be
18 in the step in which Leary uses PCR on the
19 subsequent samples.

20 So if you'd like, I can spend more
21 time going through my initial declaration;
22 but at a high level, based on Leary and just

1 the knowledge of a person of ordinary skill
2 in the art, that's the place where one would
3 make the substitution if one wanted to, as
4 Dr. Furneaux suggests.

5 But remember that Dr. Furneaux is
6 trying to differentiate between
7 hybridization-based capture probes and
8 PCR-based capture probes, and that's not
9 consistent with the board's definition of
10 what a "capture probe" is.

11 MR. LUMAN: We've been going for over
12 an hour. Would now be a good time for a
13 break?

14 MR. KRAUSE: Sure.

15 THE WITNESS: The court reporter is
16 nodding. So fine with me.

17 MR. LUMAN: All right. Off the record
18 at 11:28.

19 (Recess from the record.)

20 THE WITNESS: If I may, Mr. Luman, in
21 response to your previous question,
22 Dr. Furneaux apparently missed the section in

1 my report starting at paragraph 221 and going
2 through 228, where I explicitly refer to the
3 use of PCR -- the use of hybridize capture
4 probes replacing PCR capture probes and
5 provide combinations of prior art references.
6 So that's in there if you'd like to discuss
7 it.

8 MR. LUMAN: Thank you.

9 We're back on the record at 11:40, and
10 the transcript has your -- your clarification
11 on it.

12 THE WITNESS: All right. Thank you.

13 BY MR. LUMAN:

14 Q. Can we take a look in your
15 declaration, Exhibit 1225; right? Would you turn
16 with me to paragraph 4, please?

17 A. Yes.

18 MR. KRAUSE: Just to break there, it
19 looks like the clarification didn't go on the
20 record. It seemed like the reporter had gone
21 back on before Dr. Quackenbush started and it
22 was being transcribed in realtime, but now

1 it's not appearing.

2 So, Dr. Quackenbush, if you can just
3 repeat that.

4 THE WITNESS: Sure. You had
5 mentioned, I believe, Mr. Luman, that it
6 didn't appear -- I pointed to a PCR -- excuse
7 me, biotinylated solution-based hybridization
8 probes as possibly replacing Leary's PCR
9 capture probes, and Dr. Furneaux missed this.

10 But during the break I went back and
11 looked in my report, and it actually appears
12 in paragraphs 221 through 228, where I
13 explicitly discuss those steps that I
14 referred to earlier, the PCR-based steps, as
15 being places where PCR capture probes or --
16 excuse me, the solution-based hybridization
17 capture probes could be used in place of PCR
18 capture probes and cited to prior art
19 references, including Chan, which explicitly
20 referred to the use of hybridization-based
21 capture probes in place of PCR.

22

1 BY MR. LUMAN:

2 Q. Okay. So in paragraph 4 of your
3 declaration, do you see that there's the board's
4 construction of whole genome sequencing?

5 A. Yes.

6 Q. And do you think that this
7 construction is an appropriate way of viewing whole
8 genome sequencing in this case?

9 MR. KRAUSE: Objection, vague. So the
10 board has construed the term to mean whole
11 genome sequencing as being a nontargeted
12 approach to sequencing all or almost all of
13 the genome. The use of a nontargeted
14 approach is definitely something which is an
15 element of what anyone in the art would refer
16 to as whole genome sequencing.

17 The definition of "all or almost all
18 of the genome" is a bit open to
19 interpretation, and I'll point you to a
20 variety of different references that I cite,
21 including later patents from Personalis, that
22 refer to low coverage whole genome sequencing

1 at 50 percent of the genome or lower.

2 So, in general, I concur with the
3 board's description. I'm just not sure how
4 they define "all or almost all," but it's
5 consistent with my understanding of a
6 nontargeted approach to the whole genome.

7 BY MR. LUMAN:

8 Q. Would you turn to paragraph 68 with
9 me?

10 A. Sure. All right.

11 Q. And I'm looking in the second
12 sentence. And do you see a reference in the second
13 sentence to "physical and sequence coverage"?

14 A. Yes.

15 Q. Can you explain what the difference is
16 between a physical coverage and a sequence coverage?

17 A. So in the context of Leary, Leary is
18 doing a mate-paired analysis. And Leary, I believe,
19 is looking at leukemias common polymorphisms that
20 are actually what we would refer to as driver
21 mutations in blood-based cancers like leukemias,
22 myelomas are translocations.

1 So this is a place where two
2 chromosomes are broken, and the pieces are
3 physically joined together. So you have a piece of
4 one chromosome and a piece of another chromosome.
5 The one that always sticks with me is in multiple
6 myeloma, there's a translocation. It's referred to
7 as T for translocation 414. So part of chromosome 4
8 and part of chromosome 14 are merged together.

9 And Leary in his -- in her analysis, I
10 believe -- yeah, in her analysis was searching for
11 these types of translocations. So in her analysis,
12 there are two important elements. One is getting
13 enough of the genome physically represented DNA
14 samples, right -- this is what we refer to as the
15 physical coverage -- to ensure that she reliably was
16 able to detect these break points by having her
17 paired-ends land on either side of the
18 translocation. So one end would be on chromosome 4,
19 the other end would be on chromosome 14, if this
20 were multiple myeloma. So that's the physical
21 coverage.

22 She also described sequencing the ends

1 of those large DNA fragments, and the sequence
2 coverage -- because not the entire clone or not the
3 entire fragment was sequenced. The sequence
4 coverage would be somewhat lower than the physical
5 clone coverage. Because the sequence coverage
6 wouldn't be the entire piece of DNA, right. And --

7 Q. I'm trying to think if there's a
8 way --

9 A. No, go ahead. I'm sorry.

10 Q. I was going to try and see if there
11 was a way that you could succinctly explain to the
12 board what physical coverage is and what sequence
13 coverage is. Do you have a --

14 A. Sure. So I refer you to the Meyerson
15 reference, which I quote. Meyerson explained,
16 "Physical coverage is important for detecting
17 rearrangements and this detection is aided by
18 analysis of 'paired reads.' In standard shotgun
19 library methods, the fragments of DNA are typically
20 200 to 400 bases long, and second-generation
21 sequencing technologies" -- at the time of Meyerson,
22 which I believe it was 2010, but I'm not sure -- and

1 second-generation -- excuse me, "and
2 second-generation sequencing technologies currently
3 yield 50 to 100 base pair reads to each end of the
4 fragment (known as paired ends). The expected
5 distance between the paired ends is used to uniquely
6 place the reads on the reference genome and
7 unexpected read pairing can be used to detect
8 structural anomalies [sic]."

9 So if I'm doing a 100 base pair reads
10 from both ends of a 400-base pair DNA fragment,
11 right, the 200 bases I read, 100 from each end, is
12 one half of the length of the DNA fragments.

13 So in this case, the physical coverage
14 would be twice as large as the sequence coverage,
15 because each DNA fragment is twice as big as the 200
16 bases that I read from the ends of these fragments.

17 Q. Thank you. And if you'll turn to
18 paragraph 60 of your declaration with me.

19 A. All right. So going backwards.

20 Q. Yeah, backwards.

21 I'm looking at the last sentence that
22 talks about Leary's whole genome sequencing is

1 nontargeted because it's -- has the part about the
2 sequence data that were mapped to the human genome.

3 Do you see that sentence?

4 A. Yes, I do.

5 Q. The mapping part of Leary's approach
6 is the part that determines it's the location of the
7 sequence read within the genome; is that fair?

8 MR. KRAUSE: Objection, incomplete
9 hypothetical.

10 THE WITNESS: So I'm sorry, would you
11 repeat your question, please? I was just
12 reading the entire paragraph to get context.

13 BY MR. LUMAN:

14 Q. I'm trying to understand the mapping
15 part.

16 Is the mapping part of Leary's
17 approach the part that determines the location of a
18 sequence read within the genome?

19 A. So inherent in any modern DNA sequence
20 analysis is a step that involves mapping the
21 sequence reads to some reference. Leary is doing
22 whole genome shotgun sequencing in the initial step,

1 and the paragraph differentiates later targeted
2 steps from the initial step.

3 Leary is doing nontargeted whole
4 genome sequencing in that first step, generating
5 reads across the genome. The analysis of those
6 reads involves mapping those reads back to the
7 genome, right. If I give you a string of As, Cs,
8 Gs, and Ts, there's no way of knowing if looking at
9 them, at least not for most people, of exactly where
10 those land in the genome.

11 So Leary is using this unbiased,
12 nontargeted approach and then, as part of the
13 analysis, mapping each individual end back to the
14 genome. By mapping those back to the genome, in the
15 example I gave you earlier of a translocation
16 between chromosome 4 and chromosome 14, if one end
17 of a DNA fragment maps to chromosome 4 and the other
18 maps to a region of chromosome 14, then what it
19 tells me is in that narrow window of that 400-base
20 pair fragment, there is a translocation.

21 Q. So the mapping portion is where you
22 take the sequence data and determine where the data

1 belongs within the human genome. Is that -- is that
2 appropriate?

3 A. So it tells you for that physical
4 piece of DNA where the ends likely reside within the
5 context of the physical human genome, right. So the
6 sequence is a way of characterizing each fragment.
7 The fragments represent loci distributed through the
8 genome. And the mapping step is providing
9 annotation and context for interpreting the state of
10 the genome, right. So one out- -- excuse me. One
11 outcome -- one second. Sorry, I wanted to spare you
12 from the coughing.

13 One outcome of that mapping step is
14 going to be a set of physical coordinates in the
15 genome, yes, but it's really a tool for
16 understanding the state of the genome in the context
17 of all the data that's been generated.

18 Q. Would you turn with me to paragraph 12
19 of your declaration.

20 MR. LUMAN: And, Henry, I got a
21 challenge for you. I'd actually like to get
22 two things side by side. I'd like

1 paragraph 12 on the left-hand side of the
2 screen. And I'd like to look at Exhibit 1061
3 from IPR 2023-00546 on the right-hand side of
4 the screen. So -- and what I'd like to do is
5 start understanding what sequence coverage
6 is, and let's get this set up correctly.
7 So --

8 THE WITNESS: So I don't think I have
9 Exhibit 1061; do I?

10 MR. LUMAN: Not yet.

11 THE WITNESS: Okay.

12 MR. LUMAN: Let's make that available
13 to Dr. Furneaux.

14 THE WITNESS: Dr. Quackenbush.

15 MR. LUMAN: Sorry, Dr. Quackenbush.
16 Make that available to Dr. Quackenbush.

17 THE WITNESS: I'm much better looking.

18 THE DOCUMENT TECH: Did you say
19 Exhibit 1061?

20 MR. LUMAN: Yes, please, 1061 for --
21 into the Box location, please.

22 THE DOCUMENT TECH: Yeah, no problem.

1 So the only problem with the setup
2 here is that I can only bring up two pages at
3 a time, and I already have two pages up.

4 So -- but that's -- but if you would like, I
5 can bring up one aspect of this document at a
6 time, and then bring --

7 MR. LUMAN: Yeah.

8 THE DOCUMENT TECH: -- up the other
9 one.

10 MR. LUMAN: Yes, that will work.

11 THE DOCUMENT TECH: Let me bring the
12 other one up.

13 MR. LUMAN: And we will mark as
14 Exhibit 2182 in this proceeding what was
15 previously marked as Exhibit 1061 in
16 IPR 2023-00546.

17 (Exhibit 2182, No Exhibit Numbers,
18 Declaration of John Quackenbush, Ph.D. in
19 Support of Petition for Inter Partes Review,
20 IPR2023-00546, U.S. Patent No. 10,450,611,
21 received and marked.)

22

1 BY MR. LUMAN:

2 Q. Dr. Quackenbush, can you let me know
3 when you've got the Exhibit 2182, which was
4 previously marked as Exhibit --

5 A. I have it.

6 Q. Yeah.

7 A. 1061; right?

8 Q. Yes.

9 A. All right. I have 1061 open, yes.

10 MR. LUMAN: And so, Henry, on the --

11 MR. KRAUSE: I apologize, I was muted.
12 I was lodging an objection to timeliness and
13 relevance of this new exhibit.

14 MR. LUMAN: You want me to get them on
15 now?

16 MR. KRAUSE: Yeah, I think they were
17 just marked, but to be clear, the newly
18 marked Exhibit 2182 is untimely and
19 irrelevant to this proceeding.

20 MR. LUMAN: So, Henry, on the
21 left-hand side, could you go down one more
22 page so that we can see the -- yes, that

1 equation.

2 And on the right-hand side, could you
3 turn to paragraph 66. Thank you.

4 BY MR. LUMAN:

5 Q. So, Dr. Quackenbush on the left-hand
6 side we're looking at --

7 A. Okay. I've got 66 up, yes.

8 Q. Yes. And do you still need some more
9 time?

10 A. I've got 66 up. I was just trying to
11 make sure I had the paragraph up.

12 Q. So on the left-hand side, we're
13 viewing sequence coverage equation with 90 percent
14 equals X base pairs over Y base pairs.

15 Do you see that?

16 A. Yes, that's Dr. Furneaux's -- I
17 believe that's excerpted from Dr. Furneaux's
18 declaration.

19 Q. And the equation labeled "Sequence
20 Coverage" in paragraph 12 of Exhibit 1225 is not the
21 Lander/Waterman equation; correct?

22 A. This was Dr. Furneaux's definition of

1 "sequence coverage." It's not the Lander/Waterman
2 equation.

3 Q. Now, the Lander/Waterman equation in
4 paragraph 66 has the word "coverage" as the first
5 word, right, of paragraph 66?

6 A. Yes.

7 Q. So in some instances sequence coverage
8 can refer to the Lander/Waterman equation; is that
9 fair?

10 A. Lander/Waterman refer to coverage
11 using the Lander/Waterman equation, and it's a
12 fairly well-accepted definition of coverage in
13 particular context, yes.

14 Q. And in that instance, Lander -- the
15 Lander/Waterman equation, the type of sequence
16 coverage is a depth of coverage; is that fair?

17 MR. KRAUSE: Objection, form.

18 THE WITNESS: So the Lander/Waterman
19 equation sometimes -- Lander and Waterman, I
20 believe -- and I don't have the paper open in
21 front of me -- sometimes refer to coverage,
22 sometimes refer to sequencing depth or depth

1 of sequencing. And they talk about a
2 percentage of genome, genome coverage.

3 And in the equation C equals L times N
4 over G , C , G , L , and N are all defined in the
5 subsequent sentence.

6 BY MR. LUMAN:

7 Q. So I'd like to take down the
8 right-hand -- yes, thank you.

9 MR. LUMAN: And what I'd like to do is
10 make Exhibit 2022 available to
11 Dr. Quackenbush in the Box and also put that
12 now on the right side of the screen.

13 (Exhibit 2022, No Bates Numbers,
14 Sequencing depth and coverage: key
15 considerations in genomic analyses, Nature
16 Reviews|Genetics, 2014, Sims et al., marked
17 for identification.)

18 BY MR. LUMAN:

19 Q. Dr. Quackenbush, can you tell me let
20 me know when you've had a chance to download 2022?

21 A. It has not appeared yet.

22 THE DOCUMENT TECH: And just give me

1 one second. The Box is choking up a little
2 bit.

3 THE WITNESS: And it has now appeared,
4 and I'll tell you when I have it downloaded
5 and open.

6 THE DOCUMENT TECH: So that's not it.
7 Hold on.

8 There you go.

9 THE WITNESS: So you don't want the
10 story about Rick Wilson.

11 BY MR. LUMAN:

12 Q. Okay.

13 A. All right.

14 Q. And in Exhibit --

15 A. Hold on, please.

16 All right. I have 2022 opened.

17 MR. LUMAN: And on the first page of
18 Exhibit 2022, which is page 121, I'd like to
19 zoom in on the left column in the kind of
20 bottom part of the text where -- yeah, that's
21 great right there.

22

1 BY MR. LUMAN:

2 Q. Do you see a sentence that starts
3 with, "Although the terms depth and coverage,"
4 Dr. Quackenbush?

5 A. I see that sentence, yes.

6 Q. So that says, "Although the terms
7 depth and coverage can be used interchangeably (as
8 they are in this Review), coverage has also been
9 known -- has been used to denote the breadth of
10 coverage of a target genome."

11 Do you see that?

12 A. I see that, yes.

13 Q. Is the sequence coverage equation in
14 paragraph 12 of your declaration a type of equation
15 to get the breadth of sequence coverage?

16 A. I'm sorry, repeat the question,
17 please.

18 Q. In paragraph 12 of Exhibit 1225, is
19 that equation labeled "Sequence Coverage" a type of
20 equation that would determine the breadth of
21 sequencing coverage?

22 A. So this is something Dr. Furneaux has

1 asserted.

2 Q. To be fair --

3 A. Is this the -- pardon me?

4 Q. And to be fair, counsel for Foresight
5 generated the equation and then asked questions of
6 Dr. Furneaux about it, but I didn't mean to
7 interrupt you.

8 A. I'm sorry, I thought this was -- I
9 thought this had appeared in Dr. Furneaux's expert
10 report. So if I look at --

11 (Document review.)

12 THE WITNESS: So is this part of --

13 BY MR. LUMAN:

14 Q. This came up during Dr. Furneaux's
15 deposition, and it was an exhibit that was put
16 together by Foresight's counsel and shown to
17 Dr. Furneaux.

18 A. All right. So I'm not sure in what
19 context Dr. Furneaux was testifying at the time, and
20 I'm not sure what he's referring to in terms of X
21 base pairs and Y base pairs. I believe Dr. Furneaux
22 makes a number of arguments about one full coverage

1 being determined by taking the length of the genome
2 and dividing it by the number of -- sorry, the
3 length of the genome and dividing it by the length
4 of each individual read, which would be a definition
5 which would be consistent with the Lander/Waterman
6 definition.

7 So if I recall Dr. Furneaux's
8 argument, this definition, which is provided here,
9 would be consistent with the Lander/Waterman
10 definition.

11 Q. The sequence coverage equation in
12 paragraph 12, you're saying is consistent with the
13 Lander/Waterman equation?

14 A. Based on my understanding of how
15 Dr. Furneaux presented his arguments -- so we can
16 look back at the transcript, and we can also look at
17 Dr. Furneaux's report -- I do recall Dr. Furneaux
18 arguing -- making an argument about Leary's
19 sequencing and the number of sequence reads that
20 would be required that came from an assertion he had
21 made about the reads being 50 bases in length and
22 the genome -- the length of genome, I think, being

1 3.2 billion bases in length.

2 So that 3.2 billion bases in the
3 context of this would essentially be the
4 denominator, the length of the genome. And the
5 numerator, X base pairs, would be 50 bases times the
6 number of reads. And I believe that's how
7 Dr. Furneaux defines "sequence coverage."

8 So this is consistent with the way in
9 which Dr. Furneaux defines "sequence coverage," and
10 that's consistent with Lander/Waterman.

11 Q. So I just want to make sure, do you
12 think that this sequence coverage equation, which is
13 in paragraph 12 of your declaration, is consistent
14 with the Lander/Waterman equation?

15 MR. KRAUSE: Objection, asked and
16 answered.

17 THE WITNESS: I'm sorry, what did you
18 say, Andrew?

19 MR. KRAUSE: I was just lodging the
20 objection. I think the court reporter
21 recorded it.

22 THE WITNESS: Okay.

1 MR. KRAUSE: So you can answer.

2 THE WITNESS: All right. So I'd like
3 to look back at Dr. Furneaux's transcript,
4 and I'd like to look at his report.

5 MR. LUMAN: Okay. So let's make
6 Exhibit 1223 available to Dr. Quackenbush.
7 But we don't need to bring it up on the
8 screen. We'll just have it available to
9 Dr. Quackenbush.

10 (Exhibit 1223, No Bates Numbers,
11 Deposition of Henry Morrice Furneaux, Ph.D.,
12 marked for identification.)

13 MR. KRAUSE: You can look at the
14 available exhibits and not just the excerpts
15 displayed on the screen.

16 MR. LUMAN: That's correct, yeah.

17 And let me see if we've already given
18 you the Furneaux declaration.

19 Let's make Exhibit 2031 available --
20 oh, that's already in the Box for you. 2031
21 is the Furneaux declaration.

22 THE DOCUMENT TECH: Sorry, I just

1 realized that there are two 1223. One of
2 them says incorrect. So can I delete it?

3 THE WITNESS: Yeah, I have the one
4 that says "incorrect." So...

5 MR. LUMAN: What's the question?
6 There's a 1223 incorrect? Let's do the
7 correct one.

8 THE DOCUMENT TECH: Okay. Yeah.
9 So, Doctor, just refresh your page,
10 and you're going to see that there's a
11 deposition transcript now, 1223.

12 THE WITNESS: All right. This one
13 doesn't have "incorrect" on it.

14 BY MR. LUMAN:

15 Q. So do you have the transcript
16 available to you now?

17 A. Yes, I do.

18 Q. Okay. And do you want to take -- are
19 you going to take some time to review it, or should
20 I just keep going?

21 A. I'm going to take some time to look
22 because this is referring to a specific place.

1 (Document review.)

2 THE WITNESS: I'm sorry, Mr. Luman.

3 You can continue with your questions, please.

4 MR. LUMAN: Okay. On the right-hand

5 side of our screen, can we bring back up

6 paragraph 66 from Exhibit 1061 of

7 IPR 2023-00546.

8 THE DOCUMENT TECH: It was 1061?

9 MR. LUMAN: Yes, 1061. Thank you.

10 THE WITNESS: And what paragraph,

11 please?

12 BY MR. LUMAN:

13 Q. That was paragraph 66.

14 A. Okay.

15 THE DOCUMENT TECH: Just give me one

16 second. 1061 has eluded me right now.

17 MR. LUMAN: Okay. It's the one that

18 we've marked as Exhibit 2182. Oh, I think

19 you've got it.

20 THE DOCUMENT TECH: Yeah, that's why

21 it was hiding on me. Yeah, sorry.

22 MR. LUMAN: And if you'll take us to

1 paragraph 66, please.

2 BY MR. LUMAN:

3 Q. So looking at paragraph 12 of your
4 declaration and the equation that's shown there, is
5 that an appropriate equation for determining
6 sequence coverage where sequence coverage refers to
7 sequencing depth?

8 A. So we have to define "depth" in
9 context, and this is important. So you referred to
10 the Sims article earlier, and you actually
11 highlighted a phrase, I believe. It says, "Although
12 the terms depth and coverage can be used
13 interchangeably (as they are in this Review),
14 coverage has also been used to denote the breadth of
15 coverage of a target genome" -- and then goes on to
16 define this in a different way.

17 So "coverage" can have different
18 meanings in different context. And it's important
19 to understand that if one were to sequence a genome,
20 the coverage of that genome would not necessarily be
21 uniform. And throughout my various depositions that
22 you've taken and the reports I've provided, that is

1 something which has become clear, that even at a
2 great depth of coverage, and I think it's -- in some
3 places I refer to 30-fold coverage, not every base
4 in the genome would be covered, right. So -- not
5 every base in the genome would be sequenced.

6 And, in fact, as I think Dr. Furneaux
7 and Dr. West both acknowledged, sequencing the
8 entirety of the human genome was something that
9 wasn't completed until sometime in 2023, and there
10 are still people who would debate whether or not
11 every base in the genome has been covered.

12 So sequencing depth or depth of
13 coverage is defined as -- and this is 66 --
14 paragraph 66 in the declaration -- my declaration
15 that you have, right. The coverage is going to be
16 equal to L , the length of read, times N , the number
17 of reads. So that's the total number of bases
18 sequenced. And that would be what Dr. Furneaux --
19 what in this diagram refers to X base pairs. And
20 then G is the genome size. That would refer to the
21 Y base pairs.

22 And this was all in a discussion that

1 occurred in Dr. Furneaux's deposition in the context
2 of him making an estimate, but trying to figure out
3 what to use for the denominator. Because he was
4 able to, as pointed out in the Lander/Waterman
5 equation, that the coverage was the number of reads
6 times the lengths of reads. So the numerator would
7 be those X base pairs.

8 And then Dr. Furneaux was arguing
9 about how big the genome was or what's used for the
10 denominator. And I believe in that deposition
11 eventually came to the conclusion that the best way
12 to calculate coverage given this definition, right,
13 from Lander/Waterman, is to use the expected or
14 known size of the genome at the time, which I
15 believe I cite to in my report as evidence --
16 evidenced by websites that had the ungapped genome
17 size of being about 2.86 billion bases, so 2.86
18 gigabases.

19 So it was really a discussion about
20 what to choose for the denominator here, and
21 Dr. Furneaux was arguing about whether or not this
22 coverage of the genome should be 0.9, right, but

1 that -- with the understanding 90 percent is 0.9,
2 and it's going to be how many bases you sequence
3 divided by the expected size of the genome. That's
4 consistent with Lander/Waterman, and that's
5 consistent with -- in the Sims paper, where Sims
6 says the depth and coverage can be used
7 interchangeably, as they are in the Sims review.

8 Q. So looking at the equation in
9 paragraph 12 of your declaration in order to get a
10 sequence coverage, you have to assume that the
11 X base pairs are evenly distributed across the
12 genome; is that fair?

13 A. No, that's not fair, right. If you
14 look at the Lander/Waterman equation, the
15 Lander/Waterman equation is actually based on the
16 assumption that they're randomly distributed across
17 the genome, right. And so this is going to
18 represent the number of reads times the length of
19 reads, right, which is Dr. Furneaux's X base pairs
20 divided by the expected size of the genome Y base
21 pairs.

22 Q. So the X base pairs need to be

1 randomly distributed across the genome in order for
2 the equation to accurately give a sequence coverage;
3 is that fair?

4 MR. KRAUSE: Objection,
5 mischaracterizes.

6 THE WITNESS: So I don't know what you
7 mean by accurately, right. The definition
8 that you're showing on the right-hand side in
9 paragraph 12 is consistent with the
10 definition you're showing -- excuse me, on
11 the left-hand side in paragraph 12 is
12 consistent with the definition you're showing
13 in the right-hand side in paragraph 66, and
14 it's consistent with the way that one of
15 skill in the art would refer to the depth of
16 coverage or the sequence coverage.

17 And that's explicitly spelled out in
18 that paragraph from Sims that you referred me
19 to earlier, right. Sims acknowledges that
20 other people use terms in different ways, but
21 "depth" and "coverage" he uses in this review
22 interchangeably.

1 And that's the definition of
2 "coverage" which appears in both the
3 paragraphs we referred to, with the caveat
4 that the left-hand side is already -- in
5 paragraph 12, the left-hand side is already
6 set to 0.9.

7 BY MR. LUMAN:

8 Q. And the equation in paragraph 12, if
9 all of the X base pairs were localized just on
10 chromosome 6, then this equation wouldn't get you
11 the sequence coverage for the whole genome; right?

12 MR. KRAUSE: Objection, incomplete
13 hypothetical.

14 THE WITNESS: So you're asking a
15 hypothetical question about something that
16 wouldn't be whole genome shotgun sequencing
17 or whole genome sequencing, right. Whole
18 genome sequencing is going to be unbiased.
19 It wouldn't just be chromosome 6.

20 And so if we're doing a whole genome
21 sequencing, the basic assumption is that it's
22 unbiased. The reads are going to be randomly

1 distributed across the genome. And given the
2 way that this is referred to in the art, as
3 affirmed by Dr. Sims, the Lander/Waterman
4 equation gives us the way of calculating
5 coverage.

6 I mean, you can come up with
7 hypothetical examples. You know, I could
8 also say, well, if all the sequences were
9 from the mouse genome, the coverage of the
10 human genome would be zero. But that doesn't
11 seem to have any bearing on either of the two
12 patents in question or the definition of
13 "whole genome sequencing" that the board has
14 arrived at.

15 BY MR. LUMAN:

16 Q. So in paragraph 12, the sequence
17 coverage equation, the X base pairs have to be
18 randomly distributed across the genome in order to
19 give you a sequence coverage of the genome; is that
20 fair?

21 A. So that's not what I said, right.

22 And --

1 Q. Yeah, please go ahead. I do know what
2 X means. So please give me the explanation, please.

3 A. Well, it's right there in paragraph 66
4 in the other report you called up. X is going --
5 and Dr. Furneaux applies this definition, right. I
6 forget -- I can look in Dr. Furneaux's declaration,
7 which I believe I already have. And if you'd like,
8 I'm take time to look through it.

9 In Dr. Furneaux's declaration, he
10 calculates Leary's coverage of the genome. And he
11 does that by taking the number of reads, right,
12 which in the Lander/Waterman equation would be N,
13 multiplying it by 50, the length of the reads, and
14 dividing it by the size of the genome to come up
15 with an estimate of the size.

16 So I'm going to take a look at and see
17 where I can find that, right. But this is the
18 Lander/Waterman equation, with our definition of
19 "coverage," which is widely accepted, as
20 acknowledged by Sims, among persons of skill in the
21 art, is based on an assumption that, as the board
22 concluded, whole genome sequencing is unbiased, and

1 I believe the term they use is "random."

2 Q. So an assumption with the
3 Lander/Waterman equation is that -- is it L that's
4 unbiased across the genome, or is it N that's
5 unbiased across the genome?

6 We have the N; right?

7 A. N is simply the number of reads, and L
8 is the read length.

9 Q. And the assumption is that those
10 are -- did you say unbiased across the genome?

11 A. So what's the board's construction?
12 So I've got a bunch of documents open, and I don't
13 have them marked.

14 So can you tell me what paragraph I
15 cite to the board's construction page 7?

16 Q. It's paragraph 4 of your declaration.
17 It has the board's definition of "whole genome
18 sequencing" as a nontarget approach to sequencing
19 all or almost all genome.

20 A. So I'm going to write that down, just
21 nontargeted. I want to use the words properly.
22 Okay. And then we're referring to paragraph 12.

1 Q. So paragraph 12, the X base pairs must
2 be nontargeted across the genome; is that fair?

3 A. So if we look at paragraph 8 in the
4 same report, right, this is -- this is the equation
5 that appears in paragraph 12 reflects Dr. Furneaux's
6 arguments. So, I write, for example, Dr. Furneaux
7 contends that "to cover all of the base pairs in the
8 whole human genome using the mate pair approach in
9 Leary, one would need to very accurately sequence
10 was 64 million non-overlapping mate-pairs."

11 So 64 million in Dr. Furneaux's
12 interpretation of the Lander/Waterman equation would
13 be N. It's the number of -- the number of
14 sequences, right. And his argument is this
15 3.2 billion divided by 50. So his assumption,
16 right, is that the size of the genome, the Y base
17 pairs, is 3.2 billion, right, and that one would
18 need 64,000,050 base pairs in length.

19 So Dr. Furneaux's assumption is L is
20 50, N is 3.2 billion, right, and the size -- excuse
21 me, that N is 64 million, L is 3 -- sorry, L is 50,
22 N is 64 million, and G is 3.2 billion, right. And

1 so that's the way Dr. Furneaux is calculating the
2 coverage, which is consistent with what appears in
3 the Lander/Waterman equation. And that's -- that's
4 really the point that's being made here.

5 Q. And an assumption in the
6 Lander/Waterman equation is that the sequence reads
7 are non-randomly distributed across the genome; is
8 that right? Or would you say it differently?

9 A. Well, you said non-randomly. The
10 assumption in Lander/Waterman, for what we in the
11 art refer to as coverage, is that they're
12 nontargeted, right. So if you read the literature,
13 people talk about onefold coverage, twofold
14 coverage, 30-fold coverage, 0.9-fold coverage. The
15 references that I cite to that even have as low as
16 0.1-fold coverage whole genome sequencing.

17 And everyone is using "coverage," I
18 believe, in the way that the Lander/Waterman
19 equation refers to it, which is also consistent with
20 what's disclosed in the Sims reference from 2014,
21 right, that the way they use "coverage" is the way a
22 person of skill in the art uses coverage, and its

1 depth and coverage are used interchangeably.

2 Q. And so the Lander/Waterman equation
3 has an assumption that the sequence reads are
4 nontargeted across the genome.

5 Is that phrased right?

6 A. So the sequence reads would be
7 nontargeted. Otherwise, it wouldn't make sense to
8 talk about this whole genome sequencing, right.

9 Q. Yeah.

10 A. So if you look at the Sims reference,
11 which we referred to earlier, on page 1 -- it's
12 going to jump screens. So I want to get it here.
13 It's on page 122. They actually have a box which
14 discusses the Lander/Waterman equation and sequence
15 coverage theory, right. So Sims is explaining
16 exactly what I explained in the second report that
17 you've called up.

18 "Much of the original work on
19 sequencing coverage stemmed from early genome
20 mapping efforts. In 1988, Lander and Waterman" --
21 and it cites to the same paper I do -- "described
22 the theoretical redundancy of coverage (c) as LN

1 over G , where L is the read length, N is the number
2 of reads and G is the haploid genome length. The
3 figure shows the theoretical coverage (shown as
4 diagonal lines; c equals 1x onefold or 30x 30-fold)
5 according to the Lander-Waterman equation for human
6 genome or exon sequencing [sic]," right.

7 So if you're doing exon, right, if
8 it's a targeted approach, then the expected size of
9 the genome would be the size of the exon.

10 In your hypothetical example earlier
11 about sequencing just chromosome 6, the genome in
12 that case would be chromosome 6. That's what you're
13 targeting, right. The coverage is achieved by
14 sequencing technologies, according to the
15 manufacturer's websites, are also indicated.

16 So this really goes through and
17 discusses the coverage in the context of the
18 Lander/Waterman equation. And if you look at the
19 graph on page 122, right, they're showing those
20 lines, they're straight lines in these graphs, that
21 represent -- that are looking at the read lengths
22 and essentially the number of reads per run, N .

1 So the coverage is going to depend on
2 the length of the reads, the number of reads, and
3 the size of the target. In the case of whole genome
4 sequencing, it's going to be the genome size.

5 Q. And looking at paragraph 12, that
6 equation, if all the X base pairs were localized on
7 a portion of the genome, such as like chromosome 2
8 and 4, but there were no X base pairs on the
9 remaining chromosomes, then that simply dividing X
10 base pairs by 2.86 billion base pairs for the
11 degapped genome, that wouldn't get you a sequence
12 coverage that's relating to whole genome sequencing;
13 right?

14 MR. KRAUSE: Objection to --

15 THE WITNESS: So I'm not sure I
16 understand your question, since you're
17 talking about a targeted approach rather than
18 a whole genome sequencing approach. The best
19 place I can point you is to the Sims paper,
20 which actually discusses the situation of
21 exome sequencing, in which case the relevant
22 numerator would actually be the size of the

1 exome, not the size of the genome, right. So
2 that's a targeted approach.

3 But we don't want to mix the targeted
4 approach and the whole genome approach in the
5 context of talking about whole genome
6 sequencing.

7 BY MR. LUMAN:

8 Q. Would you turn with me to paragraph --

9 MR. LUMAN: We can take down the
10 right-hand side of the screen. And can we
11 turn to paragraph 65 of your current
12 declaration, Exhibit 1225, please.

13 THE WITNESS: Paragraph 65?

14 BY MR. LUMAN:

15 Q. Yes, please.

16 A. Okay.

17 MR. LUMAN: And we can take down -- we
18 don't need the side by side anymore. Thank
19 you.

20 THE WITNESS: All right.

21 BY MR. LUMAN:

22 Q. Do you see where we've got a quote

1 from Dr. Furneaux about 64 million nonoverlapping
2 mate pairs?

3 A. Yes.

4 Q. And Dr. Furneaux went on to assume
5 that -- or, actually, he calculated that Leary's
6 mate pairs did have overlap.

7 Do you remember that?

8 A. No, I don't recall that.

9 Q. Okay. Let's look at Exhibit 2031
10 that's the Dr. Furneaux declaration. And if we'll
11 turn to paragraph 99. Paragraph 99 is on page 66.

12 And do you see in the first sentence,
13 Dr. Furneaux said that the mate-paired tags in Leary
14 are very likely overlapping.

15 Do you see that?

16 A. I see that, yes.

17 Q. Do you agree with Dr. Furneaux that
18 Leary's mate pairs likely overlapped?

19 A. So it says, "the data presented in
20 Leary confirms that the mate-paired tags in Leary
21 are very likely overlapping to a very significant
22 degree."

1 So I would concur that they overlap.

2 I don't know what Dr. Furneaux is referring to when
3 he says "a very significant degree."

4 Q. What degree do you think Leary's mate
5 pairs overlapped by?

6 A. I couldn't say. I'd have to analyze
7 the data. And I don't think Dr. Furneaux has any
8 basis for -- for reaching this conclusion. At least
9 he doesn't provide any.

10 Q. In paragraph 100, he performs the
11 calculation that arrives at his 1.7 approximation.

12 Is there anything in paragraph -- I
13 guess, do you agree with his calculation in
14 paragraph 100 that arrives at the 1.7 approximate
15 overlap of Leary's mate pairs?

16 (Document review.)

17 THE WITNESS: So I'm not really sure
18 what Dr. Furneaux is doing here, right. And
19 I'd have to sit down and really write this
20 out to try to sort it all out, but let's give
21 Dr. Furneaux the benefit of the doubt. Okay.

22 If as Dr. Furneaux argues that the

1 average coverage per base is about 1.7 times
2 for those bases that are sequenced, then
3 Dr. Furneaux is arguing that about
4 1.71 gigabases of DNA are sequenced, right,
5 and if we divide 1.71 by 2.86, which is the
6 size of the ungapped genome at the time which
7 it was published, that would yield a coverage
8 of 59-point -- actually, 60, rounding --
9 59.79, so 60 percent of the genome being
10 covered, right.

11 So even if we're assuming that
12 Dr. Furneaux's correct and Dr. Furneaux is
13 walking away from the standard definition of
14 depth of coverage that's used in the field,
15 right, if we make that assumption, then this
16 still represents an untargeted -- the result
17 of a nontargeted approach to sequencing the
18 whole genome, which is consistent with the
19 board's description.

20 And it's actually consistent with
21 Personalis' own representation of what whole
22 genome sequencing means. And I'll point to

1 you paragraph 22 in my report, where I refer
2 to Personalis patent 11,456,058, which claims
3 priority to August 30th, 2013. One of the
4 inventors is John West, who was deposed and
5 whose testimony I referred to.

6 And they repeatedly use the term
7 "whole genome sequencing" as synonymous with
8 untargeted sequencing and distinguish this
9 from targeted sequencing, like exome
10 sequencing or just sequencing chromosome 4, I
11 think as you used in the hypothetical example
12 before.

13 And in their reports -- in the patent,
14 in the written description, it says, In
15 another embodiment, the whole genome
16 sequencing data comprises paired-ends, right,
17 and talks about mate pairs where insert size
18 is about 1-point -- a whole long list that
19 includes 1.4 kilobases, which is the size
20 that Leary uses.

21 And then says, In some cases -- and
22 this is further on down. In some cases, the

1 untargeted sequencing, i.e., whole genome
2 sequencing can cover sequences of the whole
3 genome of nucleic acid sample of about or at
4 least -- and he goes through a whole list
5 down to 50 percent.

6 So even if we take Dr. Furneaux at his
7 word -- and I haven't reproduced his
8 calculation, but even if we take him -- and
9 we assume his calculation is correct, then
10 he's telling us that Leary is sequencing
11 60 percent of the bases in the expected size
12 of the genome, 2.86 gigabases, and that falls
13 clearly within what one of ordinary skill in
14 the art would understand to be a type of
15 whole genome sequencing and completely
16 consistent with the disclosure in a number --
17 another Personalis' own patents describing
18 whole genome sequencing.

19 BY MR. LUMAN:

20 Q. What degree do you think that Leary's
21 mate pairs overlapped by?

22 A. I haven't done that calculation.

1 So -- I haven't done that calculation. So I don't
2 know.

3 MR. LUMAN: We've been going for a
4 little bit more than an hour. Would it be a
5 good time for a break? Or I can keep going.

6 THE WITNESS: I defer to the court
7 reporter. I assume she'd like a break.
8 She's smiling. So let's take a break.

9 MR. LUMAN: Okay. We'll take a break.
10 It's -- off the record at 12:49. How about
11 another ten-minute break.

12 (Recess from the record.)

13 MR. LUMAN: It's 12:59, and we are
14 back on the record.

15 I'd like to look at Leary -- can we
16 bring Exhibit 1002 back up, please.

17 Okay. I'd like to go on the first
18 page and -- which is page 1, and there's the
19 "Description of the approach" on the
20 left-hand side. Can we blow that part up.
21 Yes, thank you.

22

1 BY MR. LUMAN:

2 Q. All right. I'm looking at the part --
3 there's -- after the parentheses on Table 1, it
4 starts with "Genomic." Do you see the sentence that
5 says, "Genomic DNA," Dr. Quackenbush? "Genomic
6 DNA"?

7 A. Yes.

8 Q. Okay. So Leary generated libraries
9 with mate-paired tags that were approximately 1,400
10 bases apart and sequenced just the 25 base pairs of
11 each fragment.

12 And my question is: What's
13 advantageous about Leary's approach that didn't
14 sequence the 1.4 kilobases in the middle of each
15 sheared DNA strand?

16 A. So, first, Leary was using a
17 technology that was an earlier -- well, I don't know
18 if earlier, but it was an alternative sequencing by
19 synthesis instrument called the SOLiD System from a
20 company called Applied Biosystems, which I think was
21 eventually bought by Thermo Fisher.

22 The Applied Biosystems SOLiD sequencer

1 had a read length of about 25 base pairs. So the 25
2 base pairs that are referred to here represent a use
3 of the sequencing technology that -- for whatever
4 reason they chose to use in this setting.

5 The PARE method is personalized
6 analysis of rearranged ends. I think I got the
7 acronym wrong before, but I'm bad at acronyms. And
8 this refers to looking at fragments of DNA that span
9 a chromosomal break point as often occurs in
10 leukemias, other blood cancers, but we also see it
11 in solid tumors, as well.

12 So the SOLiD technology, I don't know
13 what the maximum read length was that they had in
14 2010. I'm assuming it was bigger than 25 base
15 pairs. Why they chose this, I can't really
16 speculate about. But the sequencing of the 25 base
17 pairs, as we talked about Leary before, allowed them
18 to map those ends, right, to the genome and then to
19 use the ends as a way of identifying places where
20 chromosomal breaks, infusions might have occurred,
21 right.

22 So there are other types of

1 alterations that one could detect, including
2 deletions, insertions, but one of the primary ones
3 they discuss here are these translocation break
4 points. And that's illustrated in, I believe,
5 Figure 1, where they have a little cartoon showing
6 the method.

7 The advantage of using the 1.4
8 thousand bases -- or 14,000 bases -- 1,400 bases is
9 they can use large physical coverage of the clones,
10 right, and use the sequencing at the end.
11 Sequencing 1,400 bases from a single fragment would
12 have been difficult at the time.

13 And so if they had chosen to sequence,
14 say, 50 base-pair fragments to ensure that they
15 got -- one of the reasons they chose the bigger
16 clones is to increase their clone coverage, their
17 physical coverage, while optimizing the amount of
18 sequence that they generated.

19 Q. How does having the 1.4-kilobase
20 separation help the Leary protocol versus if they
21 had just sheared the DNA strands down to strands
22 around 50-kilobases long?

1 A. If they're only 50 bases long?

2 Q. Yeah, 50 bases long. Thank you.

3 A. So, you know, think about it, right.

4 You've got a place in the genome where the two
5 chromosomes are broken, right. They would have to
6 do a lot more sequencing of smaller fragments to get
7 the same physical coverage of the genome.

8 So if they have 1,400 bases and they
9 were trying to cover that with 50 base-pair
10 fragments, they would need -- I think I'm doing the
11 math right -- 270 fragments for each 1,400 base pair
12 or fragment they cover to get the same physical
13 coverage in the genome.

14 In their strategy, it was just easier
15 using whole genome sequencing at the ends of these
16 bigger fragments to identify those break points.

17 Q. Is there anything else about Leary's
18 use of the 1.4-kilobase spacing between the
19 mate-paired tags that provides an advantage to
20 Leary's approach?

21 A. So I said 2700. I should have said
22 28, 28 fragments for each. So they would have had

1 to do 28 times more sequencing. I'm sure there are
2 others. That's just the first one I could think of,
3 right.

4 What they're looking to do is to get a
5 large amount of physical coverage in the genome
6 while optimizing the amount of sequencing that they
7 did. So they made particular decisions based on
8 what they thought was best for their goal of
9 identifying these rearranged ends and chromosomal
10 break points.

11 Q. Now, Leary never uses the phrase
12 "whole genome sequencing"; right?

13 I can withdraw that question.

14 A. But if you want to withdraw it, that's
15 fine. I can answer the question for you if you'd
16 like.

17 Q. If you can do so specifically, that
18 would be fine.

19 A. Sure. One skilled in the art would
20 realize that when Leary says that genomic DNA from
21 each sample is purified, sheared, and used to
22 generate libraries with mate-paired tags, that that

1 sharing was random, it's nontargeted, and that that
2 is consistent with the definition of "whole genome
3 sequencing."

4 So one skilled in the art wouldn't
5 need an explicit reference to whole genome
6 sequencing, and many contemporaneous references
7 refer to Leary as a whole genome sequencing
8 approach.

9 Q. Would you turn with me, please, to
10 paragraph 32 of your declaration Exhibit 1225.

11 A. Sure. Paragraph 32?

12 Q. Yes, please.

13 MR. LUMAN: And we can stay at the
14 top. We don't have to scroll down. Thanks.

15 BY MR. LUMAN:

16 Q. Dr. Quackenbush, let me know when
17 you're ready.

18 A. I'm there, yes.

19 Q. Okay. In paragraph 32, the first
20 bullet point is to a Leary 2012 reference.

21 Do you see that?

22 A. Yes, I do.

1 Q. Did you consider -- did you review the
2 Leary 2012 reference in preparing your declaration?

3 A. Yes. Let's see.

4 Q. The reason I'm asking you is it's not
5 an exhibit currently.

6 (Document review.)

7 THE WITNESS: So I don't believe I
8 cited to this Leary 2012 paper in my report.
9 I call it out here simply to note that I
10 believe Dr. Furneaux mischaracterizes genome
11 sequencing studies presented in Newman, and I
12 refer to that up in paragraph 30, simply to
13 point out that Newman, this reference that
14 Dr. Furneaux does cite to, mentions a number
15 of papers, including this 2012 Leary paper,
16 which is clearly entitled "Detection of
17 Chromosomal Alterations in the Circulation of
18 Cancer Patients with Whole-Genome
19 Sequencing."

20 MR. LUMAN: So I'm going to mark
21 Exhibit 2183, which is the Leary 2012
22 reference.

1 Henry, can you make that available to
2 Dr. Quackenbush.

3 (Exhibit 2183, No Bates Numbers,
4 Detection of Chromosomal Alterations in the
5 Circulation of Cancer Patients with
6 Whole-Genome Sequencing, Diagnostics,
7 www.ScienceTranslationalMedicine.org 28
8 November 2012, received and marked.)

9 MR. KRAUSE: I'm going to object as
10 untimely, outside the scope.

11 BY MR. LUMAN:

12 Q. Dr. Quackenbush, can you let me know
13 when you get it?

14 A. I have it, and it's open.

15 Q. So the first author on this paper is
16 Rebecca Leary. That's the same first author of the
17 Leary 2012 publication we've been looking at and
18 discussing.

19 That's Exhibit 1002 in this
20 proceeding; right?

21 A. It almost certainly is, yes.

22 Q. Would it be okay if we refer to

1 Exhibit 2183 as "Leary 2012"?

2 A. That would be fine.

3 Q. Now, Leary 2012 in the title has the
4 words "whole genome sequencing"; right?

5 A. Yes.

6 Q. Would you turn to page 6 with me,
7 please?

8 A. Certainly.

9 Q. And on page 6, on the left-hand side,
10 the second full paragraph starts with
11 "Rearrangements." Do you --

12 A. Yes.

13 Q. On page 6 in the second full
14 paragraph, there's a discussion of "PARE," and then
15 it says -- let's start with the "Analyses of the
16 nine patient plasma."

17 Do you see that one?

18 A. Yes, I do.

19 Q. "Analyses of the nine patient plasma
20 samples with plasma rearrangements were found to
21 have concentrations of circulating mutant DNA
22 ranging from 4.7 to 47.9 percent as determined by a

1 digital -- by digital PCR with a PARE, P-A-R-E,
2 biomarker...[sic]"

3 The next sentence, "The absence of
4 detected rearrangements in the plasma of CRC12 could
5 be a result either of the absence of structural
6 alterations in the tumor DNA or of the failure to
7 detect consumption rearrangements in the plasma
8 DNA."

9 And then it says, "To distinguish
10 between these possibilities, we searched for
11 rearrangements in the DNA of this patient's tumor
12 using the whole-genome sequencing."

13 Do you see that?

14 A. Yes, I do.

15 Q. And so this paper is explaining that
16 PARE could not distinguish between the absence of
17 detected rearrangements being due to the absence of
18 structural alterations or the failure to detect such
19 rearrangements. So it had to turn to something
20 different, namely, whole genome sequencing; right?

21 MR. KRAUSE: Objection,
22 mischaracterizes the reference, lacks

1 foundation, untimely, outside the scope of
2 the reply.

3 THE WITNESS: So I would disagree with
4 your assessment of what's presented here. So
5 I have not read this paper in detail, but a
6 quick read shows that they didn't actually
7 use the entire PARE process, right.

8 It says, "Such break point biomarkers
9 as identified by PARE could be useful for
10 providing measures of circulating tumor DNA,"
11 right. So they didn't say in patient --
12 again, I'm reading just this paragraph. I
13 haven't read the entire paper.

14 But they looked at a patient they call
15 CRC12. I'm assuming this is a patient with
16 colorectal cancer and the 12th patient in
17 their series. And I know Victor Velculescu,
18 the last author, has done a lot of pioneering
19 work on colon cancer.

20 So what you read to me earlier says,
21 "Analyses of nine patient plasma samples with
22 plasma rearrangements were found to have a

1 certain concentration as determined by
2 digital PCR with a PARE biomarker."

3 So they used biomarkers they had
4 identified previously as rearrangements
5 occurring in colon cancer patients. They
6 didn't take CRC -- patient CRC12 and use
7 PARE.

8 So they did this digital PCR analysis.
9 When the digital PCR analysis failed to
10 reveal any translocations, then they asked
11 the question: Did the digital PCR fail or --
12 or is there an absence of structural
13 alterations in the tumor DNA, right, or is it
14 a failure to detect such rearrangements in
15 the plasma?

16 So what they're telling us,
17 actually -- and I'd have to read and see
18 exactly what whole genome sequencing approach
19 they're using, but what they're saying is,
20 having failed to detect a rearrangement by
21 simply doing digital PCR, let's go back and
22 do PARE, right. Let's start by doing whole

1 genome sequencing, like we did in PARE where
2 we found de novo translocations, and look to
3 see what happened, right.

4 So they're not replacing PARE with
5 whole genome sequencing. They're replacing
6 digital PCR with PARE, which is whole genome
7 sequencing. So I think you've got the
8 interpretation of this kind of backward from
9 what Dr. Leary is telling us she actually
10 did.

11 BY MR. LUMAN:

12 Q. Well, the PARE approach uses digital
13 PCR; isn't that correct?

14 A. That's not necessarily true, right.
15 We can go back and look at the PARE analysis. I'd
16 have to look back and see. I think they did
17 sequencing of the amplicons. And here they're
18 trying an alternative approach. They're taking the
19 biomarkers that they found invalidated, using the
20 PARE approach in the original Leary reference, and
21 now they're using them to do digital PCR.

22 So if I recall correctly in the

1 original Leary reference, and I'm happy to go back
2 and look at that, the original reference actually
3 used sequencing instead of digital PCR -- I believe
4 that's correct -- to confirm the break points that
5 they had identified.

6 So this is a different approach.
7 They're taking PARE biomarkers. They're doing
8 digital PCR. Having failed that, they go back and
9 do PARE, which is whole genome sequencing.

10 Q. Are you aware of any time before 2012
11 where the Leary research group used the term "whole
12 genome sequencing" to describe their approach?

13 MR. KRAUSE: Objection, relevance.

14 THE WITNESS: In the 2010 Leary paper,
15 they say genomic DNA from each sample is
16 purified, sheared, and used to generate
17 libraries with mate-paired tags, about 1,400
18 kilobase -- or 1.4 kilobases apart, which a
19 person of skill in the art would understand
20 is whole genome sequencing.

21 MR. LUMAN: I'd like to mark another
22 exhibit, which is Exhibit 2184 now. That

1 will be the number for it. And that will be
2 the Leary Oncotarget paper.

3 If we can make that available to
4 Dr. Quackenbush, please.

5 (Exhibit 2184, No Bates Numbers,
6 Cancer detection using whole-genome
7 sequencing of cell free DNA, Oncotarget,
8 August, Vol. 4, No. 8, 2013, received and
9 marked.)

10 MR. KRAUSE: Object on relevance,
11 foundation, timeliness, and outside the scope
12 of the reply.

13 BY MR. LUMAN:

14 Q. And, Dr. Quackenbush, can you let me
15 know when you've got it.

16 A. I've got it.

17 Q. So we've marked as Exhibit 2184 a
18 publication by first author Leary in the journal
19 Oncotarget from the year 2013, from pages 1119 to
20 1120.

21 Dr. Quackenbush, did you review this
22 paper in preparing your declaration?

1 A. I don't recall. Can you tell me if
2 I've cited to it in my report?

3 Q. I don't believe so, no. It's not
4 cited in your report.

5 A. In any of my reports?

6 Q. I'm not aware of it in the other
7 reports, but I'm not for sure.

8 A. All right. So I don't recall seeing
9 this previously.

10 Q. The first author is Rebecca Leary, the
11 same first author from Leary 2010 and Leary 2012; is
12 that right?

13 A. That would be my guess, yes. And this
14 is also a 2012 paper.

15 Q. Is this a 2013 paper? I think this
16 one was published in 2013.

17 A. Well, it says down at the bottom 28
18 November 2012. But -- whoops, sorry, is that the
19 same one? I'm sorry, I had the wrong paper. Maybe
20 I have the same one twice. Hold on, I don't have
21 the one you have up. So let's see.

22 THE DOCUMENT TECH: So you want the

1 document that says EX 2184.

2 THE WITNESS: Okay. That just came
3 up. I'm sorry. I downloaded the same Leary
4 twice.

5 All right. So this is a 2013 paper,
6 yes.

7 BY MR. LUMAN:

8 Q. So on the first page in the left-hand
9 column, I'd like to take a look at the last sentence
10 of that column. It starts with "We have recently."

11 Do you see that?

12 A. Yes, I do.

13 Q. It says, "We have recently developed a
14 non-invasive approach using whole-genome sequencing
15 to identify chromosomal alterations in the
16 circulation of cancer patients." And it has
17 citation 1.

18 Do you see that?

19 A. Yes, I do.

20 MR. KRAUSE: I object on relevance,
21 foundation, outside the scope of the reply,
22 and untimeliness. And I'll apply that to all

1 questions about this document that's just
2 been produced now.

3 BY MR. LUMAN:

4 Q. Dr. Quackenbush, Citation No. 1 is the
5 Leary 2012 paper that we just looked at; is that
6 right?

7 A. That is.

8 MR. KRAUSE: Same objection.

9 THE WITNESS: And the important thing
10 to understand about that paper, which is also
11 called out in this sentence, is that they're
12 referring to whole genome sequencing -- they
13 call it a noninvasive approach using whole
14 genome sequencing to identify chromosomal
15 alterations in circulation of cancer
16 patients.

17 In 2012, right, that paper that they
18 refer to that you just cited to is looking at
19 circulation of cancer patients. And the 2010
20 paper actually describes whole genome
21 sequencing of solid tumors.

22 So here, what Dr. Leary is doing is

1 distinguishing for analysis of circulating
2 tumor DNA from the 2012 whole genome approach
3 to sequencing solid tumors. But recall in
4 the 2012 paper, when the circulating tumor
5 DNA approach failed, she went back and used
6 whole genome PARE to analyze the tumor
7 itself.

8 BY MR. LUMAN:

9 Q. If you'll turn to page 2 with me in
10 this document.

11 A. All right.

12 Q. Do you see the reference list?

13 A. Yes, I do.

14 Q. Citation No. 4 is the Leary 2010
15 Exhibit 1002 that we've been discussing in this
16 proceeding; correct?

17 A. That looks correct. The Science
18 Translational Medicine 2010, yes, I believe that's
19 correct.

20 And if we look at where it's cited --
21 this is actually, again, consistent with everything
22 that I've said. When primary tumor material is

1 available, right, rather than circulating tumor DNA,
2 patient specific rearrangements may be identified
3 with personalized analysis of rearranged ends (PARE)
4 or related methods. And that's where this is called
5 out.

6 So, again, this is distinguishing
7 between the circulating tumor DNA, which the 2012
8 reference refers to, and the whole genome PARE
9 approach, which is used in the 2010 paper.

10 Q. Why do you think that the Leary 2012
11 paper refers to things specifically as whole genome
12 sequencing, but Leary 2010 does not use that term at
13 all?

14 MR. KRAUSE: Objection, foundation,
15 calls for speculation, untimely, outside the
16 scope of the reply.

17 THE WITNESS: So I can't tell you why
18 certain lexicographic choices were made by
19 Dr. Leary when she wrote her 2010 paper. I
20 will tell you that a person of ordinary skill
21 in the art reading the statement that genomic
22 DNA from each sample is purified, sheared,

1 and used to generate libraries with
2 mate-paired tags would understand that as
3 whole genome sequencing.

4 That's the definition of "whole genome
5 sequencing" using a method called the shotgun
6 approach, which actually dates back to the
7 1990s and I think it was first applied by
8 Craig Venter and his colleagues in sequencing
9 microbial genomes and actually became the
10 primary method for sequencing the human
11 genome as it was published in the year 2000.

12 So, you know, that definition is whole
13 genome shotgun sequencing or whole genome
14 sequencing, and Leary would have clearly
15 understood that.

16 BY MR. LUMAN:

17 Q. So based on your answer, would any
18 type of untargeted sequencing qualify as whole
19 genome sequencing?

20 MR. KRAUSE: Object to the form.

21 THE WITNESS: So I believe that the
22 patent board got it right when they said

1 whole genome sequencing could be construed to
2 mean a nontargeted approach to sequencing all
3 or almost all of the genome, right.

4 So I'm sure you could come up with
5 some ways -- some approaches that you would
6 call nontargeted that wouldn't meet this
7 definition, but when Leary tells me that what
8 she did was she took the whole genome and
9 sheared it and then sequenced the ends, that
10 clearly falls within the scope of whole
11 genome sequencing, right.

12 This is genomic DNA from tumor
13 samples. So it's not even DNA in blood.
14 This is two colon and two breast tumors, and
15 they're matched normal samples. So they've
16 got genomic DNA. They've got many thousands
17 of representations of each genome. That DNA
18 is randomly sheared -- purified randomly,
19 sheared, and sequenced. That's whole genome
20 genomic sequencing any way you slice it.

21 BY MR. LUMAN:

22 Q. So is whether an experiment qualifies

1 as whole genome sequencing based on what the
2 sequence results actually show, or is it based on
3 what the researcher intended to cover? If they
4 intended to cover all of the genome, is that going
5 to be sufficient to be whole genome sequencing?

6 MR. KRAUSE: Objection to the form,
7 incomplete hypothetical.

8 THE WITNESS: So I think what you'd
9 have to do is look at each particular
10 application in context. I'm sure you or I
11 could dream of something that wouldn't fit
12 the definition, but if we have a nontargeted
13 approach to, as the patent board told us,
14 sequencing all or almost all of the genome,
15 Leary's approach of taking thousands of
16 copies of the genome, shearing them and
17 sequencing the ends of those sheared
18 fragments meets their definition and would
19 meet a definition that one of skill in the
20 art would understand as whole genome
21 sequencing.

22

1 BY MR. LUMAN:

2 Q. Is it your testimony that in
3 determining whether something qualifies as whole
4 genome sequencing, we don't actually have to look at
5 how much of the genome was actually sequenced?

6 A. So as I state in paragraph 3a of my
7 report, a person of ordinary skill in the art's
8 understanding of "almost all" would have taken into
9 account the techniques that the contemporaneous
10 literature, including Personalis' patents,
11 considered to be whole genome sequencing, which
12 included low coverage techniques that perform
13 nontargeted sequencing at 50 percent or less,
14 including 10 percent coverage -- and I have
15 citations to those -- according to Leary's
16 technique, Dr. Furneaux asserts, achieves between 50
17 and 90 percent sequence coverage, sequences that a
18 person of ordinary skill in the art would have
19 understood to be almost all.

20 And as I pointed out earlier, the
21 other patents from Personalis actually include
22 explicitly in the definition of "whole genome

1 sequencing" coverage down to 50 percent. So, you
2 know, we did some calculations earlier based on
3 Dr. Furneaux's estimate, and Leary covers 60 percent
4 or 90 percent, depending on how you want to do the
5 math.

6 And so by any reasonable definition,
7 that's more than half, which would be closer to all
8 than not all. So it would seem to me that's a
9 reasonable standard at least to apply to the Leary
10 paper. And I can tell you that one skilled in the
11 art would understand that taking thousands of copies
12 of the genome, shearing those copies, and randomly
13 sequencing the end would be a well-known definition
14 of "whole genome sequencing."

15 Q. Is it fair to say, based on your
16 testimony, that if someone sequences at least
17 50 percent of the genome, they have met the "almost
18 all" part of the board's construction?

19 MR. KRAUSE: Objection, incomplete
20 hypothetical.

21 THE WITNESS: So you'd have to look at
22 how this process is carried out, right. The

1 board's description isn't just a percentage.
2 It's a nontargeted approach that covers, I
3 believe, all or almost all of the genome,
4 right.

5 So you could come up with scenarios
6 where 50 percent of the genome was sequenced,
7 but one might not call it whole genome
8 sequencing. Regardless, the claims of the
9 patent, at least the '394 patent, begin with
10 the recitation of whole genome sequencing and
11 then an analysis of that sequence data. And
12 Leary clearly discloses what by any
13 reasonable measure represents whole genome
14 sequencing.

15 BY MR. LUMAN:

16 Q. So if we say somebody did a
17 nontargeted approach that sequenced 50 percent of
18 the genome, would that qualify as "almost all" under
19 your interpretation of the board's claim
20 construction?

21 A. I would have to analyze that
22 particular reference to understand what they were

1 doing. The argument that I made and presented that
2 Dr. Furneaux tried to refute was that Leary
3 represents disqualifying prior art.

4 Leary's approach includes -- and I
5 haven't been given copies of the patents yet today,
6 but Leary's approach includes a first step in PARE,
7 which is whole genome sequencing. Taking the
8 genome, randomly shearing it using a nontargeted
9 approach to generate sequence data, and covering all
10 or almost all, right -- so depending on how
11 Dr. Furneaux wants to calculate it, between 60 and
12 90 percent, right. And using the standard
13 definition, it would be 90 percent; using
14 Dr. Furneaux's altered definition, 60 percent.

15 So 0.9-fold coverage of the genome,
16 right, which I would say is almost all if one is
17 onefold coverage of the genome, right. So
18 0.9 percent of the genome, that's what O'Leary --
19 that's what Leary does. She then identifies
20 variance. She designs PCR capture probes, does
21 subsequent analysis in multiple samples, and I
22 believe they're all blood samples, and identifies

1 break points that she can use to track and estimate
2 the amount of residual disease over time.

3 So Leary clearly discloses each and
4 every element of Claim 1 of the '394 patent. And we
5 can also analyze Claim 1 of the '033 patent in the
6 context of Leary in exactly the same way. You don't
7 have to start with whole genome sequencing, but
8 using PCR capture probes and analyzing multiple
9 samples is clearly disclosed in Leary 2010.

10 Q. So I didn't ask about Leary. So your
11 response is nonresponsive to my question. Let's get
12 back to the actual question that was asked.

13 A. Okay.

14 Q. What -- if somebody did a nontargeted
15 approach that sequenced 50 percent of the genome,
16 would that meet the board's construction of whole
17 genome sequencing?

18 MR. KRAUSE: Objection, asked and
19 answered.

20 THE WITNESS: So if you'd like to
21 provide me with an example, I'd be happy to
22 analyze that and give you an opinion. The

1 important thing, though, would be to really
2 understand whether or not this was something
3 that represented disqualifying prior art.

4 BY MR. LUMAN:

5 Q. How about what's the minimum percent
6 coverage of nontargeted sequencing that would meet
7 the board's construction of whole genome sequencing?

8 MR. KRAUSE: Objection, incomplete
9 hypothetical.

10 THE WITNESS: I don't know where one
11 would draw the boundary, but given that Leary
12 is disqualifying prior art, Leary's
13 90 percent coverage or 60 percent coverage,
14 based on Dr. Furneaux' other estimate,
15 clearly meets the definition of "whole genome
16 sequencing."

17 BY MR. LUMAN:

18 Q. Is it possible that sequencing
19 10 percent of the genome in a nontargeted way would
20 possibly qualify as whole genome sequencing under
21 the board's construction?

22 MR. KRAUSE: Objection to form.

1 THE WITNESS: So, again, it would
2 depend on the context, right. So to provide
3 you with some information that might help you
4 in understanding what was represented in the
5 contemporaneous literature, I'll point you
6 back to paragraph 31, where I refer to
7 Dr. Furneaux' misinterpretation of the Newman
8 reference.

9 And one of the papers that -- that's
10 cited, actually, in Newman is reference 33.
11 It's Heitzer. And Newman himself -- if
12 you'll look at the callout I have in
13 paragraph 30, it says, Previously published
14 methods employing amplicon, reference 8, 10,
15 11, whole exon reference 12, or whole genome
16 reference 9, 32, 33, and 24 sequencing. So
17 whole genome sequencing includes reference
18 33.

19 Reference 33 is Heitzer. And Heitzer
20 explains that previously it had been shown
21 that whole genome sequencing with a shallow
22 sequencing depth of about 0.1X, which we'd

1 read as 0.1-fold is sufficient for a robust
2 and reliable analysis of copy number changes
3 from single cells. Okay.

4 So there are potential scenarios where
5 one skilled in the art would call 10 percent,
6 or 0.1-fold coverage by the Lander/Waterman
7 definition, as shallow whole genome
8 sequencing, right.

9 And Heitzer goes on to say, We
10 performed whole genome sequencing from plasma
11 at the shallow depth to establish a genome
12 multiple copy number profile of the tumor at
13 low cost within two days, right.

14 And Heitzer confirms that his whole
15 genome plasma sequencing is performed at a
16 shallow depth of approximately 0.1-fold. So
17 there are at least some situations in which
18 very low coverage is still referred to as
19 whole genome sequencing, right.

20 Beyond that, though, where one, based
21 on the board's definition, would draw that
22 lower bound, I can't speak to. I will say

1 that given everything we've discussed today,
2 Leary is clearly within the scope of whole
3 genome sequencing as a nontargeted
4 genome-wide approach that covers a
5 substantial portion of the genome which
6 contemporaneous references would -- I believe
7 concur are all -- not all, but almost all of
8 the genome, 60 percent or 90 percent, anyone
9 would call almost all.

10 BY MR. LUMAN:

11 Q. Would a person of ordinary skill in
12 the art know what whole genome sequencing means --
13 let me try that again.

14 If a person of ordinary skill in the
15 art is looking at a prior art reference, would they
16 be able to determine whether the type of sequencing
17 in that reference qualifies as whole genome
18 sequencing using the board's claim construction?

19 A. Using the board's claim construction,
20 I can tell you without doubt that Leary is whole
21 genome sequencing.

22 Q. And could you do that with any prior

1 art reference or just Leary is the only one?

2 MR. KRAUSE: Objection, calls for
3 speculation, incomplete hypothetical,
4 relevance.

5 THE WITNESS: So Leary is a good
6 example, and I cited it as invalidating prior
7 art. I haven't done a complete analysis of
8 everything that had been published prior to
9 2012, where people refer to what they do as
10 whole genome sequencing.

11 To make that determination, I would
12 have to look at a paper and analyze it. The
13 reason I chose Leary is that Leary really
14 represents each and every element of what's
15 claimed, at least in Claim 1 of the '394
16 patent and I would also assert in Claim 1 of
17 the '033 patent. And that would include in
18 '394 whole genome sequencing, identifying
19 polymorphisms, designing probes to those
20 polymorphisms, and using those -- those
21 probes in the case of Leary PCR capture
22 probes to subsequently profile samples from

1 the same individual and to make a
2 determination and produce a report describing
3 its findings.

4 So -- and I chose Leary for very
5 specific reasons. I could have chose other
6 references, potentially, but Leary was just
7 the best -- Leary was far and away the best
8 example.

9 BY MR. LUMAN:

10 Q. Leary was looking at rearrangement
11 variance. Consider instead a person of ordinary
12 skill in the art had been looking to identify single
13 nucleotide variance, what would be the minimum
14 percent coverage in that instance that would have to
15 be demonstrated to meet the board's construction of
16 whole genome sequencing in a nontargeted manner?

17 MR. KRAUSE: Objection, form,
18 incomplete hypothetical.

19 THE WITNESS: So I haven't done that
20 analysis. One skilled in the art would
21 understand that translocations are one type
22 of polymorphism. Single nucleotide

1 polymorphisms are another type of
2 polymorphism.

3 One skilled in the art would
4 understand that if one were looking for SNPs,
5 one might choose an alternate strategy for
6 how to shear the genome. So one might shear
7 the genome into smaller fragments. One
8 skilled in the art would also understand that
9 it might be advantageous to sequence more
10 deeply.

11 So running -- loading more libraries
12 under the sequencer and sequencing more was
13 not a barrier to generating data. Once [sic]
14 the art would also understand that in the
15 early 2000s, in projects like the thousand
16 genomes project, DNA from individuals
17 representing populations across the globe
18 were sequenced at low coverage to
19 determine -- to identify polymorphisms that
20 were subsequently used in genetic studies.

21 So, you know, one skilled in the art
22 would understand that whole genome sequencing

1 can cover a breadth of different coverage
2 depths, depending on the particular
3 application, and the generating deeper
4 coverage did not require anything other than
5 taking the leftover library you didn't load
6 on the first sequencing run and putting it on
7 run two or run three or run ten of the
8 sequencer.

9 BY MR. LUMAN:

10 Q. If a person of ordinary skill in the
11 art were seeking to identify a heterozygous single
12 nucleotide polymorphism, would they be able to do so
13 with a coverage that was less than 100 percent of
14 the genome?

15 MR. KRAUSE: Objection to form,
16 incomplete hypothetical.

17 THE WITNESS: It might depend on which
18 single nucleotide polymorphism one was trying
19 to analyze or which one had identified. So I
20 can imagine many scenarios in which low
21 coverage of the genome would actually
22 identify heterozygous SNPs within that genome

1 sequence.

2 So, you know, it would really depend
3 on the individual application. Again, the
4 thousand genomes project in the early 2000s
5 used low coverage sequence to identify SNPs
6 that were at least variable at a population
7 level, and I'm sure identified -- although I
8 can't recall the details, I'm sure identified
9 SNPs that were heterozygous within a single
10 individual.

11 BY MR. LUMAN:

12 Q. Would you mind turning with me to
13 paragraph 49 of your declaration, which is
14 Exhibit 1225.

15 A. All right. I have that here.

16 Q. And hold on, we've got the wrong
17 paragraph. Hold on, let me get the right one.

18 Okay. I'm sorry, it's page 49. Can
19 you turn to page 49?

20 Would you let me know when you arrive
21 at page 49, Dr. Quackenbush.

22 A. Sure. I'm typing in numbers to try to

1 jump. And there we are, page 49.

2 Q. And about halfway through, there's a
3 sentence that starts with "While cost and data
4 storage."

5 Do you see that?

6 A. Yes, I do.

7 Q. It says, "While cost and data storage
8 issues presented challenges and constraints..."

9 So my question is: What were some of
10 the constraints that were based on cost that you
11 reference in this paragraph?

12 MR. KRAUSE: Objection, 403.

13 BY MR. LUMAN:

14 Q. Let me try -- let me ask it slightly
15 differently.

16 What are some of the constraints due
17 to costs that you reference in this paragraph
18 relating to whole genome sequencing?

19 MR. KRAUSE: Same objection.

20 THE WITNESS: So I'm actually
21 responding to a suggestion that Dr. Furneaux
22 puts forth that the literature -- and I'm

1 quoting him now -- consistently describes
2 whole genome sequencing as being undesirable.

3 And I believe Dr. Furneaux is just
4 misreading what's in the literature and then
5 also not recalling what the state of the
6 field was in 2009 and 2010, right.

7 "As I noted in my initial declaration,
8 in 2008, Ley nicely summarized this fact by
9 explaining that its approach was possible
10 because 'Whole-genome sequencing is now
11 possible at a reasonable cost and time frame
12 to use this approach for the unbiased
13 discovery of tumor-specific somatic mutations
14 that alter protein-coding genes.'"

15 So cost and data storage did present
16 some challenges for individuals trying to do
17 this. But as I pointed out, I believe, in
18 both my initial report on the '394 patent and
19 the '033 patent, in the mid-2000s, the cost
20 of genome sequencing was dropping by
21 33 percent per quarter.

22 So in 2009, I got the first whole

1 genome -- or the first Illumina whole genome
2 sequencer at the Dana Farber Cancer
3 Institute.

4 In 2009 or 2010, we sequenced two
5 ovarian cancer genomes. The first one we
6 sequenced took a few weeks. And I don't
7 remember what the cost was, but we went back
8 and sequenced another genome a few months
9 later, and it took only days to generate
10 sufficient data, the same quantity of data.
11 And I think we sequenced the genome at
12 30-fold, maybe it was a hundred-fold in both
13 cases, and the cost was substantially lower.

14 So it was almost the time when people
15 would hesitate to sequence because they knew
16 in a few months it would be much less
17 expensive. So, you know, cost is always a
18 factor.

19 In the early 2000s, people were
20 profiling gene expression using a technique
21 called DNA microarray analysis. By 2008,
22 2009, microarray analysis had almost

1 disappeared, and everyone was doing RNA
2 sequencing because it had become cost
3 competitive and the data was much more
4 reliable.

5 So cost is always an issue, and I
6 think the Mertes reference you referred me to
7 earlier included the fact that one should
8 consider cost in making decisions about the
9 technique that one chose to use.

10 So, you know, the -- but Ley really
11 underscores the fact that the cost and time
12 frame for getting to the point that this
13 approach of whole genome sequencing was
14 really rapidly emerging as a standard for
15 generating data on mutational status, right.

16 Leary, in 2010, actually said, "the
17 cost of massively parallel sequencing, which
18 has decreased substantially over the last
19 2 years, continues to spiral downward."

20 And that's that 33 percent per quarter
21 drop that is shown in empirical data from the
22 National Human Genome Institute and which I

1 cited to previously.

2 BY MR. LUMAN:

3 Q. So when you referenced challenges
4 relating to cost, are you just saying that if
5 something's too expensive, it wouldn't be feasible?

6 MR. KRAUSE: Objection,
7 mischaracterizes, 403.

8 THE WITNESS: So I wouldn't say it's
9 not feasible. I would say that one would
10 have to factor cost into one's decision. But
11 when the cost is dropping so rapidly, right,
12 it's dropping by a third every three months.
13 What might not be feasible for me in my own
14 lab in 2009 or 2010 would clearly be feasible
15 in 2008, 2009, 2010, 2011, 2012.

16 I believe by 2012, the cost of
17 sequencing in genome had gotten down to a few
18 thousand dollars. I was at the Dana Farber
19 Cancer Institute in the early 2000s. And
20 some of the papers we cited to earlier,
21 Matthew Meyerson was there. I forget the
22 first author, but Levi Garraway was one of

1 the last authors. Oh, Wagle.

2 These were people at the Dana Farber
3 Cancer Institute. And in the relevant time
4 frame, we were building an assay, and I was
5 part of the team developing this assay, at
6 least really focusing on the data management
7 pieces.

8 We moved from thinking about how we
9 were going to profile patients to developing
10 the profile assay, which was essentially used
11 to sequence the genome of every cancer
12 patient who qualified who walked in the door.

13 So, you know, it -- cost is sort of a
14 relative issue and has to be balanced against
15 the opportunity cost you lose by not
16 sequencing a genome.

17 BY MR. LUMAN:

18 Q. How about data storage issues
19 referenced here, were they sold just by buying
20 computers with more hard drive space or something
21 like that?

22 MR. KRAUSE: Objection, 403.

1 THE WITNESS: So there are a variety
2 of different ways in which data storage was
3 addressed. Some was better compression
4 algorithms for dealing with data. Some was
5 moving data quickly, mapping it to the genome
6 and producing compressed files and moving the
7 raw data to long-term storage rather than --
8 what we think of as cold storage rather than
9 hot storage.

10 And some of the way these problems
11 were solved was by using low-cost cloud-based
12 providers with the appropriate data security
13 and encryption protocols in place to satisfy
14 the requirements of the Health Insurance
15 Portability and Protection Act, or what we
16 refer to as HIPAA.

17 BY MR. LUMAN:

18 Q. Do the data storage issues you
19 reference in this paragraph include any privacy
20 issues?

21 MR. KRAUSE: Objection, relevance,
22 403.

1 THE WITNESS: Privacy is something
2 that one always has to consider in dealing
3 with human subjects data. And there were
4 well-established protocols as of 2008, 2009,
5 clearly by 2012 or '13, for handling those
6 data storage issues. So...

7 BY MR. LUMAN:

8 Q. Were there any data processing issues
9 associated with whole genome sequencing in the 2011
10 time frame?

11 MR. KRAUSE: Same objection.

12 THE WITNESS: Clearly, Ley, Leary, the
13 other reference I cited -- references I cited
14 to did not present any substantial problems
15 associated with data storage or data
16 processing. They were able to analyze the
17 data and use that data in an informed way to
18 monitor status of cancer patients serially
19 over time.

20 BY MR. LUMAN:

21 Q. What about -- what were some of the
22 challenges relating to data storage that are

1 referenced in your paragraph?

2 MR. KRAUSE: Same objection.

3 THE WITNESS: So I'm pointing out that
4 Dr. Furneaux mischaracterizes the state of
5 the art and state of the field at the time,
6 right. If you don't -- I can tell you that
7 even today, if you don't have a rational data
8 storage policy, then you're going to run into
9 data storage issues.

10 My laptop, my hard drive may fill up
11 if I let junk accumulate, but if I have a
12 rational approach to handling data and data
13 management, then it's no longer a challenge.
14 My e-mail inbox gets full, and so that I
15 would consider a data storage issue, but if
16 I'm smart and clean it out and then delete
17 the junk e-mail I get, it's no longer a
18 problem.

19 So there are potentially data storage
20 issues, but these aren't insurmountable
21 barriers to using whole genome sequencing as
22 the first step in a process of identifying

1 polymorphisms that can then subsequently be
2 used to track the status of a cancer
3 patient's tumor over time.

4 MR. LUMAN: So we've been going for
5 about an hour. Should we take a break or
6 keep going?

7 THE WITNESS: Well, I think our court
8 reporter likes to stretch her legs a little
9 bit. So why don't we take a break.

10 Can I ask how much time is still left?

11 MR. LUMAN: Off the record at 2:03.

12 (Recess from the record.)

13 MR. LUMAN: Let's go back on the
14 record at 2:14.

15 BY MR. LUMAN:

16 Q. Dr. Quackenbush, would you please turn
17 to page 62 of your declaration, please.

18 Not -- yeah, page 62. Thank you. I
19 thought I said paragraph.

20 A. Not paragraph 62.

21 Q. Page 62.

22 A. All right.

1 Q. And I'm looking in paragraph 105. And
2 the last sentence refers to Forshe's reference has
3 suggested at least two 1-ml plasma samples.

4 Do you see that part of your
5 declaration?

6 A. Yes, I do.

7 Q. So I'd like to determine is the amount
8 of DNA in two 1-milliliter plasma samples in Forshe
9 patient.

10 MR. LUMAN: So if we could pull up
11 Exhibit 1030, which is Forshe.

12 BY MR. LUMAN:

13 Q. And I'm going to double-check and make
14 sure that you've already got that, Dr. Quackenbush.

15 Yes, that's already been made
16 available.

17 A. There are a substantial number of
18 documents. I'm sorry, it's one of the earlier ones.
19 Okay.

20 Q. Can we turn to Table 2 in
21 Exhibit 1030?

22 A. All right. So I have Table 2.

1 Q. And let's look at the first sample,
2 Sample No. 1.

3 A. Okay.

4 Q. If you wanted to get the concentration
5 of DNA in a 1-mL sample for patient 1, you'd take
6 the 0.9 nanograms, which is the amount of DNA for
7 amplification reaction, and divide by the volume,
8 which was 70 microliters, and then wouldn't you also
9 divide by a thousand because there's a thousand
10 microliters in 1 milliliter?

11 MR. KRAUSE: Objection, 403.

12 (Document review.)

13 THE WITNESS: I'm sorry, I'm not sure
14 what calculation you're asking me to do.

15 BY MR. LUMAN:

16 Q. For sample No. 1, can you calculate
17 the concentration of DNA that would exist in
18 1 milliliter for that sample?

19 Can you take the amount of DNA and the
20 volume of the reaction and come up with a
21 concentration in terms of nanograms per milliliter?

22 MR. KRAUSE: Objection, 403,

1 incomplete hypothetical.

2 THE WITNESS: So I'm not fully sure
3 what exactly is being reported here. So not
4 understanding that, we have 70 microliters,
5 which is going to be 70 times 10 to the minus
6 3 milliliters.

7 BY MR. LUMAN:

8 Q. So there would be .9 nanograms in 70
9 times 10 to minus 3 milliliters. That would be the
10 concentration?

11 MR. KRAUSE: Objection, vague,
12 incomplete hypothetical, mischaracterizes.

13 THE WITNESS: I'm thinking about how
14 to do this. So --

15 (Pause from the record.)

16 THE WITNESS: I wasn't expecting to
17 have to pull out a calculator.

18 All right. So -- sorry it took so
19 long. So if we have 0.9 nanograms, that's
20 9 times 10 to the minus ninth grams, divided
21 by 70 microliters. So it's going to be 70
22 times 10 to the minus 3 liters. That tells

1 me I have 1-point -- or sorry, 70 times to
2 the minus 3 microliters, that tells me I have
3 1.29 times 10 to the minus 8 grams or over
4 2,000 genome equivalents per milliliter.

5 Because you'll recall, hopefully, that
6 the mass of a genome is about six times to
7 the minus 12 grams.

8 BY MR. LUMAN:

9 Q. And so what was the concentration in
10 grams per milliliter?

11 A. 1.29 times 10 to the minus 8 grams per
12 milliliter or over 2,000 genome equivalents per
13 milliliter, actually 2,143.

14 Q. And if you did the -- how long would
15 it take you to do the same calculation on Sample 40,
16 if we just did one more?

17 A. Sample 40?

18 Q. Yeah.

19 A. Not that I have it set up. All I have
20 to do is plug in the numbers. So Sample 40 is 160
21 and 8.5.

22 MR. KRAUSE: I'll just lodge an

1 objection on 403 and completeness grounds.

2 THE WITNESS: So that would be 5.31
3 times 10 to the minus 8 grams per milliliter,
4 or 8,844 genomes per milliliter.

5 BY MR. LUMAN:

6 Q. And Sample 40 was the one that's got
7 19.7 nanograms in 160 microliters?

8 A. Oh, I'm sorry, I pulled out a
9 different one. Let me just redo that. So it's -- I
10 did 42. I'm sorry.

11 (Pause.)

12 THE WITNESS: So that would be 1.23
13 times 10 to the minus 7 grams for about --
14 over 20,000 genome equivalents per
15 milliliter.

16 MR. LUMAN: I'd like to mark as
17 Exhibit 2185 the document that was marked as
18 Exhibit 2165 in IPR 2023-00545.

19 (Exhibit 2185, No Bates Numbers,
20 Predicting Radiotherapy Responses and
21 Treatment Outcomes Through Analysis of
22 Circulating Tumor DNA, Seminars in Radiation

1 Oncology, 2015, marked for identification.)

2 THE WITNESS: Before we go there, you
3 know, I just want to state I'm not sure
4 exactly, you know, if these are -- this is
5 accurately what's being reported in Table 2
6 or how it's been determined. I haven't had
7 time to go through and validate that. All
8 I'm doing is doing the division you requested
9 and then converting this to genome
10 equivalents, assuming that your assertion
11 about what these represent is correct.

12 MR. KRAUSE: And with respect to
13 what's now been marked as Exhibit 2185, we
14 object as to relevance, timeliness, and
15 exceeding the scope of the reply and
16 foundation.

17 (Discussion of the record.)

18 BY MR. LUMAN:

19 Q. Dr. Quackenbush, can you let me know
20 when you've had a chance to look at what's been
21 marked as Exhibit 2185 in this proceeding?

22 (Document review.)

1 THE WITNESS: I have it open in front
2 of me now, yes.

3 BY MR. LUMAN:

4 Q. This is an article that was published
5 in Seminars in Radiation Oncology in the year 2015;
6 correct?

7 A. That's what it says, and that appears
8 to be what it is.

9 Q. If we can look on page 305 and on the
10 right-hand side.

11 A. Okay.

12 Q. Sorry, let's look in the abstract
13 instead. I want to look in the first sentence in
14 the abstract. It says, "Tumors continuously [sic]
15 shed DNA into the blood where it can be detected as
16 circulating tumor DNA (ctDNA). Although this
17 phenomenon has been recognized for decades,
18 techniques that are sensitive and specific enough to
19 robustly detect ctDNA have only become available
20 recently."

21 Dr. Quackenbush, do you agree with
22 what the authors have written here in the year 2015?

1 MR. KRAUSE: Same objections.

2 THE WITNESS: I haven't read this
3 paper. If you'd like, I'm happy to read it.
4 I will say that the first sentence is
5 absolutely correct, tumors continually shed
6 DNA into the blood where it can be detected
7 as circulating tumor DNA.

8 I don't know how they're qualifying
9 the second sentence. So at this point,
10 reading two sentences of an eight-page paper,
11 I'm not going to render an opinion as to what
12 they might mean by that.

13 BY MR. LUMAN:

14 Q. Do you see that this paper, one of the
15 authors is Dean V-I-E-H-N, that's the last author?

16 A. Yes, I do.

17 Q. And the author before that is
18 Alizadeh.

19 Do you see that?

20 A. Yes.

21 MR. KRAUSE: Objection, relevance,
22 403.

1 BY MR. LUMAN:

2 Q. Are you aware that those two authors
3 are founders of the company Foresight?

4 A. You mentioned, I think, at least Diehn
5 earlier. So I believe that's correct.

6 MR. LUMAN: I'd like to mark as
7 Exhibit 2186 the document that was previously
8 marked as Exhibit 2164 in IPR 2013-00545.

9 (Exhibit 2186, No Bates Numbers,
10 Potential clinical utility of ultrasensitive
11 circulating tumor DNA detection with
12 CAPP-Seq, Expert Reviews Mol. Diagn., 2015,
13 received and marked.)

14 MR. LUMAN: And can we make that
15 document available to Dr. Quackenbush,
16 please?

17 THE WITNESS: Exhibit 2164?

18 BY MR. LUMAN:

19 Q. Yes. And that's now been marked in
20 this proceeding is 2186. All right?

21 MR. KRAUSE: I object, timeliness,
22 lack of foundation, irrelevance, and outside

1 the scope of the reply.

2 BY MR. LUMAN:

3 Q. Do you see that this article is
4 written by two of the same folks we just looked at,
5 Dr. Alizadeh and Dr. Diehn?

6 A. Yes, I can see that.

7 MR. KRAUSE: Objection, 403.

8 THE WITNESS: It's an editorial. We
9 can call it an article.

10 BY MR. LUMAN:

11 Q. Thank you for that clarification.

12 If we look at page 715, on the
13 left-hand column -- sorry, the right-hand column,
14 the very top of the right-hand column, where it
15 says -- it begins with "A major technical
16 challenge."

17 Do you see that?

18 A. I do.

19 Q. The authors wrote, "A major technical
20 challenge in the analysis of ctDNA is that the vast
21 majority of the cell-free DNA found in plasma
22 originates in the patient's healthy cells.

1 Therefore, highly sensitive techniques are necessary
2 for reliable detection and quantitation of the
3 tumor-derived fraction. For example, in patients
4 with stage IV non-cell -- non-small cell lung
5 cancer, the percentage of circulating DNA that is
6 tumor-derived has been shown to vary between median
7 values of approximately 0.1 to 5 percent and is
8 affected by factors such as disease burden and
9 treatment status [sic]."

10 Dr. Quackenbush, do you agree with the
11 authors and what they've written here?

12 MR. KRAUSE: Objection, relevance,
13 foundation, exceeds the scope of the reply,
14 untimely.

15 THE WITNESS: So they're citing -- so,
16 again, you're giving me a five-page paper
17 that I've never seen before, right. You're
18 calling out a citation -- or calling out one
19 statement -- or a series of statements. They
20 actually refer to references 5 through 7,
21 which I haven't read. And I'm not familiar
22 with how much tumor-derived cell-free DNA

1 circulates in plasma stage IV in non-small
2 cell lung carcinoma patients.

3 I will agree that one of the
4 challenges in analyzing any type of cell-free
5 DNA is -- the identifying the tumor-derived
6 elements, and if we look at references like
7 Leary, part of the reason Leary uses
8 techniques like PCR capture probes is to
9 overcome some of these challenges.

10 So discussion here is about a method
11 called CAPP, Cancer Personalized Profiling by
12 deep Sequencing (CAPP-Seq). And my
13 assumption is that given the fact that
14 they're pointing this out in the
15 introduction, what they're disclosing here is
16 that the CAPP-Seq process that they're
17 describing in this editorial actually
18 overcomes those limitations.

19 So I can't really comment on the
20 voracity of what you're pointing out here or
21 the challenges, just like in the previous
22 paper you pointed out something that occurs

1 at the beginning of the abstract.

2 The way scientists typically write
3 papers is to point out what a challenge is
4 and then to describe how one overcomes that
5 challenge. So, you know, is that a
6 challenge? Well, at least they see it as a
7 challenge that needs to be overcome. I'm
8 more than happy to spend time reading the
9 paper, but my assumption is that they're
10 going to describe ways of overcoming this.

11 And I'll turn your attention to
12 page 717, right, where at the bottom it's
13 conclusions and future directions. And they
14 tell us, "With CAPP-Seq, the possible
15 clinical applications of circulating tumor
16 DNA continue to expand, and additional
17 innovations can be expected. Once thought to
18 be applicable primarily to advanced stage
19 cancers, NGS, next-generation sequencing,
20 analysis of circulating tumor DNA is now
21 technically feasible in earlier stages as
22 well. As with every new biomarker, the

1 clinical utility of circulating tumor DNA
2 analysis will need to be proven through
3 well-designed clinical trials [sic]."

4 So, you know, there again, I haven't
5 read this entire study, but my -- the way I
6 would frame this is, yes, they see this as a
7 problem and, yes, if we read the conclusion,
8 this CAPP-Seq method, which they describe
9 here but I haven't read and I can't tell you
10 what it does, overcomes those problems and
11 the clinical applications with CAPP-Seq
12 continue to expand and additional innovations
13 as of 2015 were to be expected.

14 BY MR. LUMAN:

15 Q. And sitting here today, do you have
16 any reason to disagree with what the authors wrote
17 in Exhibit 2185 and 2186?

18 MR. KRAUSE: Objection, relevance,
19 foundation, outside the scope of the reply,
20 untimely.

21 THE WITNESS: So I just talked about
22 the conclusion and future directions and the

1 2015 editorial.

2 If I look at the 2015 paper you
3 referred me to earlier -- and, I'm sorry, I
4 can't tell you the exhibit number, but it's
5 the Chaudhuri and Alizadeh and Diehn paper --
6 they tell us in the conclusions and future
7 directions, "Analysis of circulating tumor
8 DNA is a noninvasive approach to detect,
9 genotype, and quantify tumor burden that has
10 the potential to be incorporated into the
11 practice of radiation oncology [sic]," right.

12 So I haven't read the paper, but I
13 have no reason to doubt that they identify
14 what they believe is a problem and, in this
15 scientific paper, identify what they believe
16 is the solution. But not having read the
17 paper, I can't tell you how they claim to
18 have overcome the difficulty.

19 There is a description -- or there's a
20 table in this first paper you showed me on
21 page 307 that talks about the detection limit
22 of the CAPP-Seq method, which I'm assuming is

1 what they're writing about, and some of the
2 advantages and limitations. And apparently
3 the CAPP-Seq detection method -- we talked
4 about circulating tumor DNA being relatively
5 low abundance. They can tell us they can
6 detect circulating tumor DNA down to
7 0.01 percent.

8 So I'm assuming, as we suggested, that
9 they identified a problem and then presented
10 a solution to that problem.

11 BY MR. LUMAN:

12 Q. Would you turn with me to
13 paragraph 106 of your declaration, Exhibit 1225,
14 please?

15 A. All right.

16 Q. Let me know when you're ready.

17 A. I'm there.

18 Q. All right. So the first sentence
19 talks about Wagle's DNA was PCR amplified and pooled
20 before being exposed to its hybridization capture
21 probes.

22 Do you see that?

1 A. Yes, I do.

2 Q. And the reason that Wagle's DNA was
3 PCR amplified and pooled before using hybridization
4 capture probes is because without PCR, there
5 wouldn't be enough DNA to capture with the
6 hybridization capture probes used by Wagle; correct?

7 MR. KRAUSE: Objection, incomplete
8 hypothetical.

9 THE WITNESS: So I would have to go
10 back and read Wagle to really understand what
11 Wagle might be referring to, but if we look
12 at the block quote that I have, it says,
13 "Massively parallel sequencing libraries for
14 Illumina that contain barcoded universal
15 primers were generated with the use of
16 genomic DNA from formalin-fixed
17 paraffin-embedded tumor material [sic]."

18 So now we're not dealing with
19 circulating tumor DNA. We're dealing with
20 DNA from pathology samples. So in a typical
21 pathology lab, the tumors fixed with formalin
22 and embedded in paraffin as an archival

1 sample, in part because it preserves tissue
2 structure and biological molecules like DNA.

3 "After preamplification and DNA
4 quantification, equimolar pools were
5 generated consisting of 12 barcoded tumor
6 DNAs," right. So the DNA is taken and
7 preamplified, then amplified. For it to
8 become barcoded, that DNA amplification is
9 introducing those barcodes as sample-specific
10 barcodes.

11 So there could be a variety of reasons
12 why the amplification was done first in this
13 instance, but clearly one of those was to
14 introduce the sample-specific barcodes,
15 right. These DNA pools of 12 samples, each
16 of which has the sample barcode, were then
17 subjected to hybrid capture with biotinylated
18 RNA baits targeting all exons from 137
19 actionable cancer genes.

20 So, you know, it's a strategy. At
21 least the amplification here is designed to
22 barcode the samples so they can be

1 multiplexed and analyzed more efficiently and
2 more cost effectively, right.

3 So -- and there's a discussion down
4 below of the pooling and hybrid capture that
5 talks about the amount of DNA that was
6 available. So I don't believe your
7 characterization is correct. But, again, I
8 would have to go back and read the Wagle
9 paper to fully understand all of the reasons
10 they might have selected to do the
11 amplification first.

12 The important thing to recognize is
13 that there are a variety of different
14 references, some of which capture, then
15 amplify; some of which amplify, then capture.

16 BY MR. LUMAN:

17 Q. So why would -- you said one reason
18 that you would amplify first and then capture is to
19 include barcodes.

20 Why -- I guess my question is: Can
21 you add barcodes by using solution-phase hybrid
22 capture probes?

1 MR. KRAUSE: Objection to form.

2 THE WITNESS: So I've thought about
3 this question a number of times, and I
4 believe I speak to it possibly in this
5 report, possibly in others. The introduction
6 of barcodes will require a PCR amplification
7 step, right.

8 If, as you alluded to earlier, the
9 capture probes are simply capturing the DNA,
10 that capture is not going to put on a barcode
11 unless the barcode is in the noncapture
12 region, which wouldn't be complementary
13 base-paired to the target. And the only way
14 then to introduce that barcode would be
15 through a DNA extension reaction like what
16 occurs in PCR that would capture that
17 barcode.

18 So barcoding, one skilled in the art
19 would understand, would imply the use of a --
20 of an amplification, and that's exactly what
21 Wagle is telling us in this excerpted portion
22 of the paper.

1 BY MR. LUMAN:

2 Q. And you had mentioned that there's a
3 variety of circumstances where you would amplify
4 first and then use solution-phase hybrid capture
5 probe second or the other way around.

6 And when a researcher chooses to use
7 both techniques, those techniques would not be
8 selected because they're redundant to each other;
9 right?

10 MR. KRAUSE: Objection to form,
11 incomplete hypothetical.

12 THE WITNESS: So I'm trying to parse
13 the question because I don't fully understand
14 what you're asking. We've looked at multiple
15 examples today of barcoding. And we've
16 talked about so many references I'm actually
17 forgetting which ones we talked about
18 earlier. It could have been Wagle. It could
19 have been others in which -- well, in almost
20 any of them, and there was an explicit
21 callout in one of them simply describing --
22 and I remember there were P5 and P7

1 explicitly mentioned in the reference -- that
2 after using a hybridization capture probe,
3 PCR was performed to attach the sequencing
4 adapters.

5 So, you know, your question
6 presupposes that it's sort of one or the
7 other that these are, you know, redundant.
8 And really I think the best way to think of
9 them is that all of these capture
10 technologies, PCR with PCR capture probes
11 identifying or amplifying a region that's
12 then later analyzed or hybridization and PCR
13 to generate the sequencing libraries which
14 are later amplified are really flavors of the
15 same basic technique that rely on
16 complementary base-pairing between a probe
17 and a target molecule or multiple probes and
18 a target molecule, and that that definition
19 is completely consistent with the way in
20 which the board has construed capture probes
21 in this IPR action.

22

1 BY MR. LUMAN:

2 Q. Let's turn to paragraph 98 in your
3 declaration, please.

4 A. All right.

5 Q. And in this paragraph you reference
6 the Chan publication; right?

7 A. Yes.

8 MR. LUMAN: I'd like to make Chan
9 available to you. That is Exhibit 1008.

10 (Exhibit 1008, No Bates Numbers,
11 Cancer Genome Scanning in Plasma: Detection
12 of Tumor-Associated Copy Number Aberrations,
13 Single-Nucleotide Variants, and Tumoral
14 Heterogeneity by Massively Parallel
15 Sequencing, Clinical Chemistry 59:1, 2013,
16 Chan et al., received and marked.)

17 BY MR. LUMAN:

18 Q. And then we'll actually look at it
19 once you've had a chance to download it.

20 A. Okay. So it hasn't appeared yet.

21 Now it has.

22 Q. Let me know if you're ready for some

1 questions on Chan.

2 A. I have downloaded Chan, and Chan is
3 open.

4 Q. Now, it's your contention that Chan
5 discloses whole genome sequencing; correct?

6 A. So on the very first page of Chan,
7 which is page 2011, in the "Methods" section, "Four
8 hepatocellular carcinoma patients" -- so this is
9 kidney cancer -- "and a patient with synchronous
10 breast and ovarian cancers were recruited. DNA was
11 extracted from tumor tissues, and the preoperative
12 and postoperative plasma samples of these patients
13 were analyzed with shotgun MPS."

14 And in the right-hand column, we're
15 told that MPS is an acronym for massively parallel
16 sequencing, which is high-throughput sequencing,
17 which is whole -- typically described as whole
18 genome shotgun sequencing.

19 Q. Can you turn with me --

20 A. I'm sorry, and it also goes on to tell
21 us that tumor and buffy coat DNA were sequenced to
22 median depth of 29.5-fold and 43-fold haploid genome

1 coverage, respectively.

2 So -- and we can go on and look at
3 some of the other analysis that was done; but at the
4 very least, the tumor DNA and buffy coat, that's
5 white blood cells and blood plasma, that was
6 subjected to whole genome sequencing.

7 Q. Would you turn with me in this article
8 to page 216, where Figure 1 is?

9 A. Sure. All right.

10 Q. These are Circos plots, C-I-R-C-O-S;
11 right?

12 A. That's correct.

13 Q. Do these Circos plots help inform your
14 decision -- your opinion on whether Chan performed
15 whole genome sequencing?

16 A. So the Circos plots are ways of
17 representing data. They don't describe the methods
18 that were used. To do that, one would really look
19 at the "Methods" section of the paper.

20 Q. When you reached your determination
21 that Chan discloses whole genome sequencing, was
22 Figure 1 something that you relied on to reach that

1 conclusion?

2 A. As I mentioned, to really determine
3 this, what one has to do is look at the "Methods"
4 section of the paper. This paper on page 212 has a
5 section called "Materials and Methods." In
6 laboratory -- in papers describing laboratory
7 science, this is where the laboratory methods are
8 disclosed.

9 At the bottom of page 212, there's a
10 section entitled "Genomic DNA Extraction." So it
11 says, "Genomic DNA was extracted from patients'
12 buffy coat samples" -- so that's the white blood
13 cells in blood -- "according to the blood and bodily
14 fluid protocol of the QIAamp DSP Blood Mini Kit.
15 DNA was extracted from tumor tissues" -- so the
16 prior tumors -- using "the QIAamp DNA Mini Kit."

17 So QIAamp is a trademark name for DNA
18 extraction, whole genome extraction from a company
19 called QIAGEN.

20 "DNA Sequencing," the next section.
21 "Sequencing libraries of the genomic DNA samples" --
22 so those we referred to earlier -- "were constructed

1 with Paired-End Sample Preparation Kit" -- from
2 Illumina according to the manufacturer's
3 instructions, right, and were told that 1 to 5
4 micrograms of genomic DNA was sheared. The DNA
5 molecules were end-repaired, right.

6 And it goes through various steps of
7 preparing the libraries for sequencing, doing
8 quality control, running these on the Illumina
9 sequencer, and then doing alignment and filtering
10 downstream.

11 So I would have to say at least for
12 the tumor-derived DNA and the reference normal DNA
13 which would come from the white blood cells, that --
14 the buffy coat, that whole genome shotgun sequencing
15 was -- the whole genome sequencing was used on these
16 samples.

17 MR. LUMAN: I'd like to mark as
18 Exhibit 2187 the Bentley article.

19 (Exhibit 2187, No Bates Numbers,
20 Accurate whole human genome sequencing using
21 reversible terminator chemistry, Nature,
22 2008, David Bentley et al., received and

1 marked.)

2 MR. LUMAN: And if we can make that
3 available to Dr. Quackenbush, please.

4 THE WITNESS: So it has not come up
5 yet.

6 THE DOCUMENT TECH: Give me one second
7 because I --

8 THE WITNESS: All right.

9 THE DOCUMENT TECH: Oh, okay. I see.
10 It was recently uploaded; right? Give me one
11 second.

12 THE WITNESS: You want to tell me when
13 you post it, Henry?

14 THE DOCUMENT TECH: Yes, it's posted
15 now.

16 THE WITNESS: All right. Now I see
17 it.

18 MR. KRAUSE: One second, please. And
19 I object for relevance, timeliness, lack of
20 foundation, and exceeding the scope of the
21 reply.

22

1 BY MR. LUMAN:

2 Q. So I've marked as Exhibit 2187 an
3 article that was published in Nature in the year
4 2008. And the list of authors is all the way at the
5 end. And the first named author is Bentley.

6 Dr. Quackenbush, have you reviewed
7 this reference recently?

8 A. I don't recall citing it in my report.
9 If you can point me to where I cited it, I'd be
10 happy to refresh my memory.

11 Q. Earlier today, you had testified about
12 Chan's sequencing depth to 29.5-fold and 43-fold.

13 Do you remember mentioning that
14 earlier today?

15 A. A short time ago, yes. I believe
16 that's disclosed in the Chan paper.

17 Q. If you'll turn with me to page 57 in
18 Exhibit 2187, please.

19 A. The Bentley paper?

20 Q. Yes, the Bentley paper.

21 A. All right.

22 Q. And there's a section on the

1 right-hand column that talks about the effect of
2 sequence depth on coverage and accuracy.

3 Do you see that?

4 A. I'm sorry -- oh, yes, I see it.

5 Q. And they're reporting that they
6 investigated the impact of varying input read depths
7 on SNV calling. And they say that essentially all
8 homozygous positions are detected at 15X, whereas
9 heterozygous positions accumulate more gradually to
10 the 33X. And they reference Figure 5a.

11 Do you see that?

12 A. I do.

13 Q. And then Figure -- if we turn to the
14 next page, Figure 5a has -- that is where Figure 5a
15 is located.

16 Do you see Figure 5a?

17 A. Yes, I do.

18 Q. So would you agree with me the authors
19 that in order to use -- in order for SNV discovery
20 for heterozygous positions to accumulate, 33X
21 sequencing depth was a desirable sequencing depth?

22 MR. KRAUSE: Objection --

1 THE WITNESS: So that would depend on
2 the application --

3 MR. KRAUSE: Hold on. Hold on a
4 second.

5 THE WITNESS: -- right. Okay.

6 MR. KRAUSE: Hold on. I need to
7 object to relevance, foundation, timeliness,
8 and exceeding the scope of the reply.

9 THE WITNESS: So that would depend on
10 the application one would have, right. Here,
11 they talk about detecting all homozygous
12 positions and, I believe at 33X, all
13 heterozygous positions.

14 So I don't know what their application
15 is. I don't recall ever reviewing this paper
16 in the context of preparing my reports.
17 However, if I look back -- and you haven't
18 provided me with copies of either the '394 or
19 the '033 patents, but I don't believe in any
20 of the claims of either of these patents
21 there's a requirement for sequence depth or
22 sequence accuracy. I don't believe there's

1 even a requirement for sequencing in the
2 '033.

3 In the '394, the first step is whole
4 genome sequencing. And that whole genome
5 sequencing is then used as a way of
6 identifying polymorphisms. It doesn't have
7 to identify them with any degree of accuracy.
8 It doesn't have to identify all of them. It
9 simply has to identify -- it's used to
10 identify polymorphisms.

11 I do not recall in the '394 patent
12 whether or not the subsequent targets have to
13 be chosen solely from whole genome sequencing
14 or if they can be chosen from a variety of
15 different sources.

16 I do recall in the '033 patent that
17 the targets for subsequent analysis can be
18 chosen from a variety of different resources,
19 including databases that -- publicly
20 available databases.

21 So while Bentley may in his
22 application find that this depth of coverage

1 is useful if wants to discover all SNPs,
2 discovering all SNPs is not required by these
3 patents. And, therefore, to the best of my
4 read, while this may be -- and I have great
5 respect for David Bentley and his colleagues.

6 While this may be relevant for their
7 particular application, I'm not -- I can't
8 see any way that this is relevant in the
9 analysis of the prior art for the '033 or
10 '394 patent, right. Whole genome sequencing
11 the claims don't have any requirement for a
12 particular degree of accuracy, degree of
13 coverage, right. Simply in the '394, whole
14 genome sequencing is the first step.

15 And clearly, even based on this, we
16 could infer that one would discover at least
17 some of the variance at lower depths of
18 coverage than 15-fold or 30-fold, right.

19 It says lower homozygous -- a
20 homozygous could be detected at a redepth of
21 twofold or higher. So I don't know how --
22 how low the coverage is that Bentley would

1 refer to here, but clearly that upper bound
2 is for an application that doesn't seem to me
3 to be relevant to the patents being reviewed
4 by the patent board.

5 BY MR. LUMAN:

6 Q. Dr. Quackenbush, do you recall that
7 the board's construction of whole genome sequencing
8 was a nontargeted approach to sequencing all or
9 almost all of the genome?

10 A. I believe that's correct, yes.

11 Q. In order for a sequencing method to
12 qualify as whole genome sequencing under the board's
13 construction, is there both a depth of coverage and
14 a breadth of coverage requirement?

15 A. So I don't believe the patent
16 claims -- and, again, I haven't been provided with
17 copies of the patents. I don't believe the patent
18 claims themselves have any specification about the
19 depth of coverage, the breadth of coverage.

20 I know we referred to a Sims article
21 earlier that started to describe those, but what the
22 Sims article did tell us is that the way they

1 referred to depth of coverage throughout their
2 article was the standard accepted version, which is
3 consistent with the Lander/Waterman equation.

4 And Sims actually on page 2 -- or the
5 second page of their paper had a box describing
6 Lander/Waterman where they -- they called -- or they
7 laid out exactly the same coverage equation that I
8 had included in my report and which was consistent
9 with Dr. Furneaux's calculation of 90 percent
10 coverage.

11 So I don't believe that's called out
12 in the patent anywhere. As I mentioned,
13 contemporaneous literature refers to whole genome
14 sequencing, which is what is called out in the
15 patent. Contemporaneous literature refers to whole
16 genome sequencing at various depths of coverage down
17 to as low as 0.1-fold.

18 So I leave it to the patent board to
19 determine what depth is relevant. In my analysis of
20 the prior art, Leary is clearly invalidating prior
21 art because the first step in Leary is performing
22 whole genome sequencing in a way that's consistent

1 with the patent board's claim construction for whole
2 genome sequencing.

3 Q. And if a person of ordinary skill in
4 the art were seeking to use whole genome sequencing
5 in 2011 to detect minimal residual disease, what
6 sequencing depth would be desirable for that?

7 MR. KRAUSE: Objection, incomplete
8 hypothetical.

9 THE WITNESS: So there are two
10 elements at play here, right. The first is
11 the whole genome sequencing, and if -- excuse
12 me, if you look at Leary, as an example, one
13 of the things that Leary describes, I believe
14 the first step in Leary is whole genome
15 sequencing of the tumor itself, right. Leary
16 describes that whole genome sequencing of the
17 tumor to identify polymorphic loci. Okay.

18 From that, capture probes are
19 developed, and the type of capture probe that
20 Leary uses is PCR-based capture probes.
21 Leary uses those because they're able to
22 capture and specifically amplify target loci.

1 What that capture and amplification
2 step allow is actually a greater depth of
3 coverage in those subsequent analyses, and I
4 believe Leary uses blood samples or plasma
5 samples in his subsequent -- excuse me, her
6 subsequent analysis and could use that to
7 detect -- I don't know if it's minimal
8 residual disease, but at least residual
9 disease.

10 So the whole genome sequencing piece
11 to a certain extent is irrelevant in terms of
12 its depth of coverage for monitoring residual
13 disease. And I wouldn't know -- I'd have to
14 look at some of the references to tell you
15 what they suggest as the depth of coverage in
16 these subsequent analyses with PCR capture
17 probes would be important for accurately
18 determining the amount of residual disease.

19 MR. LUMAN: Why don't we take a
20 ten-minute break, and we'll see if we can
21 wrap this up.

22 MR. KRAUSE: All right.

1 MR. LUMAN: We're off the record at
2 3:18.

3 (Recess from the record.)

4 MR. LUMAN: Back on the record at
5 3:25.

6 BY MR. LUMAN:

7 Q. Dr. Quackenbush, where are you located
8 right now?

9 A. I'm in Dover, Massachusetts, in my
10 wife's office, which is our home office.

11 Q. Is anyone else in the room with you?

12 A. No, no one else is in the room.

13 Q. And has that been the case throughout
14 today's deposition?

15 A. Yes, I have a cat waiting outside the
16 door. There were people home earlier, but no one
17 was in the room with me.

18 Q. Do you have any physical documents in
19 the room with you?

20 A. I have a pad of paper that I've been
21 writing on, but nothing on it. Other than that,
22 there are no documents.

1 Q. Did the notepad have notes on it when
2 we began our deposition?

3 A. No, the notepad was completely blank
4 before the deposition. I actually got a call. My
5 wife's mother who lived in Greece passed away. And
6 it was an international moving company. So we're
7 trying to get things moved back to the U.S. I wrote
8 on that and tore it off. So if you want Greek
9 movers, I have that. That's the only thing that's
10 written on on the desk other than what was a blank
11 notepad in which I scribbled some notes.

12 Q. Sorry to hear about the passing in
13 your family.

14 Did you look at any electronic
15 documents today other than the ones that were
16 provided to you through our court reporter?

17 A. Once the deposition started, I looked
18 at -- I cleared my desktop. I looked at nothing but
19 the documents that were provided by the court
20 reporter.

21 Q. During today's deposition, did you
22 have any communication with Mr. Krause?

1 A. No, I did not.

2 Q. And did you have any communications
3 from any other people, such as e-mail communications
4 or a chat line, text messaging, phone call?

5 A. During breaks, I checked e-mail and
6 deleted it, but nothing relevant to this case. I
7 sent a text message to my wife and son telling them
8 I wasn't going to make a 5:30 appointment, and now
9 my wife during the last break wrote to me about
10 bringing home some food for dinner since she's
11 bringing my son home. Other than that, no.

12 Q. And what did you do to prepare for
13 today's deposition?

14 A. So I started a few days ago reading
15 over the patents. The reply report I wrote in
16 response to Dr. Furneaux, I reviewed parts of his
17 report. Reviewed some of the documents I cited,
18 such as Leary, Ley, a few of the -- I think most of
19 the other documents that I cited. I also met with
20 Mr. Krause via Zoom briefly on -- on Tuesday and
21 briefly on Wednesday.

22 Q. Other than meeting with Mr. Krause,

1 did you meet with anybody else to prepare for
2 today's deposition?

3 A. No, I did not.

4 Q. And other than the meetings on Tuesday
5 and Wednesday, did you have any other preparation
6 sessions for today's deposition?

7 A. No, we exchanged e-mails simply to
8 arrange those times. Other than that, no.

9 Q. About how long did you meet on Tuesday
10 in terms of hours?

11 A. I don't recall. I can look at my
12 calendar. We met maybe four hours. I don't really
13 recall. I had some meetings in the morning that I
14 had to attend to, and then he and I met for a while.

15 Q. How about on Wednesday, about how many
16 hours did you guys meet on Wednesday?

17 A. Again, without looking at my calendar,
18 my best guess would be about an hour, maybe an hour
19 and a half, but I don't recall.

20 MR. LUMAN: I don't have any further
21 questions.

22

1 EXAMINATION

2 BY MR. KRAUSE:

3 Q. So, Dr. Quackenbush, I have three
4 short questions for you.

5 A. All right.

6 Q. This proceeding involves U.S. Patent
7 No. 11,384,394 and U.S. Patent No. 11,408,033; is
8 that correct?

9 A. Yes, it does. That's correct.

10 Q. And I'm looking at the exhibit share
11 that's been used today, and there's over 20
12 documents that have been added to the exhibit share.

13 And my question is: During
14 Personalis' cross-examination, were either of those
15 patents introduced as exhibits to this deposition?

16 A. No, they were not. And I pointed out
17 multiple times that I did not have access to
18 those -- to either one of the two patents multiple
19 times.

20 Q. Were you asked any questions about the
21 specifications of those patents during this
22 deposition?

1 A. I was not asked about the
2 specification, no.

3 MR. KRAUSE: No further questions.

4 THE REPORTER: Okay. Are we done?

5 MR. LUMAN: Let's take a five-minute
6 break. We're off the record at 3:31. And
7 we'll come back in five minutes.

8 (Recess from the record.)

9 MR. LUMAN: We are back on the record
10 at 3:33.

11 I have no further questions.

12 Dr. Quackenbush, thank you for your
13 time.

14 THE WITNESS: Thank you.

15 MR. KRAUSE: Dr. Quackenbush --

16 THE WITNESS: I was just saying thank
17 you.

18 MR. KRAUSE: -- that concludes the
19 deposition.

20 I will note for the record that we've
21 interposed numerous contemporaneous
22 objections with the untimely torrent of

1 exhibits that's been introduced now. I'm
2 just making it very clear for the record that
3 we reserve all rights, including to seek
4 authorization from the board to move to
5 strike those exhibits, as well as any
6 portions of the forthcoming surreply that
7 make arguments relating to them.

8 MR. LUMAN: And I'll make a statement
9 that we needed to introduce those exhibits to
10 properly cross-examine Dr. Quackenbush on the
11 contours of the opinions provided in his
12 declaration, which was Exhibit 1225, and they
13 were provided to test the voracity of his
14 opinions. And that's precisely -- and also
15 we introduced a few party admissions from the
16 founders of Foresight. So they were
17 appropriate exhibits to introduce into this
18 proceeding.

19 MR. KRAUSE: Yeah. Well, we disagree.
20 They're entirely inconsistent with the
21 board's rules, but it's not for your eyes to
22 decide. And the deposition's over.

1 Thanks, everyone.

2 MR. LUMAN: All right. And I would
3 thank the court reporter and Mr. Marte for
4 their help today.

5 MR. KRAUSE: Yes, thank you.

6 THE REPORTER: Are we off the record?

7 MR. LUMAN: Off the record at 3:35.

8 (Off the record at 3:35 p.m.)
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1 STATE OF NEW YORK)

2 ss:

3 COUNTY OF WESTCHESTER)

4 I, EILEEN MULVENNA, CSR/RMR/CRR, a
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6 Certified Realtime Reporter, and Notary Public in
7 and for the State of New York, do hereby certify:

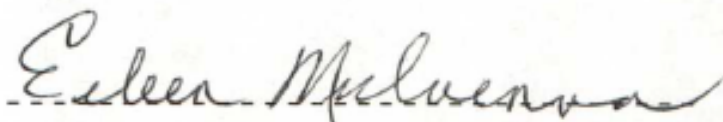
8 That I reported the taking of the
9 deposition of the witness, DR. JOHN QUACKENBUSH,
10 commencing on the 1st day of February, 2024, at the
11 hour of 10:00 a.m.

12 That prior to being examined, the witness
13 was duly sworn by me to testify to the truth, the
14 whole truth, and nothing but the truth.

15 That I thereafter transcribed my said
16 shorthand notes into typewriting and that the
17 typewritten transcript of said deposition is a
18 complete, true and accurate transcription of my
19 said shorthand notes taken down at said time, and
20 that a request has been made to review the
21 transcript.

22 I further certify that I am not a relative
or employee of an attorney or counsel of any of the
parties, nor a relative or employee of any attorney
or counsel involved in said action, nor a person
financially interested in the action.

IN WITNESS WHEREOF, I have hereunto
set my signature this 5th day of February, 2024.


Eileen Mulvenna, CSR/RMR/CRR

1 John Quackenbush, Ph.D., c/o
Irell & Manella LLP
2 1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067

3
Case: Foresight Diagnostics Inc. v. Personalis, Inc.
4 Date of deposition: February 1, 2024
Deponent: John Quackenbush, Ph.D.

5
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12 signature page to counsel noticing the deposition, noting the
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9 Witness Name: John Quackenbush, Ph.D.
10 Deposition Date: February 1, 2024

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22 Signature Date

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