

In the Matter Of:

Natera vs

NeoGenomics Laboratories

MICHAEL METZKER

November 14, 2023



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1	APPEARANCES:	1	INDEX TO EXHIBITS
2	FOR PLAINTIFF NANYA, INC.:	2	MICHAEL METZKER, PhD
3	QUINN EMANUEL URQUHART & SULLIVAN LLP	3	Tuesday, November 14, 2023
4	BY: SARAH CORK, ESQ.	4	Tammy Moon CSR No. 13184, RPR, CRR
5	865 S. Figueroa St., Flr 10	5	MARKED DESCRIPTION PAGE
6	Los Angeles, California 90017-5003	6	Exhibit 1 Reply Declaration of Dr. Michael
7	213.443.3000	7	Metzker
8	Sarahcork@quinnemanuel.com	8	Exhibit 2 U.S. Patent No. 11,530,454
9	FOR DEFENDANT NEOGENOMICS LABORATORIES, INC.:	9	Exhibit 3 U.S. Patent No. 11,519,035
10	WEIL, GOTSHAL & MANGES LLP	10	Exhibit 4 Declaration of Dr. Michael L.
11	BY: AUGUST MELCHER, ESQ.	11	Metzker in Support of Plaintiff
12	201 Redwood Shores Parkway	12	Natera Inc.'s Motion for
13	Redwood Shores, California 94065	13	Preliminary Injunction
14	650.802.3285	14	Exhibit 5 U.S. Patent No. 5,952,170
15	August.melcher@weil.com	15	Exhibit 6 U.S. Patent No. 6,156,504
16	ALSO PRESENT: MIKE BRATKOWSKI, THE VIDEOGRAPHER	16	Exhibit 7 "Cell-free DNA (cfDNA): Clinical
17	(REMOTE)	17	Significance and Utility in Cancer
18		18	Shaped by Emerging Technologies,"
19		19	article written by Stanislaw
20		20	Volik, et al.
21		21	Exhibit 8 Paper entitled "Field Guide to
22		22	Next Generation DNA Sequencers" by
23		23	Travis C. Glenn
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7	EXAMINATION PAGE	7	Parallel Sequencing by Isaac
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10		10	in Support of NeoGenomic's
11		11	Laboratories Inc.'s Response in
12		12	Opposition to Natera Inc.'s Motion
13		13	for Preliminary Injunction
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1 Tuesday, November 14, 2023, 7:53 a.m. 2 THE VIDEOGRAPHER: Good morning. We are on 3 the record at 7:53 p.m., Pacific Time [sic]. 4 My name is Michael Bratkowski, a 5 videographer from Lexitas, and this is the 6 videotaped -- the videotaped deposition for the 7 United States District Court, for the Middle 8 District of Northern -- of North Carolina. 9 Today's deposition is being held on the 10 Zoom platform in the matter of Natera, Incorporated, 11 v. NeoGenomics Laboratory [sic], Incorporated, Case 12 No. 1:23-CV-629. Today's deponent is Michael 13 Metzker, PhD. 14 Counsel, please identify themselves for the 15 record. 16 MR. MELCHER: Hi. This is August Melcher 17 of Weil, Gotshal & Manges on behalf of defendant, 18 NeoGenomics. 19 MS. CORK: Sarah Cork from Quinn Emanuel on 20 behalf of plaintiff, Natera, and the witness. 21 (Reporter clarification.) 22 THE VIDEOGRAPHER: Our court reporter today 23 is Tammy Moon with Lexitas. 24 Would you please swear in the witness. 25 MICHAEL METZKER, PhD,	1 A. No. 2 Q. And I'm going to ask you some questions. 3 And at times, your counsel may object. But unless 4 she instructs you not to respond, you will need to 5 answer. Does that make sense? 6 A. I understand. 7 Q. As you can see, there's a court reporter 8 here today that will take down what we say. So 9 you'll need to state your answers orally so the 10 court reporter can record your answers. The court 11 reporter can't record a head shake or a nod. Does 12 that make sense? 13 A. I understand that. 14 Q. And the court reporter will only be able to 15 capture our conversation if one of us is talking at 16 a time. I will do my best to wait until you are 17 finished with your answer before asking my next 18 question. 19 And I would ask that you wait until I am 20 finished with my question before you begin your 21 answer. Does that make sense? 22 A. I understand that. 23 Q. And if you don't hear a question, please 24 tell me, and I'll repeat it. And if you don't 25 understand a question, please tell me, and I'll try
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1 called as a witness, having been duly sworn, 2 testified as follows: 3 THE WITNESS: I do. 4 EXAMINATION BY MR. MELCHER 5 MR. MELCHER: 6 Q. Could you please state your full name and 7 address for the record. 8 A. Yes. My name is Michael Metzker, 9 M-E-T-Z-K-E-R. My home address is 12015 Surrey, 10 S-U-R-E-Y, Lane, Houston, Texas 77024. 11 Q. Have you been deposed before? 12 A. Yes. 13 Q. How many times? 14 A. More than I can count. 15 Q. So I guess I'll still go over these ground 16 rules, but I'm sure you know what I'm about to say. 17 You understand that you are under oath, 18 correct? 19 A. I do. 20 Q. Is there anything that would prevent you 21 from testifying truthfully today? 22 A. No. 23 Q. So you haven't used, you know, any 24 medication or anything like that that would make it 25 difficult for you to testify today?	1 to rephrase it in a way that you do understand. 2 Does that make sense? 3 A. I do understand that. 4 Q. And even if you anticipate the rest of the 5 question, please let me finish asking before you 6 answer so that the transcript is clear. In other 7 words, let's not talk over each other. Does that 8 work? 9 A. Yes, that -- I agree with that. 10 Q. And we'll take a break every so often so 11 that we can stretch our legs. If you need a break, 12 just let me know, and I'll find a convenient 13 stopping point. I only ask that we not break while 14 a question is pending. Is that fair? 15 A. I understand that. 16 Q. Let's see. Have you spoken with anyone 17 other than counsel about this litigation? 18 A. No. 19 Q. Other than meeting with counsel, did you do 20 anything to prepare for this deposition? 21 A. Yes. 22 Q. What did you do? 23 A. I reviewed my reply report, or declaration. 24 Q. Did you review any other documents? 25 A. Yes.

Page 10 1 Q. What were those? 2 A. I would have reviewed documents that are 3 cited in my reply declaration. 4 Q. Any other documents? 5 A. Not that comes to mind at this moment. 6 Q. How much time would you say you spent 7 preparing overall? 8 A. Maybe 20 hours since I submitted my 9 declaration. 10 Q. And how much of that was reviewing your 11 report? Just a guess. 12 A. I don't know. Maybe a couple of hours. 13 Q. And how much -- how many times did you 14 speak with counsel to prepare for this deposition? 15 A. I don't understand the question. 16 Q. So you spoke with counsel in preparation of 17 this deposition, correct? 18 A. Right. I had a meeting yesterday, and we 19 spoke all day long. So I -- if you are asking how 20 many times did we meet, I -- we met yesterday. 21 Q. Thank you. Did you take any notes during 22 preparation for your testimony today? 23 A. I did not. 24 Q. Other than what we already discussed, did 25 you do anything to prepare for your deposition	Page 12 1 submitted sometime in July? 2 MR. MELCHER: 3 Q. That's correct. 4 A. Okay. Can you repeat the question. 5 Q. Yes. Would a POSA have been interested in 6 monitoring and detecting cancer? 7 MS. CORK: Same objection. 8 THE WITNESS: So can you help me what -- in 9 the context of the -- assorted patents, timeframe -- 10 can you help provide a little more detail to your 11 question. 12 MR. MELCHER: 13 Q. Yes. So in the -- a POSA, with respect to 14 the '454 patent, on the priority date in 2015 -- 15 would that POSA have been interested in monitoring 16 and detecting cancer? 17 MS. CORK: Same objections and vague. 18 THE WITNESS: Well, I kind of define what 19 the person of ordinary skill in the art is: 20 PhD-level experience, several disciplines, has -- I 21 don't know word-for-word. 22 It's in my opening declaration. But -- 23 would have done work in the fields of DNA sequencing 24 and molecular biology and all of that. So that's 25 how I would think a POSA -- the knowledge of a POSA
Page 11 1 today? 2 MS. CORK: I'll instruct the witness not to 3 answer to the extent that it invades the province of 4 communications with counsel in preparation for his 5 deposition. 6 Other than that, you may answer. 7 THE WITNESS: I did basically what I 8 explained, plus meeting with counsel yesterday. 9 MR. MELCHER: So I'll note for the record 10 that I have already marked a few exhibits. 11 Exhibit 1 is the reply declaration of Dr. Michael 12 Metzker. Exhibit 2 is U.S. Patent No. 11,530,454. 13 (Exhibits 1-2 were marked for identification.) 14 Q. If I use the term "POSA," will you know 15 what I'm talking about? 16 A. I do. 17 MS. CORK: Objection. Vague. 18 MR. MELCHER: 19 Q. Would a POSA have been interested in 20 monitoring and detecting cancer? 21 MS. CORK: Objection. Calls for 22 speculation. 23 THE WITNESS: So the POSA that we are 24 talking about is the person of ordinary skill in the 25 art that I have defined in my opening declaration	Page 13 1 would be. I don't know if they would be interested 2 in or not. I hadn't really considered that. 3 MR. MELCHER: 4 Q. And would a POSA have understood that 5 cell-free DNA could be used to monitor and detect 6 cancer? 7 MS. CORK: Same objections. 8 THE WITNESS: Well, I -- I spent a lot of 9 time in my reply declaration explaining how a POSA 10 would have understood the application of cell-free 11 DNA in the context of cancer detection. 12 And although they would have been aware of 13 that, they would have also been aware of the 14 challenges of using cell-free DNA in cancer 15 detection. 16 MR. MELCHER: 17 Q. Would a POSA have understood that SNPs or 18 SNVs could be used to monitor and detect cancer? 19 MS. CORK: Same objection. 20 THE WITNESS: I believe a person of 21 ordinary skill in the art would have been aware of 22 what a single nucleotide polymorphism, an SNP, or 23 single nucleotide variant, an SNV, is and would have 24 understood its relationship to cancer detection. 25 ///

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1 MR. MELCHER: 2 Q. And so just for clarity, we have been 3 discussing a POSA with respect to the '454 patent. 4 Would a POSA with respect to the '035 patent have 5 understood that cfDNA could be used to monitor and 6 detect cancer? 7 MS. CORK: Same objection and compound. 8 (Reporter clarification.) 9 THE WITNESS: I probably would give you the 10 same answer I did for an understanding of a person 11 of ordinary skill in that we're five years earlier 12 from the priority date from '454 -- the '454 patent. 13 So there probably were more challenges in 14 that five-year gap, but they would have understood 15 that cell-free DNA could be used but would have also 16 understood all of the challenges associated with the 17 use of cell-free DNA, particularly in monitoring 18 cancer. 19 MR. MELCHER: 20 Q. So I'm going to ask -- you mentioned that 21 there was a five-year difference between the 22 priority dates. What is your understanding of the 23 priority date for the '035 patent? 24 A. I think I have that in my reply report, or 25 it may be in my opening report. And I haven't	1 MS. CORK: Same objections. 2 THE WITNESS: For either priority date, a 3 person of ordinary skill, as a PhD, has a high level 4 of skill in the art; as a PhD, would have been aware 5 of how the PCR method works and performs; and would 6 have been capable of performing a polymerase chain 7 reaction in the laboratory. 8 MR. MELCHER: 9 Q. Would a POSA, with respect to the '454 10 patent, have been capable of designing primers for 11 PCR? 12 A. Again, the level of skill is high, at least 13 in the definition I've proposed. And part of the 14 experience of performing polymerase chain reaction 15 experiments in the laboratory involves designing 16 primers. 17 Particularly when you are interested in 18 targeting specific regions in the genome, a person 19 of ordinary skill in the art would know how to 20 design those target-specific primers. 21 Q. And if I asked you the same question with 22 respect to the '035 patent, would you give the same 23 answer? 24 A. Yes, I would. 25 Q. Would a POSA, with respect to the '454
Page 15	Page 17
1 really provided an opinion of what the priority date 2 should be at this point. But I'm going to page 26 3 of my report. And I just state: 4 "Dr. Van Ness agrees with Natera's 5 contention that the priority date for 6 the '454 patent is April 21st, 2015, and 7 that the priority date for the '035 8 patent is May 18th, 2011." 9 So I guess that difference is about four 10 years, not five years. But I'm not really offering 11 an opinion whether that's correct or not, but I'm 12 just using that for this purpose as the priority 13 date. 14 Q. And to -- would a POSA have understood -- 15 would a POSA, with respect to the '035 patent, have 16 understood that SNPs or SNVs could be used to 17 monitor and detect cancer? 18 MS. CORK: Object to speculation and vague. 19 THE WITNESS: I would probably give you the 20 same answer I did when you asked about the '454 21 patent and just use that as a marker for my answer. 22 MR. MELCHER: 23 Q. Would a POSA, with respect to the '454 24 patent, have been capable of performing PCR 25 amplification?	1 patent, have been capable of using commercial 2 sequencing instruments? 3 MS. CORK: Objection. Vague. Calls for 4 speculation. 5 THE WITNESS: Well, either priority date, 6 2011 or 2015, are later than when next-generation 7 sequencing instruments had been developed and were 8 used. 9 I would say a person of ordinary skill in 10 the art would have understood at least how the 11 technologies perform. Whether they actually perform 12 them themselves, I would not know that. 13 MR. MELCHER: 14 Q. Would they have been -- would a POSA, with 15 respect to the '454 patent, maybe, you know, have 16 worked on a team or have some lab they could send 17 their PCR results to to get sequenced? 18 MS. CORK: Same objections and compound. 19 THE WITNESS: A person of ordinary skill in 20 the art would be someone who could work in a 21 laboratory, and it is not uncommon to send genetic 22 material to a core facility and have a core facility 23 run the sample to generate sequencing data. 24 MR. MELCHER: 25 Q. Do you agree that cell-free DNA is

Page 18	Page 20
1 fragmented to an average length of 140 to 170 base 2 pairs? 3 MS. CORK: Objection. Calls for 4 speculation. 5 (Reporter clarification.) 6 THE WITNESS: Well, I do cite to a 7 reference, Forshew 2012. And I'll point you to that 8 paragraph. 9 MR. MELCHER: 10 Q. You might check Footnote 181. 11 A. Right. So I'm looking at paragraph 163, 12 and I am saying: "It was known that cell-free DNA 13 has a typical size range of 140 to 170 base pairs," 14 citing to Forshew 2012. And I believe that's on the 15 first page of the Forshew article. 16 Q. And that would have been well known to a 17 POSA? 18 MS. CORK: Same objections. 19 THE WITNESS: So, again, we have two 20 different priority dates. In my opinion, they 21 probably would have been aware of that with respect 22 to either priority date. 23 MR. MELCHER: 24 Q. Would a POSA have been aware -- would a 25 POSA, with respect to the '454 patent, have been	1 enabling and informing further treatment 2 decisions." Do you see that? 3 A. Yeah. Can I have a moment to review 4 paragraph 34. 5 Q. Yes. 6 A. Thank you. 7 Right. I have reviewed that paragraph. 8 Can you repeat your question. 9 Q. Yes. My question is -- at the end of 10 paragraph 34, the last sentence states: 11 "The ability to detect MRD as early 12 as possible is beneficial for patient 13 outcomes and overall survival by 14 enabling and informing further treatment 15 decisions." Do you see that? 16 A. I see that. 17 Q. Would -- is that statement and this 18 sentence representative of POSA knowledge? 19 A. Well, I guess what I'm trying to do is 20 provide some technical background of minimal 21 residual disease. And with respect to minimal 22 residual disease, I believe that is an accurate 23 statement and something that a person of ordinary 24 skill would have understood. 25 MS. CORK: And I would just pose an
Page 19	Page 21
1 aware of the value of detecting cancer as early as 2 possible? 3 MS. CORK: Objection. Vague and calls for 4 speculation. 5 THE WITNESS: Again, the person of ordinary 6 skill is very high. I haven't provided an opinion 7 of whether they would have any thought or value of 8 early cancer detection. So I have no opinion on 9 that. 10 MR. MELCHER: So I'm going to go ahead 11 and -- let's mark the '035 patent as Exhibit 3, 12 please. 13 And then we'll mark the declaration of 14 Dr. Michael L. Metzker in support of plaintiff, 15 Natera, Inc.'s motion for preliminary injunction as 16 Exhibit 4, please. 17 (Exhibits 3-4 were marked for identification.) 18 Q. Okay. So if I could direct you to 19 paragraph 34 in Exhibit 4, please. 20 A. Yes. I'm there. 21 Q. Okay. So if you look at the last sentence, 22 it says: 23 "The ability to detect MRD as early 24 as possible is beneficial for patient 25 outcomes and overall survival by	1 objection to the extent it calls for speculation and 2 exceeds the scope of this report. 3 MR. MELCHER: 4 Q. And a POSA would have known that an example 5 of an MRD could be cancer, correct? 6 MS. CORK: Calls for speculation. Vague. 7 THE WITNESS: Yeah. I actually don't 8 understand that question. 9 MR. MELCHER: 10 Q. So -- well, if we look at the first 11 sentence of paragraph 34, it states: "Minimal 12 residual disease refers to a very small number of 13 cancer cells that remain in the body after 14 treatment." Do you see that? 15 A. I see that. 16 Q. And MRD is an acronym that stands for 17 "minimal residual disease," correct? 18 MS. CORK: Objection. Misstates the 19 document. 20 THE WITNESS: It -- it does, but it also 21 stands -- and it's in the paragraph as well -- for 22 "molecular residual disease." 23 MR. MELCHER: 24 Q. Thank you. Would a POSA have been 25 interested in cell-free DNA liquid biopsies for

Page 22	Page 24
1 monitoring and detecting cancer? 2 MS. CORK: Objection. Calls for 3 speculation. Vague. And to the extent it exceeds 4 the scope of his reports. 5 THE WITNESS: As I have explained, the POSA 6 has a very high level of skill. I haven't provided 7 any opinions on what a POSA would be interested in, 8 so I have no opinion on that. 9 MR. MELCHER: 10 Q. So at the end of paragraph 36 in 11 Exhibit 4 -- 12 A. Yes. I'm there. 13 Q. So the last two sentences state -- or would 14 you like a minute to review? www.LexitasLegal.com/Premier Lexitas 15 A. Yes, please. Thank you. 16 Q. Yeah. 17 A. Okay. I have read that paragraph. 18 Q. Okay. So paragraph 36 states: 19 "A liquid biopsy may be used to 20 specifically detect and quantify 21 circulating tumor DNA in a patient to 22 determine MRD. 23 "CtDNA is a type of cell-free DNA 24 characterized by tumor-specific genomic 25 and epigenomic alterations. CfdNA	1 section titled "Technology Background." I'm just 2 providing information of the state of the art at the 3 time of either priority date. And so a person of 4 ordinary skill in the art would have understood what 5 you just read. 6 MR. MELCHER: 7 Q. And if you could please turn to Exhibit 1, 8 which is your reply declaration, and turn to 9 paragraph 255. And please let me know when you have 10 had a chance to review. 11 A. Thank you. 12 Okay. I have reviewed paragraph 252. 13 Q. Thank you. And -- oh, excuse me. 255. 14 A. Oh, apologies. 15 Q. No worries. 16 A. Okay. I have now read paragraph 255. 17 Q. Okay. Thank you. So in the second 18 sentence of this paragraph, you wrote: "By 2011, 19 one of ordinary skill in the art would have been 20 familiar with multiplex PCR amplification." Do you 21 see that? 22 A. I see that. 23 Q. So is it fair to say that a POSA, by 2011, 24 would have been aware of well-functioning multiplex 25 PCR amplification assets?
Page 23	Page 25
1 refers to short fragments of DNA found 2 in blood, as cells typically share their 3 DNA to the bloodstream through certain 4 biological processes asserted with cell 5 death -- e.g., necrosis or apoptosis -- 6 or through active secretion. 7 "Tumor cells have a similar capacity 8 to shed their DNA into the bloodstream 9 compared to normal cells, albeit the 10 former having a greater probability due 11 to higher cellular turnover. 12 "DNA with tumor-specific 13 alterations -- i.e., ctDNA -- can thus 14 be detected in blood to determine MRD." 15 Do you see that? 16 MS. CORK: Objection to the extent it 17 misstates the document. 18 THE WITNESS: I do see that paragraph. 19 MR. MELCHER: 20 Q. And is that paragraph representative of a 21 POSA's knowledge? 22 MS. CORK: Objection. Vague. Calls for 23 speculation. 24 (Reporter clarification.) 25 THE WITNESS: Again, so this is in a	1 MS. CORK: Objection. Vague. Calls for 2 speculation. To the extent it exceeds the scope of 3 his report. 4 THE WITNESS: Well, I think what I state in 5 this paragraph is a person of ordinary skill in the 6 art would have been familiar with multiplex PCR. 7 I'm now just explaining even -- now, I'm 8 not really explaining what a person would have 9 understood but more making a point that 10 well-functioning assays at the time, primer dimers, 11 are still likely to occur. 12 MR. MELCHER: 13 Q. So I might have misheard you, but I thought 14 you said, "Well-functioning assays at the time are 15 likely to occur." Is that what you meant to say, or 16 did I mishear you? 17 MS. CORK: Objection. Misstates testimony 18 and the document. 19 THE WITNESS: You did. What I said -- and 20 maybe it got muddled. Well-functioning assays at 21 the time, primer dimers, would have -- likely to 22 occur. So even with a well-functioning assay, you 23 may still get primer dimers forming in the multiplex 24 PCR reaction. 25 ///

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1 MR. MELCHER:

2 Q. So I think baked into that -- is it fair to

3 say that a POSA would have been aware of some

4 well-functioning assays even though they might have

5 had some primer dimers in those assays?

6 MS. CORK: Objection. Vague. Calls for

7 speculation. And to the extent it exceeds the scope

8 of his report.

9 THE WITNESS: I think a person of ordinary

10 skill in the art, which has a high level of skill,

11 would understand what a well-functioning assay is

12 and would have an understanding that primer dimers

13 still may exist even in those well-functioning

14 assays.

15 MR. MELCHER:

16 Q. Would a POSA have been aware of specific

17 techniques for executing a well-functioning assay?

18 MS. CORK: Objection. Same objections.

19 THE WITNESS: I'm not sure about that.

20 That -- that may be something that is determined

21 empirically in the laboratory, so I'm not sure about

22 that.

23 MR. MELCHER:

24 Q. Would a POSA have had skills and training

25 that relate to that empirical design of a

Page 27

1 well-functioning assay?

2 MS. CORK: Same objections.

3 THE WITNESS: Well, a person of ordinary

4 skill in the art that we are talking about is -- has

5 a high level of skill, and they would have an

6 understanding of designing experiments. And in some

7 cases, that may result in a well-functioning assay.

8 MR. MELCHER:

9 Q. Would a POSA have been aware of methods to

10 design primers for multiplex PCR amplification

11 assays that would avoid primer dimers?

12 (Reporter clarification.)

13 MS. CORK: Same objections.

14 THE WITNESS: Yes. The level of skill is

15 high, and there are techniques that can be employed

16 to design primers that avoid the formation of primer

17 dimers.

18 MR. MELCHER:

19 Q. And I'm not sure if I was clear, but would

20 you give the same answer as to the priority date for

21 the '454 and '035 patents?

22 MS. CORK: Same objections.

23 THE WITNESS: I would.

24 MR. MELCHER:

25 Q. Was the use of Illumina sequencers routine

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1 to a POSA?

2 MS. CORK: Same objections.

3 THE WITNESS: In what context or -- is the

4 question based?

5 MR. MELCHER:

6 Q. Okay. Let's -- let's go to paragraph 274

7 in your report, please. And let me know when you

8 have finished reading.

9 A. Okay. Could you answer -- or ask your

10 question again.

11 Q. So is it fair to say, based on this

12 paragraph, that the use of Illumina sequencers was

13 routine to a POSA?

14 MS. CORK: Same objections.

15 THE WITNESS: Well, I don't think this

16 paragraph is really providing any basis of what a

17 POSA would have understood.

18 The point I guess I'm trying to make by the

19 priority date of the '454 patent -- the use of

20 putting adapters on the end of DNA fragments or

21 amplicons were necessary if you were to run it on an

22 Illumina machine. And by 2015, Illumina machines

23 were commonly used in the field for lots of

24 applications.

25 ///

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1 MR. MELCHER:

2 Q. Is that the same in 2011?

3 MS. CORK: Same objection.

4 THE WITNESS: It would have been

5 understood, again, that there would be steps, like a

6 universal PCR to add common adapters on the ends of

7 fragments -- would be necessary to make the

8 amplicons sequence ready for various next-generation

9 sequencing platforms, including the Illumina system.

10 And by 2011, Illumina had been on the

11 market for about three years. So less well known,

12 less commonly used as what I'm trying to say here in

13 the 2015 time period.

14 MR. MELCHER:

15 Q. So you said in 2011, the Illumina

16 sequencers would have been less well known and less

17 well used, but would they still have been well known

18 to some lesser extent?

19 MS. CORK: Same objections. To the extent

20 it misstates testimony.

21 THE WITNESS: Well, I think I have said in

22 my reports that Illumina sequencing on its own, not

23 in the context of how it's applied to asserted

24 claims -- Illumina sequencing was known in 2011.

25 Illumina sequencing had been used in 2011,

Page 30	Page 32
1 and there were various groups publishing data that 2 would generate it from the Illumina sequencer. 3 MR. MELCHER: 4 Q. And was the use of Illumina sequencing 5 routine in 2011? 6 MS. CORK: Objection. Calls for 7 speculation. 8 THE WITNESS: These are very sophisticated 9 instruments. They were -- in 2011, for example, 10 there were only a couple models that had just been 11 released. And there were current revisions and 12 updates and improvements in the -- about chemistry, 13 in the informatics, in the hardware, in the methods. 14 So I don't know if it's routine or not, but 15 they were -- they were in the development of 16 next-generation sequencing platforms 2011. 17 (Reporter clarification.) 18 MS. CORK: Just to interpose again, 19 objection. Vague. And to the extent it exceeds the 20 scope of his report. 21 MR. MELCHER: 22 Q. If you could turn to paragraph 289, please. 23 And let me know when you have had a chance to 24 review. 25 A. Okay. I have read paragraph 289.	1 that if other steps can be mapped to the accused 2 product, it would still infringe. 3 I mean, that was the point of this 4 paragraph. 5 MR. MELCHER: 6 Q. But here you did describe universal PCR 7 step as routine and conventional, correct? 8 MS. CORK: Objection to the extent it 9 misstates the document and prior testimony. 10 THE WITNESS: Well, I am saying that 11 incorporating a routine and conventional use -- 12 universal PCR step after targeted multiplex 13 amplification in a single reaction volume doesn't 14 alter the functionality or the result of the claimed 15 method. 16 That's my opinion. And I think I wouldn't 17 take it out of context because I think it's specific 18 to this context with respect to RaDaR infringing the 19 asserted patents. 20 MR. MELCHER: 21 Q. So there might be other contexts in 22 which -- 23 (Reporter clarification.) 24 Q. So there might be other contexts in which 25 universal PCR is not routine and conventional in
Page 31	Page 33
1 Q. Okay. So in the second sentence, which 2 starts four lines down -- starts with the word 3 "here": 4 "Here, the incorporation of a 5 routine and conventional universal PCR 6 step after targeted multiplex 7 amplification in a single reaction 8 volume does not alter the functionality 9 or result of the claimed method." 10 Do you see that? 11 MS. CORK: Objection. Misstates the 12 document. 13 THE WITNESS: I do, but the sentence 14 continues with an i.e.: "detecting one or more of 15 the tumor-specific SNV mutations." 16 MR. MELCHER: 17 Q. And is it your opinion that universal PCR 18 was routine and conventional to a POSA in 2015? 19 MS. CORK: Objection. Calls for 20 speculation. And to the extent it exceeds the scope 21 of his report. 22 THE WITNESS: I wasn't making or offering 23 an opinion of what a POSA would have understood. I 24 was more making a point that adding an additional 25 step in the accused method doesn't change the fact	1 2015, correct? 2 MS. CORK: Objection. Vague. Calls for 3 speculation. And to the extent it exceeds the scope 4 of his report. 5 THE WITNESS: I haven't thought about all 6 the ways that universal PCR could be used and, 7 within specific contexts, whether it would qualify 8 or not as conventional or routine. 9 So I really don't -- haven't really thought 10 about that far enough to give you any opinion on 11 that question. 12 MR. MELCHER: 13 Q. Would the use of universal PCR after a 14 targeted -- 15 (Reporter clarification.) 16 Q. Would the use of a universal PCR step after 17 targeted multiplex amplification in a single 18 reaction volume be routine and conventional in 2015? 19 MS. CORK: Same objections. 20 THE WITNESS: I don't know. Again, I 21 haven't thought about it in the way you are asking 22 the question. Again, the way I was thinking about 23 what I wrote in paragraph 289 -- it was in the 24 context of RaDaR's infringement of the asserted 25 claims.

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1 MR. MELCHER: 2 Q. So is it your testimony that you did not 3 describe universal PCR as routine and conventional 4 in paragraph 289? 5 MS. CORK: Same objections. And misstates 6 the document in his prior testimony. 7 THE WITNESS: Yeah. I didn't describe it 8 as a sound byte without the context of the entire 9 sentence and the context of the entire paragraph. 10 But the point I'm trying to make is an 11 additional step involving universal PCR doesn't 12 change the fact that, in my opinion, RaDaR infringes 13 the asserted claims. 14 MR. MELCHER: www.LexitasLegal.com/Premier Lexitas 15 Q. So you are not able to offer an opinion on 16 whether universal PCR is routine and conventional 17 outside the narrow construction of this single 18 sentence? Is that your testimony? 19 MS. CORK: Misstates the document, 20 testimony. Argumentative. Also calls for 21 speculation. 22 THE WITNESS: It's possible I could. I 23 haven't really thought about that. And maybe in the 24 future, I could provide an opinion. But today, I 25 haven't really prepared to give you an opinion on	1 to -- of an Alice inquiry. 2 MR. MELCHER: 3 Q. So if Dr. Van Ness said that universal PCR 4 is routine and conventional, you wouldn't be 5 disputing that? 6 MS. CORK: Objection. Outside the scope of 7 his report. Calls for speculation. And to the 8 extent it misstates either his testimony or any of 9 the reports. 10 THE WITNESS: I don't remember actually 11 opining on Dr. Van Ness's statement, if he made such 12 a statement, that universal PCR was conventional and 13 routine. So unless it's in my report, I'm not 14 prepared to offer an opinion today on that. But I 15 may in the future. 16 MR. MELCHER: 17 Q. If you could turn to paragraph 291, please. 18 MS. CORK: Of which document? 19 MR. MELCHER: This same document we are 20 looking at, the reply declaration. 21 MS. CORK: Exhibit 1? 22 MR. MELCHER: What was that? Yeah, 23 Exhibit 1. That's right. 24 THE WITNESS: Okay. I have had a chance to 25 review paragraph 291.
Page 35	Page 37
1 that. 2 MR. MELCHER: 3 Q. How long would it take you to -- to figure 4 that out? 5 MS. CORK: Calls for speculation. Vague. 6 THE WITNESS: I don't know. The 7 specifications are quite thick. There's lengthy 8 prosecution history. I would want to review at 9 least the intrinsic evidence if I was asked to 10 provide such an opinion. 11 MR. MELCHER: 12 Q. So in reviewing Dr. Van Ness's declaration 13 in this case, you didn't form an opinion as to 14 whether universal PCR was routine and conventional? 15 MS. CORK: Misstates testimony. Calls for 16 speculation. 17 THE WITNESS: Well, I was responding to 18 opinions provided by Dr. Van Ness with respect to 19 whether certain procedures were routine, 20 conventional, and well known. 21 And I think the mistake that Dr. Van Ness 22 makes is he just looks at the individual elements, 23 and he doesn't consider the claim as a whole. And I 24 think that's an important -- as I understand, an 25 important analysis in what -- it sounds like a step	1 MR. MELCHER: 2 Q. Okay. So at the end of paragraph 291, you 3 wrote: 4 "One of ordinary skill in the art 5 would have readily recognized that an 6 additional PCR could be performed using 7 a proofreading polymerase, as opposed to 8 Taq polymerase, such that there's no 9 substantial increase in error." 10 Do you see that? 11 A. I see that. 12 Q. So is it your opinion that the use of a 13 proofreading polymerase would have been well known 14 to a POSA? 15 MS. CORK: Objection to the extent it 16 exceeds the scope of his report and misstates the 17 document and any prior testimony and calls for 18 speculation. 19 THE WITNESS: As I have testified, the 20 level of skill is high for a person of ordinary 21 skill in the art. And my opinion is they would have 22 understand -- they would have understood 23 proofreading polymerases, and they would have 24 understood how to use proofreading polymerases. 25 ///

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1 MR. MELCHER: 2 Q. Would a POSA have known other methods of 3 controlling for error in PCR? 4 MS. CORK: Objection. Vague. Calls for 5 speculation. And to the extent it exceeds the scope 6 of the reports. 7 THE WITNESS: Yes. I think a person of 8 ordinary skill in the art with a high level of skill 9 would have understood there are other ways of 10 altering the polymerase chain reaction conditions to 11 affect the error profile in the amplicon product. 12 MR. MELCHER: 13 Q. And if we could please turn to paragraph 17 14 of this same document. 15 A. 17? 16 Q. Yes. 17 MS. CORK: Of Exhibit 1? 18 MR. MELCHER: Exhibit 1. That's right. 19 THE WITNESS: Yes. I have reviewed 20 paragraph 17. 21 MR. MELCHER: 22 Q. And then we're going to go ahead and mark a 23 few exhibits. So I think we're on Exhibit 5 here, 24 and this is United States Patent No. 5,952,170. And 25 then Exhibit 6 will be United States Patent	1 MS. CORK: I'm going to make a general 2 objection to Exhibit 5 and 6 and any other exhibits 3 that are not disclosed in his reports -- referred to 4 in his reports/declarations in this case. 5 (Reporter clarification.) 6 THE WITNESS: Okay. I have. 7 MR. MELCHER: 8 Q. Okay. So if you could turn to the cover 9 page of Exhibit 5. 10 A. Yes. 11 Q. And do you see, under Item 22, "PCT 12 filed" -- and there's a date: December 13th, 1994. 13 Do you see that? 14 A. I do. 15 Q. And under Item 45, in the top right, says 16 "Date of patent: September 14th, 1999." Do you see 17 that? 18 A. I do see that. 19 Q. And then if we could go to Column 1, lines 20 19 through 28. And you see here it says: 21 "The purpose of this invention is, 22 hence, to provide a method for 23 diagnosing cancers which, on the one 24 hand, is more accurate and more reliable 25 and which, on the other hand, is easier
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1 No. 6,156,504. 2 (Exhibits 5-6 were marked for identification.) 3 Q. Okay. So I'm going to ask a question about 4 paragraph 17 first. So here in paragraph 17, you 5 wrote: "As of 2014/2015, scientists were beginning 6 to explore how to use cancer-associated cfDNA." Do 7 you see that? 8 A. I see that. 9 Q. Okay. And if I could direct your attention 10 to Exhibit 5, please. 11 A. Yes. 12 Q. If you want to take a moment to review. 13 MS. CORK: Are you asking him to review the 14 whole patent that is Exhibit 5? 15 MR. MELCHER: 16 Q. You don't need to look at the whole thing. 17 Just a general familiarity to see what you are 18 looking at. 19 MS. CORK: Is there a specific portion of 20 the document you were looking to -- 21 MR. MELCHER: Not yet. He's just preferred 22 to have a moment to look at things, so I'm just 23 giving that to him. 24 Q. If that would be helpful, Doctor -- 25 A. It would be. Thank you.	1 to carry out without the need of 2 resorting to invasive tests on the 3 patients. 4 "The method for diagnosing and/or 5 monitoring the evolution of cancers, 6 object of the invention and aimed at 7 achieving the above purposes, includes 8 the analysis of deoxyribonucleic acid, 9 DNA, contained in the blood plasma." 10 Do you see that? 11 A. I do see that. 12 Q. Does that describe the use of cfDNA to 13 monitor and detect cancers? 14 MS. CORK: Objection. Calls for 15 speculation. Vague. And exceeds the scope of his 16 reports in the exhibit herein. 17 THE WITNESS: Well, I believe this is a 18 document that Dr. Van Ness relied on in his 19 responsive report. 20 And I address this document in my 21 responsive report -- or my reply report -- sorry -- 22 my reply declaration that, in my view, the 23 analysis -- and I'm looking at paragraph 12 of my 24 reply declaration in the middle of the paragraph: 25 "The analysis in the Van Ness

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1 declaration does not adequately describe
2 the significant difficulties and
3 challenges that one of ordinary skill in
4 the art, with respect to the use and
5 manipulation of cfDNA, to achieve the
6 methods claimed in the Natera patents."
7 And so I am actually commenting on this
8 document. This is one that Dr. Van Ness relied on.
9 And I think this is a very brief synopsis of the use
10 of cell-free DNA, but it doesn't -- it doesn't
11 highlight all of the challenges, particularly with
12 respect to the Natera patents.
13 MR. MELCHER:
14 Q. And this is -- you said it's a brief
15 synopsis of cell-free DNA. Would it be fair to say
16 it's a brief synopsis of cell-free DNA -- of the use
17 of cell-free DNA in the context of cancer diagnosis
18 and monitoring?
19 MS. CORK: Objection. Misstates testimony.
20 Calls for speculation.
21 THE WITNESS: Well, I don't know about
22 cancer diagnosis and monitoring. The '170 patent
23 employs only single PCRs. It's not employing the
24 methods described in the Natera patents.
25 And -- and so I -- as I have commented in

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1 my reply declaration, this is kind of a simplified
2 description of the state of the art. That's why I
3 added additional context to provide some of the real
4 challenges skilled artisans face in the field in
5 this time period.
6 MR. MELCHER:
7 Q. Thank you. I guess my question is a little
8 different, though.
9 I -- just looking for an answer whether or
10 not this publication describes -- as it says here in
11 Column 1, lines 19 -- excuse me -- lines 24 to 29:
12 "The method for diagnosing and monitoring the
13 evolution of cancers" -- and it continues --
14 "includes the analysis of DNA contained in the blood
15 plasma."
16 A. Well, I'm not disagreeing. Those words are
17 in this patent. What I -- I guess I'm trying to
18 explain is I don't think the words that you have
19 just read really captures the difficulties and
20 complexities of using cell-free DNA, particularly in
21 the context of the Natera patents.
22 MS. CORK: Interpose an objection to the
23 extent it exceeded the -- the prior question
24 exceeded the scope of this report. Calls for
25 speculation.

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1 MR. MELCHER:
2 Q. So you said the words are in the patent,
3 but I'm -- I'm just asking you to interpret the
4 words. Is this a disclosure of the use of cell-free
5 DNA to detect and monitor cancers?
6 MS. CORK: Same objections.
7 THE WITNESS: Sorry. Can you repeat that
8 question.
9 MR. MELCHER:
10 Q. Yeah. So you said -- I asked you
11 whether -- about certain words in this -- in this
12 patent, and you said, "I agree" -- "I'm not
13 disagreeing. Those words are in this patent."
14 But my question is is it your
15 interpretation of this -- was that this is a
16 disclosure of the use of cell-free DNA to detect and
17 monitor cancer?
18 MS. CORK: Same objections.
19 THE WITNESS: No, I don't think so. And
20 the reason why I say that is this patent, the '170
21 patent, is cited in Dr. Van Ness's background on
22 what he thought the field of cell-free DNA was in
23 the relevant time period.
24 And I write in my reply declaration that I
25 think he didn't adequately describe the field, and

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1 he didn't really highlight the significant
2 difficulties and challenges that one of ordinary
3 skill in the art would have faced. So I don't think
4 this is an adequate description in the '170 patent.
5 MR. MELCHER:
6 Q. An adequate description of the challenges
7 that a POSA would have faced? That's what you are
8 saying?
9 MS. CORK: Objection. Misstates testimony.
10 THE WITNESS: I'm saying I don't think it's
11 an adequate description of the state of the art of
12 cell-free DNA and its use in the Natera patents.
13 MR. MELCHER:
14 Q. Okay. What about outside the context of
15 the Natera patent? Do you think it is outside of
16 the context of the Natera patents -- and not looking
17 for a -- a fulsome disclosure of everything that's
18 known in the art.
19 Is this an individual disclosure of the use
20 of cell-free DNA to detect and monitor cancer?
21 MS. CORK: Objection. Compound. Vague.
22 Calls for speculation. And to the extent it exceeds
23 the scope of his reports.
24 THE WITNESS: Yeah. If you can write that
25 sentence down so I can -- I'll deal with one

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1 question at a time.

2 MR. MELCHER:

3 Q. So is it fair to say the patent discusses

4 the use of cell-free DNA to detect and monitor

5 cancer?

6 MS. CORK: Vague. Calls for speculation.

7 And to the extent it exceeds the scope of his

8 reports.

9 THE WITNESS: I have agreed that the words

10 are there in what you have read in the record. I --

11 I agree the words are there. I don't think it

12 adequately captures the difficulties and challenges

13 in the field of using cell-free DNA.

14 MR. MELCHER: www.LexitasLegal.com/Premier Lexitas

15 Q. Okay. Let's take a look at Exhibit 6,

16 please. And if you just want to refer -- it will be

17 the cover. This one is a little bit longer.

18 A. Yeah. Thank you very much.

19 Okay. Can you ask your question again,

20 please.

21 Q. Yes. So if you look at cover -- Item 22,

22 it says "Filed March 14th, 1997." Do you see that?

23 A. I see that.

24 Q. And under Item 45, date of patent, it

25 states December 5th, 2000. Do you see that?

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1 A. I do see that.

2 Q. Okay. And under abstract, it states:

3 "This invention relates to detection

4 of specific extracellular nucleic acid

5 in plasma or serum fractions of human or

6 animal blood associated with neoplastic

7 or proliferative disease."

8 Then if you look at the last sentence, it

9 states:

10 "The invention thereby provides

11 methods for early detection of

12 colorectal, pancreatic, lung, breast,

13 bladder, ovarian, lymphoma, and all

14 other malignancies carrying

15 tumor-related mutations of DNA and

16 methods for monitoring cancer and other

17 neoplastic disorders in humans and other

18 animals." Do you see that?

19 MS. CORK: Objection. Mischaracterizes the

20 document.

21 THE WITNESS: I do see those two sentences

22 that you have read into the record.

23 MR. MELCHER:

24 Q. So those two sentences are discussing the

25 use of cell-free DNA to detect and monitor cancer,

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1 correct?

2 MS. CORK: Calls for speculation.

3 Mischaracterizes the document.

4 THE WITNESS: I can agree that that's

5 what's written in this document.

6 MR. MELCHER:

7 Q. And if you could look -- turn to, please,

8 your reply declaration at paragraph 20, please.

9 MS. CORK: Is this Exhibit 1?

10 MR. MELCHER: Exhibit 1.

11 THE WITNESS: Okay. I have read paragraph

12 20.

13 MR. MELCHER:

14 Q. Okay. So in the first two sentences, you

15 write:

16 "In addition, tumor genomes are

17 genetically unstable and prone to

18 mutate. A frequent consequence of

19 cancer-associated genetic instability is

20 that different populations of cells

21 within the same tumor from a single

22 patient can have different genetic

23 mutations." Do you see that?

24 A. I do see that.

25 Q. So within these different populations --

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1 let me back up.

2 When a tumor genome mutates, would the

3 original mutations disappear?

4 MS. CORK: Objection. Vague. Exceeds the

5 scope of his report. Calls for speculation.

6 THE WITNESS: I don't understand what you

7 mean by "disappear."

8 MR. MELCHER:

9 Q. So in order for a tumor to form, there have

10 to be a certain number of mutations to the genetic

11 code, correct?

12 MS. CORK: Same objections.

13 THE WITNESS: That is a general premise,

14 that the accumulation of mutations can lead to

15 cancer.

16 MR. MELCHER:

17 Q. Okay. So if cancer has formed, do the

18 accumulation of mutations -- and then, as you state

19 here, tumor genomes --

20 (Reporter clarification.)

21 Q. So if cancer has formed by the accumulation

22 of mutations and then the tumor mutates further,

23 would those original mutations that caused the

24 cancer to form be the sites of those further

25 mutations?

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1 MS. CORK: Objection. Vague. Lacks 2 foundation. Calls for speculation. And exceeds the 3 scope of his reports. 4 THE WITNESS: I'm not sure I understand 5 what you mean. The sites of further mutations? 6 MR. MELCHER: 7 Q. So cancer has formed by an accumulation of 8 mutations. If the tumor was going to mutate 9 further, is it likely that the mutations would be at 10 the exact same site where the original mutations 11 occurred -- the exact same place in the genetic 12 code? 13 MS. CORK: Same objections. And compound. 14 THE WITNESS: I have no idea. Cancer 15 mutations are quite heterogenous, quite different. 16 There's a lot of cellular heterogeneity. I would 17 have no idea how to answer that question. 18 MR. MELCHER: 19 Q. Okay. Let's turn to paragraph 21 in 20 Exhibit 1. 21 A. Okay. I have read that paragraph. 22 Q. Okay. So if we look at the first blocked 23 quote in this paragraph -- the second sentence in 24 that blocked quote, you wrote: 25 "As a result, mutation-specific PCR	1 demonstration for tumor origin of at 2 least some cancer patients' cfDNA. 3 "In 1994, two groups reported the 4 presence of tumor-specific mutations in 5 cfDNA. Both groups used 6 mutation-specific primers to facilitate 7 PCR amplification of tumor-specific and 8 RAS mutations in the plasma samples of 9 patients with pancreatic adenocarcinoma 10 and acute myelogenous leukemia, AML, 11 respectively. 12 "This approach to detection of 13 specific Apriori-known mutations in 14 cfDNA was to become the preferred method 15 of cfDNA studies until the advent of 16 massively parallel sequencing." 17 And then we come up to where your block 18 quote starts. Is that correct? 19 MS. CORK: Objection to the extent it 20 misstates -- mischaracterizes the document. 21 THE WITNESS: It does come up to the block 22 quote in paragraph 21 of my reply declaration. 23 MR. MELCHER: 24 Q. So this paragraph, at least this first part 25 up to the block quote, is discussing the state of
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1 was the only available technology that 2 could provide significant" -- excuse 3 me -- "that could provide sufficient 4 specificity for detection of the weak 5 tumor signal." Do you see that? 6 A. I do see that. I'm actually quoting from 7 the Volik 2016 paper. And that's what those authors 8 were describing about the state of circulating tumor 9 DNA. 10 Q. Let's go ahead and mark the Volik article 11 as Exhibit 7, please. 12 (Exhibit 7 was marked for identification.) 13 Q. Oh, have you had a chance to review? 14 A. Yes. 15 Q. Okay. Okay. So this -- this quote in your 16 report comes from this second paragraph under the 17 heading "Early Discovery and Applications of cfDNA," 18 correct? 19 A. That is correct. 20 Q. And if you look at the first sentence of 21 this report, it states -- excuse me -- the first 22 sentence of this paragraph, it states: 23 "The technological progress of the 24 1990s, fueled by the Human Genome 25 Project, allowed more direct	1 the art in the 1990s. Is that right? 2 MS. CORK: Vague. Calls for speculation. 3 THE WITNESS: Well, I think what you read 4 into the record is talking about what two different 5 groups were using. And I actually think, at least 6 for Reference 6, it's referring to the senior author 7 as Stroun, which is Exhibit 5. 8 And even in Exhibit 6, which is the Gocke, 9 G-O-C-K-E, reference that's also cited in 10 Dr. Van Ness's report, both of these are looking 11 specifically at unique tumor mutations, either in 12 NRAS or maybe another gene. 13 And that was the state of the art until 14 massively parallel sequencing came on board, where 15 you now want to look for new mutations. You are not 16 looking for things you think are there, because you 17 may miss a lot of the ctDNA in the population. 18 MR. MELCHER: 19 Q. And if we could turn to paragraph 29 in 20 Exhibit 1, please. 21 A. Okay. I have read paragraph 29. 22 Q. Okay. So at the end of this paragraph, 23 last sentence, you write: 24 "His opinions are informed with the 25 benefit of hindsight knowledge of

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1 Natera's claimed invention, which I
2 understand is impermissible in an
3 obviousness analysis."
4 Do you see that?
5 A. I do see that.
6 Q. What is your understanding of hindsight
7 with respect to obviousness?
8 A. Well, I'm not a patent attorney, but I've
9 been informed by counsel that you can't look to the
10 patent and then reconstruct combinations in such a
11 way that you arrive at the claimed invention.
12 Q. And why do you think Dr. Van Ness relies on
13 hindsight?
14 A. Because, in my opinion, he is
15 cherry-picking certain parts from different
16 references or opining the knowledge of skill but not
17 actually demonstrating a motivation to combine those
18 teachings.
19 Or, if they were combined, would the person
20 of ordinary skill in the art -- resulted in a
21 reasonable expectation of success. And I think
22 those are kind of the standards that experts rely on
23 so that they prevent the use of hindsight analysis
24 when making 103 arguments.
25 Q. Is it hindsight to rely on the teachings in

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1 the prior art?
2 MS. CORK: Objection. Calls for
3 speculation. Exceeds the scope of his report.
4 THE WITNESS: Well, I've explained the
5 extent of my understanding of hindsight, and that
6 understanding pertains to what is in the patent and
7 using the patent as a guide to reconstruct prior art
8 teachings to arrive at the claimed invention.
9 With respect to hindsight and prior art
10 without the use of a patent, I -- I wouldn't know.
11 Again, I'm not a patent attorney.
12 MR. MELCHER:
13 Q. Is it -- do you know whether it's possible
14 to do an obviousness analysis without referencing a
15 patent at all?
16 MS. CORK: Objection to the extent it
17 exceeds the scope of his report and also
18 mischaracterizes his testimony within his reports.
19 And calls for speculation.
20 THE WITNESS: Can you give me a little more
21 context of what you mean by a "patent."
22 MR. MELCHER:
23 Q. Have you -- so you've mentioned you have
24 been deposed too many times to recall, correct?
25 A. To count. Yes.

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1 Q. To count. Sure.
2 In any of those cases, were you ever
3 opining that any patent or patent claim is obvious?
4 A. I have provided opinions that an asserted
5 patent is invalid because of an obviousness
6 analysis.
7 Q. Do you think you could have done that work
8 and provided those opinions without looking at the
9 patent at any point?
10 MS. CORK: Objection. Calls for
11 speculation.
12 THE WITNESS: Again, so I'm trying to
13 understand what you mean. The patent -- is it the
14 asserted patent that you are referring to?
15 MR. MELCHER:
16 Q. I'm referring to the -- the patent and the
17 claims that you opined were obvious. I'm asking
18 you: Could you have provided those opinions without
19 ever looking at that patent in those claims?
20 MS. CORK: Same objection. And compound.
21 And to the extent it exceeds the scope of his
22 report.
23 THE WITNESS: Well, again, my understanding
24 and the way I approach an obviousness analysis, I
25 would have reviewed the patent -- the asserted

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1 patent.
2 But when I'm trying to look to the prior
3 art and make a determination whether there is any
4 art out there that would read on the claims of a
5 patent, I have to ignore the asserted patent.
6 I have to look at the prior art, look at
7 its teachings, look at what's missing, what's --
8 what's found in -- what's in common with the claims,
9 what's missing in the claims.
10 And are there any teachings or
11 motivations -- if there are missing elements in the
12 art that I could reasonably combine where -- through
13 a person of ordinary skill in the art, they would
14 have arrived at the claimed invention.
15 That's my understanding of how an obvious
16 analysis should be conducted.
17 MR. MELCHER:
18 Q. Could we please turn to paragraph 171 in
19 Exhibit 1.
20 A. Yes. I have read paragraph 171 in my reply
21 declaration.
22 Q. Okay. So here this paragraph states:
23 "Dr. Van Ness's attempt to combine
24 the teachings of '183 Patent Pub. (Han
25 and Wang, 2010) is flawed in multiple

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1 respects. 2 "Neither reference teaches or 3 suggests all limitations of the '035 4 patent's claimed methods, which 5 Dr. Van Ness does not dispute. This 6 alone renders the combination 7 insufficient." 8 Is it your understanding that a POSA's 9 knowledge is irrelevant to obviousness? 10 MS. CORK: Objection. Mischaracterizes his 11 reports. And to the extent it mischaracterizes 12 prior testimony. Calls for speculation. 13 THE WITNESS: I'm not sure how, by reading 14 paragraph 171, you concluded that I did not consider 15 what a POSA would know or understand. As I tried to 16 explain maybe in my last sentence, all of this is 17 viewed through a person of ordinary skill in the 18 art. 19 MR. MELCHER: 20 Q. So you write: "Neither reference teaches 21 or suggests all limitations of the '035 claimed" -- 22 "patent's claimed methods." And then in the next 23 sentence, you say: "This alone renders the 24 combination insufficient." 25 So it seems here that you are saying that	1 Dr. Van Ness's attempt to combine these two 2 references falls way short. 3 And in my opinion, a person of ordinary 4 skill in the art looking at Han, realizing -- are 5 there other teachings out there that can arrive at 6 the claimed invention? The Wang reference falls 7 short, and that's the opinion I'm providing in 8 paragraph 173. 9 MR. MELCHER: 10 Q. So you mentioned that there can be missing 11 limitations in an obviousness analysis. And, you 12 know, in this case, you are saying there are 13 specific missing limitations. But as a general 14 principle, can missing limitations like this be 15 supplied be a POSA's knowledge? 16 MS. CORK: Objection. Compound. Calls for 17 speculation. Exceeds the scope of his reports. 18 THE WITNESS: Well, I guess I would first 19 state that a person of ordinary skill in the art 20 would have never looked to Wang to fill in the 21 missing pieces in Han because they're doing 22 completely different things. 23 So I disagree that the combination would 24 have ever happened in the first place. But in a 25 hypothetical world, if there was a missing element
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1 because these two primary prior art references don't 2 contain every element, that -- that a POSA's 3 knowledge can't supply any elements. That's why I 4 asked the question. Is that your opinion? 5 MS. CORK: Objection. Compound. Calls for 6 speculation. Misstates the document and prior 7 testimony. 8 THE WITNESS: No, I don't think I'm saying 9 that at all. I think Dr. Van Ness is trying to use 10 these two references to render obvious the '035 11 patent. 12 And a POSA reading the patents -- for 13 example, start with Han, the '183 Patent Pub., which 14 is -- does use multiplex PCR, is not interested in 15 detecting SNIPs, does not use sequencing data, uses 16 a completely different detection mode. 17 So there's obviously missing elements that 18 need to be filled in -- nor does Han teach -- well, 19 you could also use sequencing as a detection mode. 20 But nonetheless, Dr. Van Ness then tries to 21 then combine Wang, which is not a multiplex PCR 22 system, which is not interested in looking at SNIPs, 23 but does use high-throughput sequencing. 24 In fact, Wang doesn't even cite to the '183 25 Patent Pub. So what I'm trying to say is	1 and it was well known and a person could use common 2 sense, that -- that is a possibility. But I don't 3 think that's the scenario here. 4 MR. MELCHER: 5 Q. Do you have an understanding of the concept 6 of teaching away with respect to obviousness? 7 MS. CORK: Objection. Vague. To the 8 extent it mischaracterizes his reports. 9 THE WITNESS: I understand that's sort of a 10 legal concept. From a technical point of view, 11 if -- if I were to look at something specific, maybe 12 I could have an opinion. But it's obviously 13 something that I don't do on a routine basis. 14 MR. MELCHER: 15 Q. So you -- you couldn't give me, like, a 16 couple-sentence summary of what "teaching away" 17 means with respect to obviousness? 18 MS. CORK: Objection. Calls for 19 speculation. Exceeds the scope of his reports. 20 Calls for speculation. 21 THE WITNESS: Again, I -- I understand it's 22 more of a legal concept. I rely on counsel to 23 provide me legal standards. I do not believe that 24 was provided to me in my report -- or my 25 declaration, so I couldn't really give you an

Page 62 1 example of what teaching away would be. 2 MR. MELCHER: 3 Q. Okay. Okay. Let's turn, please, to 4 Exhibit 3, the '035 patent. I'll just look at Claim 5 1. 6 A. If I can just have a moment to review. 7 Q. Sure, sure. 8 MS. CORK: I'll note for the record that 9 this document has highlighting on it. 10 THE WITNESS: I have reviewed Claim 1 of 11 the '035 patent. 12 MR. MELCHER: 13 Q. So if I wanted to practice Claim 1 of the 14 '035 patent, it requires amplifying the tagged 15 products one or more times to generate final 16 amplification products wherein one of the 17 amplification steps comprises targeted amplification 18 of a plurality of single nucleotide polymorphism, 19 SNP, loci in single reaction volume wherein one of 20 the amplification -- amplifying steps introduces a 21 barcode and one or more sequencing tags. 22 So it's -- it would be possible to do a 23 targeted amplification at the same time as 24 introducing a barcode and one or more sequencing 25 tags, correct?	Page 64 1 the document? 2 MS. CORK: To the extent it takes 3 limitations out of the context of the claim and 4 requires him to speculate on them. 5 MR. MELCHER: I see. Okay. I do see that. 6 Q. So according to this, you could amplify the 7 tagged products one time. Is that correct? 8 MS. CORK: Objection. Calls for 9 speculation. Mischaracterizes the document. 10 THE WITNESS: Again, I haven't thought 11 about that hypothetical that you are asking. It 12 would require some time to think about it in the 13 context of the -- the whole claim. 14 MR. MELCHER: 15 Q. So what does "one or more times" mean to 16 you? 17 MS. CORK: Objection. Vague. Calls for 18 speculation. 19 THE WITNESS: Well, just that phrase, "one 20 or more," means one or more. I think that's the 21 plain reading of the -- the phrase within the claim. 22 But I think you have to do -- you do have to 23 consider the whole claim to know whether you are 24 practicing the claim or not. 25 ///
Page 63 1 MS. CORK: Objection. Mischaracterizes the 2 document. Compound. Calls for speculation. And 3 exceeds the scope of his reports. 4 THE WITNESS: That would require some 5 thought to think about, that hypothetical that you 6 have just provided -- for me to provide an opinion 7 whether it would read on that claim element or not. 8 MR. MELCHER: 9 Q. So at the beginning of the claim element, 10 it says "amplifying the tagged products one or more 11 times." So it could just be amplifying once, 12 correct? 13 MS. CORK: Objection to the extent it 14 mischaracterizes the document. Calls for 15 speculation. Incomplete hypothetical. 16 THE WITNESS: I don't understand what you 17 mean by "amplifying once." 18 MR. MELCHER: 19 Q. So this claim limitation states "amplifying 20 the tagged products one or more times," correct? 21 A. I do see that in the claim limitation. 22 Q. So -- 23 MS. CORK: Objection to the extent it 24 mischaracterizes the document. 25 MR. MELCHER: How does that mischaracterize	Page 65 1 MR. MELCHER: 2 Q. So there -- there could be ways of 3 practicing this claim -- excuse me. 4 So "one or more" includes one, correct? 5 MS. CORK: Vague. 6 THE WITNESS: In the phrase that you have 7 just stated in isolation, "one or more" means one or 8 more. I mean, that's what it means. It can be one 9 or it can be more in isolation on that phrase. 10 MR. MELCHER: 11 Q. So -- but once I add "amplifying the tagged 12 products one or more times," it could mean something 13 other than one or more? Is that what you are 14 saying? 15 MS. CORK: Vague. Calls for speculation. 16 And I'll just object to this entire line of 17 questioning to the extent it exceeds the testimony 18 in his reports. 19 THE WITNESS: Well, again, there are two 20 wherein clauses where there is an amplification step 21 comprising targeted amplification. There is another 22 wherein clause where one of the amplification steps 23 introduces a barcode in one or more sequencing tags. 24 I haven't really thought about the 25 hypothetical I think you are proposing of whether

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1 that would read on the claim or not. 2 And it would require some thought 3 analysis -- for example, looking into the spec to 4 see whether the spec actually would support the 5 hypothetical that you are proposing. 6 MR. MELCHER: 7 Q. Okay. Let's look at your -- excuse me. 8 Let's look at Exhibit 1 at paragraph 30, 9 please, and let me know when you have had a chance 10 to review. 11 A. Okay. I have reviewed paragraph 30 in my 12 reply declaration. 13 Q. Oh, okay. So if you see here -- second 14 sentence of paragraph 30, you wrote: 15 "The claims are directed to 16 patent-eligible subject matter, methods 17 of sample preparation, and recite 18 specific concrete laboratory steps which 19 generate DNA sequences not found in 20 nature and which require human effort to 21 perform." 22 Is it your understanding that patent claims 23 are directed to patent-eligible subject matter if 24 they require human effort to perform? 25 MS. CORK: Objection to the extent it	1 (Break taken.) 2 THE VIDEOGRAPHER: We are back on the 3 record, 9:31 a.m. 4 MR. MELCHER: 5 Q. If we could turn to Exhibit 2, '454 patent, 6 at Claim 1, please. 7 A. Yes. I am there. 8 Q. Okay. So -- 9 A. And if I can have a minute to read through 10 it, please. 11 Q. Oh, yeah. Of course. Yeah. 12 A. Okay. I have read it. 13 Q. Okay. So at this last limitation here, he 14 cites: 15 "Sequencing the amplicons to obtain 16 sequence reads and detecting one or more 17 of the tumor-specific SNV mutations 18 present in the cell-free DNA from the 19 sequence reads wherein the sequencing 20 has a depth of read of at least 50,000 21 per target locus." Do you see that? 22 A. I do. 23 Q. And what, if anything, about that claim 24 limitation involves preparing a plasma sample? 25 MS. CORK: Objection. Calls for
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1 exceeds the scope of his reports and calls for 2 speculation. 3 THE WITNESS: Can you repeat the question, 4 please. 5 MR. MELCHER: 6 Q. Yes. Is it your understanding that patent 7 claims are directed to patent-eligible subject 8 matter if they require human effort to perform? 9 MS. CORK: Same objections. 10 THE WITNESS: Well, again, I'm not a patent 11 attorney. I do understand this is Step 1 of the 12 Alice -- that case that -- the courts decide, and 13 I'm just providing a technical opinion that I 14 believe that the subject matter is patent eligible 15 because it -- it requires human efforts to perform. 16 So I'm just providing that from a technical 17 standpoint. 18 MR. MELCHER: 19 Q. Let's take a look at Exhibit 2, please. 20 A. Is it a good time to take a break? I don't 21 know how long we have been going. 22 Q. Oh, of course. Yeah, we can break now. 23 That's fine. Let's go off the record, please. 24 THE VIDEOGRAPHER: Thank you. And we are 25 off the record at 9:23 a.m.	1 speculation. To the extent it exceeds the scope of 2 his reports. 3 THE WITNESS: Well, it's part of the method 4 of preparing a plasma sample. You also have to 5 follow the other steps that are recited in the claim 6 as a whole. And that is a method of preparing a 7 plasma sample. 8 MR. MELCHER: 9 Q. So this limitation that says "sequence in 10 the amplicons to obtain sequence reads" is a method 11 of preparing a plasma sample? 12 MS. CORK: Objection. Mischaracterizes the 13 document and his prior testimony. 14 THE WITNESS: Well, the claim as a whole 15 is: 16 "A method of preparing a plasma 17 sample of a subject having cancer or 18 suspected of having cancer useful for 19 detecting one or more single nucleotide 20 variants (SNV) mutations in a plasma 21 sample." I mean, it's all of that. 22 MR. MELCHER: 23 Q. So when you sequence amplicons to obtain 24 sequence reads, what part of preparing a plasma 25 sample is that?

Page 70 1 MS. CORK: Objection. Mischaracterizes the 2 document and his prior testimony. 3 THE WITNESS: Well, you are preparing a 4 plasma sample. It has your cell-free DNA in it. If 5 there's a cancer patient, may have cell T-DNA in it. 6 You isolate that from the blood. 7 You perform whole-exome sequencing, 8 whole-genome sequencing to identify tumor-specific 9 SNV mutations. You can then develop personalized 10 assays to perform the multiplex -- targeted 11 multiplex PCR to amplify 10 to 500 target loci. 12 So all of that is involved to get to the 13 step of sequencing the amplicons to obtain sequence 14 reads. That's all part of the -- preparing a plasma 15 sample. 16 MR. MELCHER: 17 Q. So when you -- when you put the amplicons 18 into a sequencer, are the amplicons that you put 19 into that sequencer -- is that a plasma sample, 20 those amplicons? 21 MS. CORK: Objection. Vague. Calls for 22 speculation. To the extent it exceeds the scope of 23 his reports. 24 THE WITNESS: If I understand your 25 question, next-generation sequencing instruments	Page 72 1 absent by following the claimed method. 2 MR. MELCHER: 3 Q. Okay. So the plasma sample comes in after 4 you have done your whole-exome sequencing or 5 whole-genome sequencing on a tumor sample. Is that 6 right? 7 MS. CORK: Objection. Misstates -- 8 misstates testimony. 9 THE WITNESS: I haven't really thought 10 about that, but I don't think that's necessarily 11 true. But I -- it would require some more thought 12 to -- I think your question is about an order, and I 13 don't think I have considered an order of steps as 14 part of this claim. 15 MR. MELCHER: 16 Q. Well, according to the claimed method, 17 would it be possible to identify cancer-related SNVs 18 in a plasma sample if one hadn't already performed 19 whole-exome sequencing or whole-genome sequencing on 20 a tumor sample? 21 MS. CORK: Objection. Vague. Misstates 22 the document. Calls for speculation. And to the 23 extent it exceeds the scope of his reports. 24 THE WITNESS: Can you repeat the question, 25 please.
Page 71 1 don't sequence just straight plasma sample. There 2 are steps involved in isolating DNA, preparing DNA. 3 And in this case, you perform whole-genome 4 sequencing or whole-exome sequencing to identify 5 specific tumor SNVs, to build assays that you can 6 then do targeted multiplex PCR amplification with 7 multiple loci between 10 and 500. 8 So all of that is part of the claimed 9 method which starts with the phrase "a method of 10 preparing a plasma sample." 11 MR. MELCHER: 12 Q. In what way does performing whole-exome 13 sequencing or whole-genome sequencing on a tumor 14 sample involve the use of a plasma sample? 15 MS. CORK: Same objections and incomplete 16 hypothetical. 17 THE WITNESS: Well, in the claimed method, 18 whole-genome sequencing and whole-exome sequencing 19 is sequencing from a tumor sample of a subject to 20 identify a plurality of tumor-specific SNVs -- 21 mutations. 22 So that step is necessary to then build an 23 assay that targets specifically those tumor-specific 24 SNVs. A plasma sample is then used to then identify 25 whether those tumor-specific SNVs are present or	Page 73 1 MR. MELCHER: 2 Q. Sure, sure. So you have stated this is a 3 method for detecting one or more single nucleotide 4 variations in a plasma sample, right? 5 A. Well, I -- I've stated what the claim 6 states. I've been trying to be very careful not to 7 truncate any step in the claim -- the claim as a 8 whole. 9 MS. CORK: I'll just interpose my same 10 objections. 11 MR. MELCHER: 12 Q. Okay. Okay. So if you are going to look 13 for cancer-related SNVs in a plasma sample, you have 14 to know what to look for, correct? 15 MS. CORK: Objection. Incomplete 16 hypothetical. Calls for speculation. To the extent 17 it exceeds the scope of his reports. 18 THE WITNESS: I would have to think about 19 that a little bit more. It's quite possible you can 20 collect the plasma sample before whole-exome 21 sequencing and then characterize that plasma sample 22 afterward. So I would have to think about that more 23 to give you a specific answer. 24 MR. MELCHER: 25 Q. Okay. So performing targeted multiplex

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1 amplification, would that -- would that start with 2 this plasma sample? Would a POSA put plasma into 3 the PCR machine, or how would that work? 4 MS. CORK: Same objections and compound. 5 THE WITNESS: Well, again, I don't think -- 6 just like my comments with next-generation 7 sequencing, I don't think one of ordinary skill in 8 the art would just put plasma into a PCR machine. 9 Obviously, you would need to isolate 10 cell-free DNA from the plasma sample, and you would 11 use that as a template for your PCR reaction. 12 MR. MELCHER: 13 Q. Okay. Is isolated cell-free DNA a plasma 14 sample? Are those the same thing? 15 MS. CORK: Same objections. 16 THE WITNESS: No, they're not the same 17 thing. A plasma sample is the liquid part that 18 comes from blood. And from that, you can extract 19 and isolate cell-free DNA from the plasma sample. 20 MR. MELCHER: 21 Q. So this last limitation here that starts 22 with "sequencing" -- the next line down states: 23 "Detecting one or more of the tumor-specific SNV 24 mutations present in the cell-free DNA from the 25 sequence reads." So what is a sequence read?	1 that extracts those colored signals, purifies those 2 colored signals, and creates a string of letters 3 that represent a sequence read. 4 In part of that sequence read, the 5 instrument determines how good -- what we call a 6 base call is. A, C, G, and T make up the sequence 7 reads. 8 So the read will be an order of DNA letters 9 plus some quality information of how correct the 10 machine believes it was in making the base call. 11 MR. MELCHER: 12 Q. And then -- I appreciate your expansive 13 answer, but when -- when you get that sequence of 14 letters, is that -- is that, like, printed on a 15 paper, or is that, you know, a computer file? 16 I'm just asking about the end result. 17 Like, what is the -- what is the format of that end 18 result of the sequence of letters? 19 MS. CORK: Objection. Vague and compound. 20 THE WITNESS: It ends up as a file. 21 It has a lot of information in that file in 22 addition to the order of A, C, G, and T -- for 23 example, a header file which may include which 24 sample it came from, which machine it was run on, if 25 it had barcode information, what the barcode is --
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1 MS. CORK: Objection. Compound. Calls for 2 speculation. 3 THE WITNESS: So it's -- it's a term that 4 we use in the field, and it is information that is 5 generated from a sequencing instrument. And it 6 determines the order of DNA letters -- A, C, G, and 7 T -- for a given cell-free DNA molecule. 8 And those letters are important because 9 they represent the instruction manual of life and 10 the way cells operate in our body. 11 MR. MELCHER: 12 Q. So would sequence reads -- is that, like, 13 a -- like, a computer file, or how is that -- how is 14 that embodied in the world? 15 MS. CORK: Objection. Compound. Vague. 16 Calls for speculation. 17 THE WITNESS: It's quite complex how a 18 sequence read is created. In the actual sequencing 19 process, there are fluorescent colors. We have four 20 colors. We have four letters. 21 And there's very sophisticated Optix 22 microscopes that actually can detect the four 23 colors. And the colors are sequential, so the 24 colors give you the order of the letters. 25 And there's a lot of sophisticated software	1 for grouping sequence reads into individual samples 2 that they came from. 3 The files typically are then mapped to a 4 reference genome to create a BAM file, B-A-M, which 5 has more information about the genetic location on 6 our genome, whether there are differences between 7 the reference genome and the sequence read itself. 8 So there's a lot of information there. 9 MR. MELCHER: 10 Q. So if I wanted to practice this method of 11 Claim 1 -- and assume I don't really know what I'm 12 doing here. I'm probably going to make some 13 mistakes. 14 So if I was going to try and do my targeted 15 multiplex amplification and I -- you know, I set 16 everything up. I put everything in the PCR machine. 17 Let's say I had you or Dr. Quakenbush help me up 18 through that point. 19 So I'm doing everything right up to that 20 point. But I decide that at that point, I'm just 21 going to do one PCR cycle. Are you with me so far? 22 A. Sorry. I'm not following you, actually. 23 MS. CORK: I'll interpose the objection of 24 compound and to the extent it exceeds the scope of 25 his report.

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1 MR. MELCHER: 2 Q. Okay. So if I was going to perform this 3 method of Claim 1, right -- are you with me so far? 4 MS. CORK: Vague. 5 THE WITNESS: Well, I am following your 6 hypothetical. 7 MR. MELCHER: 8 Q. Okay. 9 A. I don't think it's appropriate because you 10 are not -- I don't think -- I don't actually know 11 your qualifications, but you may not meet the bill 12 of a person of ordinary skill in the art who would 13 have actually -- 14 Q. Sure. 15 A. -- been the one that would perform the 16 claimed steps. 17 Q. Sure. Okay. Let's assume a POSA is 18 performing the claimed steps. Are you following? 19 A. I understand the last statement you just 20 made. 21 Q. Okay. So let's say a POSA is -- is 22 performing these steps, and they get up to this step 23 that says "Performing targeted multiplex 24 amplification." 25 And in their multiplex amplification, they	1 MS. CORK: Same objections. 2 THE WITNESS: Well, I can rule out that -- 3 based on what you have just said, if you -- and it 4 has nothing to do with how many cycles you are doing 5 in multiplex PCR. 6 But I do know if you don't make the 7 amplicons what we call sequence ready, you put on -- 8 for example, let's just talk about Illumina. 9 Illumina has specific DNA molecules. 10 They call them P5 and P7. If you don't add 11 those onto your amplicons, you will not sequence the 12 amplicon on an Illumina sequencer. It's a 13 requirement. 14 So regardless of whether you have stopped 15 with one cycle or if you did 30 cycles, there's not 16 enough information in what you have said. But I do 17 know if you don't hit certain requirements, you 18 won't sequence amplicons. 19 MR. MELCHER: 20 Q. Okay. Well, let's assume that these 21 amplicons are sequence ready and that I've met all 22 those other requirements. Would I be able to detect 23 any tumor-related SNVs from one single PCR cycle 24 amplification, according to this method? 25 MS. CORK: Same objections. And compound.
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1 accidentally set the PCR to only go for one cycle. 2 Are you with me so far? 3 A. I'm following your hypothetical. 4 Q. Yeah. 5 A. I mean, I understand what you are 6 suggesting. 7 Q. Yeah. And then -- 8 MS. CORK: Sorry. Interpose an objection. 9 Vague and incomplete hypothetical and to the extent 10 it exceeds the scope of his reports. 11 MR. MELCHER: 12 Q. And then if a POSA took this -- the results 13 of this single PCR amplification step, just one 14 cycle, and then they tried to sequence the amplicons 15 to obtain sequence reads, would they be able to 16 detect any tumor-related SNVs with any kind of 17 accuracy or sensitivity? 18 MS. CORK: Same objections. And calls for 19 speculation. 20 THE WITNESS: I have no idea. There's not 21 enough information in your hypothetical to determine 22 whether they would be successful or not. 23 MR. MELCHER: 24 Q. So they might be successful? You can't 25 rule it out?	1 THE WITNESS: Based on what you just said, 2 I have no idea at all. You would have to actually 3 give me some more specifics of how you get to the 4 step of sequencing the amplicon. 5 MR. MELCHER: 6 Q. Okay. So there's a chance that it could 7 work, though? You can't rule it out? 8 MS. CORK: Same objections. And misstates 9 testimony and asked and answered. 10 THE WITNESS: I think your hypothetical is 11 so incomplete that no one could even imagine whether 12 you could or couldn't. And I don't think you could, 13 but you just haven't provided me enough information 14 to even suggest whether you could or not. 15 But because there's so many missing steps, 16 I mean, I would probably say, no, you can't. But 17 you have to fill in some of those details for me to 18 understand whether you could get to the step of 19 sequencing an amplicon. 20 MR. MELCHER: 21 Q. Could you imagine a way of successfully 22 executing Claim 1? 23 MS. CORK: Objection to the extent it 24 exceeds the scope of his reports. Calls for 25 speculation. And vague.

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1 THE WITNESS: I think if you followed all
2 of the steps of Claim 1, you would successfully
3 practice Claim 1.
4 MR. MELCHER:
5 Q. Okay. And, then, I'm just offering one
6 modification where the targeted amplification is
7 just one PCR cycle. Are you with me?
8 MS. CORK: Same objections.
9 THE WITNESS: I understand what you are
10 suggesting.
11 MR. MELCHER:
12 Q. Yeah. And the question is would -- would
13 that modification make it possible or impossible to
14 detect any tumor-related SNVs? www.LexitasLegal.com/Premier Lexitas
15 MS. CORK: Same objection. Incomplete
16 hypothetical.
17 THE WITNESS: So you have only provided me
18 one specific in this hypothetical, and there are
19 lots of specifics that need to be understood before
20 you could even try to answer that question. I just
21 think it is very incomplete of a hypothetical that
22 you are asking.
23 MR. MELCHER:
24 Q. So you said, "I think" -- that can't be
25 right.

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1 So I asked, "Could you imagine a way of
2 successfully executing Claim 1?" And I think there
3 might be a minor transcription error, so I'm not
4 exactly clear what your answer is because I don't
5 think this is exactly what it is.
6 Could you -- could you answer that again so
7 I could have a clear record.
8 MS. CORK: I'm sorry. Are you asking
9 for -- the question to be reread or --
10 MR. MELCHER:
11 Q. Could you just clarify your answer.
12 MS. CORK: Vague. Unclear what question
13 you are asking him to answer.
14 THE WITNESS: Yeah. If you could repeat
15 the question, I'll try to answer it.
16 MR. MELCHER:
17 Q. So the question is could you imagine a way
18 of successfully executing Claim 1?
19 MS. CORK: Objection.
20 THE WITNESS: Yes. And my answer was if
21 you follow all of the steps of Claim 1, you could
22 successfully practice Claim 1.
23 MR. MELCHER:
24 Q. So that's a successful method, right?
25 MS. CORK: Vague.

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1 MR. MELCHER:
2 Q. You would -- okay. Excuse me.
3 So do you have -- do you have -- you have
4 no details in your mind when it comes to that, but
5 you know it would be successful? You know you would
6 detect tumorous SNVs, right?
7 MS. CORK: Objection. Vague.
8 MR. MELCHER: Yeah. Let me rephrase the
9 question because that was messy.
10 Q. If, you said, you follow all the steps in
11 order, you would successfully practice Claim 1.
12 When you say "successfully practice Claim 1," does
13 that involve accurately detecting tumor-specific SNV
14 mutations?
15 MS. CORK: Objection. Misstates prior
16 testimony. Calls for speculation.
17 THE WITNESS: Well, if you follow Claim 1,
18 it really does depend on the cancer sample.
19 If the cancer sample does not have ctDNA in
20 it, they have been identified by whole-exome or
21 whole-genome sequencing -- and hopefully the patient
22 has completely -- is cancer-free now -- you would
23 not detect anything because it's not present in the
24 sample.
25 But what I am saying is if you follow all

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1 of the steps of Claim 1, you will successfully
2 practice Claim 1.
3 MR. MELCHER:
4 Q. Okay. So let's say in the -- it's your
5 opinion that the Natera Signatera assay embodies the
6 claims of the asserted patents, correct?
7 A. I do provide that opinion, I think, in both
8 reports. Right. So, for example, I'm looking at my
9 reply declaration at paragraph 306.
10 And I'm just referencing where I describe
11 how Signatera practices Claim 1 in each of the
12 Natera patents, and I cite to my opening
13 declaration. And that is Section 9 of my opening
14 declaration.
15 Q. And how does Signatera assay perform a
16 targeted multiplex amplification?
17 MS. CORK: Objection to the extent it
18 exceeds the scope of his reports.
19 THE WITNESS: So I'm looking at my opening
20 declaration at paragraph 127. I say: "Signatera
21 satisfied this claim limitation." Claim limitation
22 is Step 1B, that starts "Performing targeted
23 multiplex amplification."
24 And I -- I write:
25 "According to Signatera's workflow,

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1 the top 16 somatic variants are selected 2 based on clonally, detectably, and 3 frequency of mutations. 4 "Multiple PCR compatible primers are 5 designed for each of the 16 somatic 6 mutations. Next, whole blood is 7 collected at a defined" -- sorry -- "at 8 predefined time points for longitudinal 9 surveillance. 10 "Subsequently, the plasma are 11 isolated and cell-free" -- "or cfDNA 12 extracted, followed by assaying with the 13 patient-specific 16-plex PCR pool. 14 Following multiplex PCR amplification, 15 ultra-deep sequencing is performed." 16 So that's my opinion of how Signatera meets 17 that claim limitation. 18 MR. MELCHER: 19 Q. If there was a patient who had been 20 diagnosed with cancer and it was known that that 21 patient has cancer cfDNA in their blood and a POSA 22 was going to use Signatera to detect the presence of 23 this cancer-derived cfDNA in this patient's blood 24 and, instead of practicing Signatera exactly as 25 the -- Natera recommends -- when they did this	1 SNVs? 2 MS. CORK: Objection. Compound. 3 Incomplete hypothetical. Calls for speculation. 4 And to the extent it exceeds the scope of his 5 reports. 6 THE WITNESS: I have no idea. I don't 7 believe a person of ordinary skill in the art would 8 have modified a CLIA-approved, Medicare-approved 9 Signatera assay and just arbitrarily perform one 10 cycle. 11 I haven't thought about that. I would need 12 a lot more information to understand the Signatera 13 workflow in great detail. And that's all I can say. 14 MR. MELCHER: 15 Q. So you think there's a chance Signatera 16 would work with only a single PCR cycle as the 17 entirety of its amplification? 18 MS. CORK: Same objections. And to the 19 extent it misstates prior testimony. 20 THE WITNESS: I did not say that at all. 21 MR. MELCHER: 22 Q. But that's my question: Do you agree with 23 that or not? 24 A. Do I agree with what? 25 Q. Is it your testimony -- is it your
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1 16-plex PCR pool, they only did one cycle of PCR -- 2 do you understand that hypothetical? 3 MS. CORK: Objection. Compound. Vague. 4 Calls for speculation. Incomplete hypothetical. 5 And to the extent it exceeds the scope of his 6 reports. 7 THE WITNESS: Well, I do understand the PCR 8 cycle, and I do understand stopping at one cycle. I 9 understand that premise. 10 MR. MELCHER: 11 Q. And do you understand the premise of a 12 patient having cancer with cancer cfDNA in their 13 blood? 14 MS. CORK: Vague. 15 THE WITNESS: I -- I understand that 16 certain cancer patients may have ctDNA in their 17 blood. Some may not. But I understand that 18 premise. 19 MR. MELCHER: 20 Q. Okay. So if there was one of these 21 patients with ctDNA in their blood and a POSA was 22 going to use Signatera to detect cancer-related SNVs 23 from a plasma sample from this patient but the POSA 24 only did a single PCR sample -- single PCR cycle, 25 would the POSA be able to detect cancer-related	1 testimony that there's a chance Signatera would work 2 and successfully identify cancer-related SNVs with 3 only a single PCR cycle as the entirety of its 4 amplification step? 5 MS. CORK: Same objection. 6 THE WITNESS: I have actually said that's 7 not my testimony. I never said those words. I have 8 told you it's an incomplete hypothetical, and I 9 would have no way of knowing how to answer that 10 question. 11 MR. MELCHER: 12 Q. That's -- incomplete hypothetical. What's 13 incomplete about it? 14 A. There are lots of steps in the Signatera, 15 many of which I probably am not even aware of 16 because I'm not in their laboratories performing the 17 very detailed protocols in the Signatera assay. 18 You've cherry-picked one step in that 19 workflow and have asked a question without 20 considering all the other steps. I have no way of 21 answering that question. 22 Q. Does Signatera work? Does it -- is it 23 capable of detecting cancer-related SNVs? 24 MS. CORK: Objection. Compound. To the 25 extent it exceeds the scope of his prior testimony

Page 90 1 and the reports. 2 THE WITNESS: My understanding -- and there 3 are several papers that I cite in my opening 4 declaration and also in my reply declaration papers 5 from Christensen 2019, Coombes 2019, and Kotani 2023 6 that use the Signatera assay and have yielded useful 7 results in clinical studies. 8 MR. MELCHER: 9 Q. But you couldn't say one way or the other 10 if, instead of doing what Natera recommends with the 11 amplification step, you just did a single cycle of 12 PCR, it could still yield useful results? That's 13 your testimony? 14 MS. CORK: Objection. Misstates prior Lexitas 15 testimony. Compound. Vague. And to the extent it 16 exceeds his reports. 17 THE WITNESS: Well, again, I disagree with 18 what you have -- the way you have stated the 19 question because I haven't provided any testimony 20 that it could provide useful results. 21 What I have testified -- it is a severely 22 incomplete hypothetical, and I would have no way of 23 answering that question. 24 MR. MELCHER: 25 Q. So you think it's incomplete to make one	Page 92 1 understanding of the way Signatera operates. When 2 it comes to actually performing it in their 3 laboratories, which are well-developed SOPs -- which 4 I understand they do not deviate from performing the 5 steps of the Signatera protocol or test. 6 You are asking the question, "Well, what 7 happens if you just haphazardly just change 8 something in the assay?" 9 And I'm saying, "Wait a minute." First, I 10 don't think that would ever happen. And, secondly, 11 I actually don't know all of the detailed steps -- 12 for example, aliquoting primers. 13 Just -- just the routine steps that are 14 done in the laboratory, how that would impact making 15 the change that you are suggesting -- I just don't 16 have that much information. And you haven't 17 provided me any more detail than "Change the cycle 18 in a multiplex PCR step." 19 MR. MELCHER: 20 Q. In your experience, is it -- is it common 21 to be able to haphazardly change an assay and have 22 that assay still work successfully? 23 MS. CORK: Objection. Vague and calls for 24 speculation. 25 THE WITNESS: Well, I don't know because I
Page 91 1 modification to the Signatera protocol? That's an 2 incomplete hypothetical? 3 MS. CORK: Same objections. And incomplete 4 hypothetical. And I'll just make that a standing 5 objection to this line of questioning. 6 THE WITNESS: What I'm saying is I don't 7 know all of the very detailed steps that go into the 8 Signatera assay. So to cherry-pick one step and 9 say, "Well, I'm going to change this. What will 10 happen?" -- I don't know, first, because I don't 11 have a good basis of the Signatera process. 12 Secondly, I hadn't really thought about the 13 impact of making that change or not in the overall 14 scheme of the Signatera assay. 15 So what I'm saying is I can't provide you 16 an answer because you haven't provided me any 17 information other than "I'm going to do one cycle in 18 my multiplex PCR. What will happen?" And I think 19 that's severely incomplete in your hypothetical. 20 MR. MELCHER: 21 Q. So your understanding of the Signatera 22 assay isn't good enough to understand a 23 modification. Is that what you are saying? 24 MS. CORK: Misstates testimony. 25 THE WITNESS: No. I have a good overall	Page 93 1 actually don't haphazardly change steps in a 2 protocol. 3 I was suggesting the way you had phrased 4 the question that it is a haphazard change that 5 deviates from a well-developed SOP that Signatera -- 6 the way the Signatera assay has been developed and 7 the way technical people in the laboratory would 8 follow the protocol to yield useful results. 9 MR. MELCHER: 10 Q. But you won't say one way or the other 11 whether making haphazard changes to well-developed 12 SOPs will allow you to yield useful results or not? 13 MS. CORK: Vague. Misstates testimony. 14 Calls for speculation. Exceeds the scope of his 15 reports. 16 THE WITNESS: Well, I'm calling the change 17 that you are suggesting a haphazard change. It 18 doesn't make sense to me why you would want to do 19 that. 20 I don't do that in my own practice. But 21 what I am saying is you don't provide enough 22 information in the incomplete hypothetical to even 23 know how to answer that question. 24 MR. MELCHER: 25 Q. So you would want me to explain the entire

Page 94 1 Signatera assay nuts and bolts from start to finish 2 to be able to even contemplate this question. Is 3 that your testimony? 4 MS. CORK: Objection. Misstates testimony. 5 Exceeds the scope of his reports. And 6 argumentative. 7 THE WITNESS: Well, your question is about 8 Signatera, and your question is about "If I made 9 this one change, what would the impact be?" And so 10 I think to do a proper evaluation, you would want to 11 understand in great detail how the entire workflow 12 operates. 13 And then you might have a little more 14 information to predict an outcome or not. But I'm 15 just taking one step and making an abrupt change in 16 the workflow. Without any other information, 17 there's no way to answer that question. 18 MR. MELCHER: 19 Q. So in your experience, making abrupt 20 changes in workflow is not something you could 21 predict whether it would impact the usefulness of 22 the results or not? 23 MS. CORK: Objection. Vague. Exceeds the 24 scope of his reports. 25 THE WITNESS: I would be speculating	Page 96 1 it. Okay. I've reviewed it. 2 Q. Okay. So in this paragraph, you state, 3 last sentence: 4 "But the ForsheW 2012 approach alone 5 would not be effective on either score, 6 as one of ordinary skill in the art 7 would have recognized. And, therefore, 8 the skilled artisan would not have 9 reasonably expected success with the 10 ForsheW 2012 strategy." 11 Do you see that? 12 A. I see that. 13 Q. Okay. And let's go to paragraph 93, 14 please. 15 MS. CORK: Of Exhibit 1? 16 MR. MELCHER: Yes. Same exhibit, 17 Exhibit 1. 18 THE WITNESS: Okay. I see that too. 19 MR. MELCHER: 20 Q. Okay. And then on page 51, this last 21 sentence of paragraph 93, you wrote: 22 "Under the ForsheW 2012 approach, 23 the rare variants are lost in the noise 24 associated with the abundant errors 25 found in the sequence read data."
Page 95 1 because, as I've testified, I don't know all of the 2 details that are part of the Signatera test. 3 Generally, I understand the steps that are 4 involved to produce useful data. And so what I'm 5 saying is without an understanding of that, I can't 6 answer the question. 7 MR. MELCHER: 8 Q. So you don't think it's likely that an 9 abrupt or haphazard change to an SAP -- SOP workflow 10 or assay would have any impact on the usefulness of 11 the results? 12 MS. CORK: Objection. Misstates testimony. 13 And my standing objection is to -- calling for 14 speculation, incomplete hypothetical, compound. 15 THE WITNESS: Yeah. I -- it's a general 16 question. There's not any details to really answer 17 that question. It would be pure speculation on my 18 part, and I'm not willing to provide answers based 19 on pure speculation. 20 MR. MELCHER: 21 Q. Let's turn to Exhibit 1, paragraph 92, 22 please. 23 A. 92? 24 Q. 92. 25 A. Okay. Give me a moment, please, to review	Page 97 1 What is your basis for suggesting that 2 there are abundant errors found in the ForsheW 2012 3 sequence read data? 4 A. Well, first, ForsheW explains that they 5 have limited sensitivity; that they can only detect 6 alleles at the 1 to 2 percent range, which is about 7 where the error rate is for next-generation 8 sequencing. 9 The error rate in next-generation 10 sequencing was known in the field. And, in fact, I 11 described that in the next section where I cite 12 papers like Schmitt -- sorry. 13 First I cite to Glenn 2011, that reports a 14 lot of the errors associated not just with Illumina 15 but '454, Ion Torrent. I believe PacBio may be in 16 there as well. 17 But then I go on to explain that there were 18 groups thinking about error detection and error 19 correction in next-generation sequencing like 20 Schmitt 2012, where preparing libraries -- DNA 21 molecules where we attach things to the end 22 introduces errors that are sequencing errors or part 23 of the sequencing workflow. 24 PCR introduces error in amplification. The 25 sequencer itself makes mistakes in calling those

Page 98 1 letters. And so groups were thinking about how to 2 figure that out. 3 And then I also point out in paragraph 96 4 an article by Kinde, K-I-N-D-E, where he states: 5 "Massively parallel sequencing cannot generally be 6 used to detect rare variants because of the high 7 error rate associated with the sequencing process." 8 So I'm providing a basis of why Forshew 9 could not find rare variants because of all the 10 noise associated with the sequencing data. 11 Q. What is the difference between sensitivity 12 and error rate? 13 MS. CORK: Objection. Vague. 14 THE WITNESS: Two different things. 15 MR. MELCHER: 16 Q. What's the difference? 17 MS. CORK: Same objection. 18 THE WITNESS: They have nothing to do with 19 one another. 20 MR. MELCHER: 21 Q. So there's no difference? 22 MS. CORK: Vague. 23 THE WITNESS: Sensitivity is -- basically, 24 what is the limit of detection? How -- can you 25 detect a rare variant at 1 percent? .1 percent?	Page 100 1 thousand times more brown ones, it affects the 2 sensitivity because no one would want to go deeply 3 into the jar because you are just pulling out a 4 bunch of brown M&M's. 5 And it's a waste of time. So that's how I 6 think about sensitivity and how I think about noise 7 or errors. 8 MR. MELCHER: 9 Q. So if you were looking for red M&M's in the 10 jar, you would be -- you would be more comfortable 11 digging through the jar if there were more red M&M's 12 relative to brown M&M's or if the ratio is more 13 balanced. Is that fair to say? 14 MS. CORK: Misstates testimony and vague. 15 THE WITNESS: If you have more red M&M's 16 than brown M&M's, you are above the noise. And so 17 your signal to noise is better, and you have a much 18 better chance of identifying the red M&M's as 19 specific mutations. 20 When the red M&M's are well below the 21 frequency of the brown M&M's, all you are doing is 22 picking out noise. And you are not actually finding 23 the rare variant. And when you do, you actually 24 don't know whether it's a true mutation or it's just 25 another sequencing error that the system produced.
Page 99 1 .01 percent? 2 The lower the percentage, the more 3 sensitive you are at detecting the rare variant. 4 The error rate, on the other hand, is all the noise 5 that's created from the sequencing workflow. 6 And it affects the sensitivity, but it's 7 not -- but they're very different things because -- 8 I always think of it like -- take an M&M jar, for 9 example. 10 And -- and I have 10,000 M&M's, and they're 11 all green. And I have one red M&M, and that's my 12 ctDNA. And I'm trying to find that needle in the 13 haystack. 14 And so just by picking out M&M's, 15 eventually I'm going to pick out a red one that's 16 different from all the green ones, and I found my 17 ctDNA. 18 But imagine noise are brown M&M's, and 19 they're present in the jar at a hundred times or a 20 thousand times more frequent than that one red M&M. 21 So every time I go into the M&M jar, I'll get a 22 green one. I'll say that's normal DNA. 23 I get a brown one, and I don't know if 24 that's because I've measured a mutation in ctDNA or 25 I have measured an error. And because there are a	Page 101 1 MR. MELCHER: 2 Q. Excuse me. So if you had -- if you had the 3 same amount of brown and red M&M's, would you be 4 able to detect the mutations in this hypothetical? 5 A. I think you would, and I think that's where 6 Forshew is. So Forshew is at the 1 percent level of 7 the tumor-specific mutation. And the NGS system 8 that Forshew is using is producing errors at about 1 9 percent. 10 So you are kind of right at that threshold 11 where Forshew can detect tumor-specific mutations. 12 But they even comment that their sensitivity is 13 limited. 14 And it's at least two to three orders of 15 magnitude higher than some of other -- some of the 16 other assays that can detect down to .01 percent 17 of -- for a given test. 18 Q. So do you recall what -- what sequencer 19 Forshew used? 20 A. Forshew is using an Illumina sequencer, and 21 I could look at the paper if you are asking me what 22 model of Illumina sequencer they were using. 23 Q. We will. We'll follow up on that. Thank 24 you. 25 Would a POSA have been aware of error rates

Page 102 1 of commercial sequencing platforms? 2 MS. CORK: Objection to the extent it 3 exceeds the scope of his reports. Calls for 4 speculation. 5 THE WITNESS: Yes. And I give an example 6 in paragraph 94 that even relatively high-fidelity 7 sequencing platforms were known to introduce 8 sequencing errors at a rate of greater than 9 .1 percent. 10 And I cite to the Glenn field guide, to 11 next-generation sequence -- next-generation DNA 12 sequencers. I -- I actually wrote a review paper in 13 2010 commenting on the errors associated with 14 next-generation sequencing. 15 So there would have been an understanding 16 of the error rate problem for next-generation 17 sequencing. For most applications, it was okay. It 18 would work. 19 It even worked for ForsheW when you are 20 looking for allele frequencies at 1 percent. But 21 when you are really trying to find that rare variant 22 and you have to deeply sequence, that's where the 23 problem becomes real -- a big issue. 24 MR. MELCHER: 25 Q. Are you citing Glenn as evidence of a	Page 104 1 the scope of his report. 2 THE WITNESS: Yeah. I believe that a 3 person of ordinary skill in the art, as we have 4 defined in the scope of the Natera patents, would 5 have been aware of the Glenn reference and anything 6 in the Glenn reference. 7 MR. MELCHER: 8 Q. Okay. Let's take a look at Exhibit 1, your 9 reply declaration, at paragraph 96, please. 10 A. Okay. I have reviewed paragraph 96 of my 11 reply declaration. 12 Q. Okay. So this -- this block quote here, 13 that's a citation from this Kinde article that you 14 mentioned earlier. Is that right? 15 A. Yes. It's from Kinde. 16 Q. Kinde. And are you citing Kinde as 17 evidence of the knowledge of a POSA? 18 MS. CORK: Objection to the extent it 19 exceeds the scope of his reports. 20 THE WITNESS: Well, I'm citing Kinde as 21 this would have been part of the state of the art. 22 So it's one thing to look to Glenn and recognize 23 machines have errors. 24 It's another thing that Kinde -- and this 25 is somewhat groundbreaking. Kinde is actually
Page 103 1 POSA's knowledge? 2 MS. CORK: Objection to the extent it 3 exceeds the scope of his report. 4 THE WITNESS: My understanding, a POSA has 5 high technical -- a high skill of -- a technical 6 level, and they would have been aware of the Glenn 7 review in the field of next-generation sequencing. 8 MR. MELCHER: Okay. We'll mark as 9 Exhibit 8 the paper entitled "Field Guide to 10 Next-Generation DNA Sequencers" by Travis C. Glenn. 11 (Exhibit 8 was marked for identification.) 12 A. Okay. I have at least looked through the 13 abstract. 14 Q. Okay. And this is the Glenn paper that we 15 have been discussing and that you cite in your reply 16 declaration, correct? 17 A. That's correct. 18 Q. And you specifically cite at your Footnote 19 95 to Table 3. So is it fair to say a POSA would 20 have been aware of the data in Table 3? 21 MS. CORK: Sorry. Are you referring to 22 Exhibit 1, Footnote 95? 23 MR. MELCHER: Yeah, that's Exhibit 1, his 24 reply declaration. 25 MS. CORK: Object to the extent it exceeds	Page 105 1 developing new methods for error detection and error 2 correction because Kinde is interested in finding 3 rare mutations. 4 And so they have one approach of figuring 5 out a way of removing the noise so that you can 6 apply next-generation sequencing to find rare 7 variants. 8 (Reporter clarification.) 9 MR. MELCHER: And we'll go ahead and mark 10 Kinde as Exhibit 9. And this is a paper entitled 11 "Detection and Quantification of Rare Mutations with 12 Massively Parallel Sequencing" by Isaac Kinde and 13 some other authors. 14 (Exhibit 9 was marked for identification.) 15 A. Okay. I have read the abstract of Kinde. 16 Q. Okay. And if you could turn to the last 17 page, which is page 93 -- excuse me -- 9535. And 18 you see there's a heading or a bolded introduction 19 to a paragraph titled "Sequencing"? 20 A. Yes. 21 Q. Based on that paragraph, would you agree 22 that Kinde used an Illumina sequencer on their work 23 on this paper? 24 A. They state they used the Illumina GA IIX 25 instrument.

Page 106 1 Q. Okay. And if we could please turn to your 2 reply declaration, Exhibit 1, at paragraph 147. 3 A. Okay. I have read paragraph 147 of my 4 reply declaration. 5 Q. And so -- excuse me -- the end of the 6 portion of the paragraph that's on page 80 of 7 Exhibit 1, you write: 8 "As the error rate dictates the 9 frequency at which SNVs can be 10 identified, Table 1 in the '189 Patent 11 Pub. (Bentley) (cited by Dr. Van Ness) 12 suggests that read depths between 400 13 and 1,000 would have been sufficient to 14 identify an SNP at the 1 percent level, 15 as shown infra (red box highlight added 16 to highlight the number of reads to an 17 SNP at 1 percent level)." 18 Do you see that? 19 A. I do. But I think you said Table 1, and it 20 is Table 2 in the Bentley reference. 21 Q. Okay. And then Table 2 from the Bentley 22 reference is reproduced on the next page, page 81. 23 Is that correct? 24 A. Yes. I see that. 25 Q. So according to the logic -- so following	Page 108 1 higher than what we've been talking about for 2 Illumina. 3 And so if -- if the floor has an error rate 4 of 1 percent, well, that's about where your 5 sensitivity will lie, because if you exceed the 6 error rate, most of the things you find are just 7 errors. You are not able to find the mutation. 8 And so what I did on page 81 of Table 2 is 9 ask the question: If my error rate is at 1 percent, 10 then my detection of the mutant alleles is going to 11 be about 1 percent. 12 That's about as good I'm going to get. And 13 if that's my limit of detection, well, then how many 14 reads would I need to perform to find the 15 tumor-specific SNV at 1 percent. 16 And based on Bentley's table, I would only 17 have to do about 400 to a thousand reads to find my 18 tumor-specific variant at the 1 percent level. 19 MR. MELCHER: 20 Q. So if your error rate was .01 percent, how 21 many reads would you need to do? 22 A. So if you did something like Kinde or 23 something like Schmitt where you can actually detect 24 and correct errors and -- down to the .1 percent, 25 you could now increase the read depth to increase
Page 107 1 the logic of that sentence we just read, would it be 2 reasonable to say that to an -- to identify an SNP 3 at the .01 percent level, a POSA would need to do 4 between 40,000 and 100,000 reads? 5 MS. CORK: Objection to the extent it 6 mischaracterizes his reports. 7 THE WITNESS: I disagree with that, and 8 that's not what the paragraph is trying to explain. 9 So, for example, the Bentley reference produces 10 Table 2. 11 And I -- I talk about this in my 12 declaration earlier -- of error-free reads, perfect 13 reads, reads that don't have any sequencing errors 14 whatsoever. 15 And it's like that jar of M&M's where 16 there's just one M&M. There's no brown M&M's. And 17 that's Bentley. And I agree that in that perfect 18 scenario, the deeper you go, the more sensitive the 19 assay can be. But the reality is these instruments 20 have errors. 21 And Bentley is using a different 22 next-generation sequencing instrument called 454 23 Life Sciences. And so I cite to the Gilles 24 reference that was published in 2011 where they 25 measured the error rate at about 1 percent, even	Page 109 1 your sensitivity because now the things you are 2 detecting are most likely true variants and not that 3 noise that you just removed by these very unique 4 methods. 5 Kinde called his method "Safe-SeqS," and 6 Schmitt called his method "duplex sequencing." So 7 they created these new methods to do the error 8 detection and the error correction to find these 9 rare variants. 10 Q. But even in those -- 11 MS. CORK: I'll just interpose an 12 objection. It calls for speculation. To the extent 13 it exceeds the scope of his report. 14 MR. MELCHER: 15 Q. Even in those methods, there's still a 16 limit of detection, correct? 17 MS. CORK: Vague. And same objections as 18 to the prior question. 19 THE WITNESS: There is. So I'm looking at 20 Kinde, Table 1. And they're doing various 21 experiments to demonstrate the Safe-SeqS method. 22 And in the capture column, without doing any type of 23 error correction or error detection, they identify 24 25,563 mutations. 25 When they performed the Safe-SeqS method

Page 110 1 and removed all of the errors based on their unique 2 way of error correction, they identified eight. So 3 over 25,000 of the mutations that were found were 4 noise, garbage. 5 And they have a detection error rate of 6 three and a half times ten to the minus six. So you 7 were right. They have a -- there is a limit, but 8 it's substantially -- it has more sensitivity 9 without identifying errors and correcting errors. 10 MR. MELCHER: Oh, would now be a good time 11 for a break? 12 THE WITNESS: Sure. 13 MR. MELCHER: Would that work? 14 THE WITNESS: Yeah. www.LexitasLegal.com/Premier Lexitas 15 MR. MELCHER: Okay. 16 THE VIDEOGRAPHER: And we are off the 17 record at 10:36 a.m. 18 (Break taken.) 19 THE VIDEOGRAPHER: We are back on the 20 record at 10:45 a.m. 21 MR. MELCHER: 22 Q. All right. If we could turn to Exhibit 1, 23 paragraph 160, please. 24 A. Okay. If I can have a moment -- 25 Q. Sure.	Page 112 1 THE WITNESS: So the point of this 2 paragraph really is about detecting a small amount 3 of tumor DNA in the polymorphic nature of tumor DNA. 4 And I'll just point you just to Claim 1 of the '035 5 patent. 6 And it's doing all of this work, the 7 amplifying steps in a single reaction volume. 8 That's -- that's kind of the point of paragraph 160 9 because what 160 is highlighting is this big 10 problem. 11 When you take a device like Kaper and 12 you cell -- and attempt to use cell-free DNA on 13 Kaper, it does not work because you have a low 14 amount of material. 15 And in that material, you even have a lower 16 amount of the tumor DNA that you are trying to 17 acquire or at least monitor or -- or find its 18 presence. 19 When you have to split up that small amount 20 of cell-free DNA into a number of reaction wells, 21 you introduce sampling bias and statistical noise 22 because not every well may have a ctDNA molecule in 23 it, whereas the claimed invention is doing 24 everything in one reaction. 25 And so it's not dividing all of the samples
Page 111 1 A. -- to review this paragraph. 2 Okay. I have reviewed paragraph 160 in my 3 reply declaration. 4 Q. Okay. So a little -- at the end of the 5 paragraph on page 89, you write: 6 "In acknowledging these problems, 7 the '035 patent reports that its methods 8 are comparatively advantageous when 9 amplifying low-abundance DNA, including 10 free-floating cfDNA found in plasma." 11 Do you see that? 12 A. Yes, I see that. 13 Q. What about the claimed methods of the '035 14 patent enabled this comparative advantage? 15 A. I'm sorry. I don't think I have offered 16 any opinions on enablement. 17 Q. No, no. I'm saying you are saying that the 18 methods of the '035 patent provide a comparative 19 advantage. Correct? 20 A. Compared to the Fluidigm Access Array, such 21 as what's described in Kaper. 22 Q. So what about the '035 patent claims create 23 this comparative advantage? 24 MS. CORK: Objection to the extent it 25 misstates his report.	Page 113 1 and introducing all of this noise. And that's the 2 point of this paragraph of highlighting the 3 comparative advantages of using the claimed method 4 of targeted multiplex PCR. 5 MR. MELCHER: 6 Q. And if you could turn, please, to paragraph 7 190 in Exhibit 1. 8 A. Did you say 191? 9 Q. No. Just 190. 10 A. 190. 11 Q. Yeah. 12 A. If I could have a minute to review this 13 one. 14 Q. Yeah. 15 A. Okay. I have reviewed paragraph 190 in my 16 reply declaration. 17 Q. Okay. So at the beginning of this 18 paragraph, you state: 19 "Regardless, from my understanding 20 of principles governing the 'directed 21 to' analysis, I believe Dr. Van Ness's 22 analysis is flawed." Do you see that? 23 A. I see that. 24 Q. What is your understanding of what it means 25 for a patent claim to be directed to something?

Page 114 1 A. Well, I think I explained that in the rest 2 of the paragraph. You know, I -- I say: 3 "Dr. Van Ness reaches these opinions 4 by focusing on certain claim limitations 5 and excluding others. I'm not aware of 6 a basis to exclude claim limitations in 7 determining what claims are directed to. 8 "Rather, I understand from counsel 9 that the 'directed to' analysis requires 10 consideration of the character of the 11 claims as a whole." 12 And I can go on and read, but that's my 13 understanding of the "directed to" analysis. 14 Q. Okay. So you don't have any understanding 15 that isn't laid out in paragraph 190 here? 16 MS. CORK: Objection. Misstates testimony 17 and the scope of his report. 18 THE WITNESS: There may be other places in 19 my report. There is a, for example, legal standards 20 section that starts on page seven of my report. 21 Paragraphs four through six are the standards that I 22 have been provided with respect to Section 101. 23 And in particular, paragraph five is 24 providing me guidance of the "directed to" inquiry 25 of Step 1.	Page 116 1 A. Well, I guess -- again, I'm not a lawyer, 2 and I'm providing my understanding of what's 3 involved in the claim. And it's my understanding -- 4 and I think I say this on page 105, paragraph 190, 5 of my reply report: 6 "I'm informed by counsel that the 7 patent-eligibility determination 8 requires more than determining that the 9 claims involve" -- just -- "the claims 10 involve an ineligible concept. 11 "Rather, claims may be eligible for 12 patenting if they recite a method for 13 achieving a new and useful result." 14 And I guess in support of achieving a new 15 and useful result, I'm making -- I'm pointing out 16 that there's a lot of human intervention to make a 17 new and useful result. 18 Q. So it's just as part of this new and useful 19 result requirement that you consider human effort to 20 an intervention. Is that right? 21 MS. CORK: Objection. Misstates testimony 22 and his reports. 23 THE WITNESS: No. I would disagree with 24 that. Again, I'm providing my opinion from a 25 technical standpoint of, you know, we're creating --
Page 115 1 MR. MELCHER: 2 Q. Okay. Is it your understanding that patent 3 claims are directed to patent-eligible subject 4 matter if they require significant human effort and 5 intervention? 6 MS. CORK: Objection. Calls for 7 speculation. To the extent it mischaracterizes his 8 report. 9 THE WITNESS: Well, again, that sounds like 10 a legal determination. I'm providing, from a 11 technical standpoint, that the claims require 12 significant human interaction. That's what I'm 13 providing. 14 MR. MELCHER: 15 Q. And does that have anything to do -- does 16 your understanding of the "directed to" analysis 17 touch on that at all? 18 MS. CORK: Same objection. And vague. 19 THE WITNESS: Can you repeat the question, 20 please. 21 MR. MELCHER: 22 Q. Yeah. You -- does your understanding of 23 the "directed to" inquiry include an analysis of 24 whether the subject matter requires significant 25 human effort and intervention?	Page 117 1 we're creating things that are not natural. 2 We're doing things that are new and useful, 3 requires a lot of human intervention. So I'm -- I'm 4 just providing a lot of support for why, at Step 1, 5 in my opinion, you should be patent eligible. 6 But as for specific requirements based on a 7 legal standard, I really am not qualified to provide 8 any opinion. 9 MR. MELCHER: 10 Q. Okay. I'm not asking what your opinion is, 11 though. I'm asking what is your understanding. Do 12 you understand the distinction? 13 A. I do. And I guess I've tried to explain 14 what my understanding is to the best that I can. 15 Q. Yeah. 16 A. And, then, I'm providing it really from a 17 basis of a technical opinion based on how I 18 understand what the claims are, what they involved, 19 do they produce a new and useful result, and what is 20 the level of effort that is needed to practice the 21 claims. 22 Q. Thank you. But that answer kind of went a 23 little sideways because I'm asking your 24 understanding of a legal standard that you applied 25 in your report.

Page 118 1 And then you started talking about 2 technical opinions based on understandings of the 3 claims. Do you understand that that's different 4 from what I'm asking? 5 A. Yes. If you are asking me what legal 6 standards I relied on, they're in my reply 7 declaration at paragraph four through six for 8 Section 101. 9 Those are the standards that I provided. 10 That's the best understanding I can give you. I can 11 read it from my declaration, but that would be the 12 best I could do for legal standards. 13 Q. Okay. And anywhere in those two 14 paragraphs, is there a mention of human effort and 15 intervention? 16 MS. CORK: Objection to the extent it 17 mischaracterizes his report. And vague. 18 (Reporter clarification.) 19 THE WITNESS: Yeah. I don't see 20 specifically those words, but I do think the human 21 intervention is described in other areas in my 22 report beyond what's stated in paragraph 190 of my 23 reply declaration. 24 MR. MELCHER: 25 Q. Okay. In your legal standards section, do	Page 120 1 "is not routine or conventional at least 2 because the method's ordered" -- "the 3 method's ordered steps recite improved, 4 invented processes for sample 5 preparation. 6 "The ordered combination of steps 7 improves upon prior art approaches in 8 several respects, as described below." 9 So I guess I'm equating if we were ever to 10 get to Step 2, which I don't think we should have -- 11 but if Step 1 was considered patent ineligible, Step 12 2 would still render the claimed method patent 13 eligible because of this ordered combination. 14 And I'm just making an observation that 15 none of the prior art approaches identify this 16 ordered combination of steps. 17 MR. MELCHER: 18 Q. Okay. If we could turn to paragraph 210 of 19 Exhibit 1, please. 20 A. Okay. I'm at paragraph 210, and I'll take 21 just a minute to review the paragraph. 22 Okay. I have reviewed paragraph 210 of my 23 reply report. 24 Q. Thank you. So at the beginning of the 25 paragraph, you state: "Second, the methods can be
Page 119 1 you see anything about whether subject matter is a 2 material improvement over prior art techniques? 3 MS. CORK: Objection. Vague. 4 THE WITNESS: I don't understand the 5 question. 6 MR. MELCHER: 7 Q. Okay. In these -- in these three 8 paragraphs, your legal standards section for Section 9 101, do you see any reference or mention of whether 10 the subject matter being a material improvement over 11 prior art techniques has any bearing on whether the 12 subject matter is patent eligible? 13 MS. CORK: Objection to the extent it 14 mischaracterizes his report. 15 THE WITNESS: Well, I don't see exactly the 16 words that you have in your question. Paragraph six 17 deals with Step 2, and I do -- I do say, for 18 example, at paragraph 208 -- because I am relying on 19 paragraph six for things like an order combination. 20 But I say in paragraph 208: 21 "When considered as an ordered 22 combination, the methods recited in the 23 asserted claims" -- paragraph 208 is 24 just dealing with '454, but I think I 25 make a similar opinion for the '035 --	Page 121 1 used to prepare small amounts of cancer-associated 2 cfdNA, which are challenging to manipulate." 3 So what about the claimed methods enabled 4 the preparation of small amounts of 5 cancer-associated cfdNA? 6 A. Well, I think I actually explain that in 7 the following sentences and provide several block 8 quotes from the '454 patent that explain the methods 9 that enable or -- or allow for the preparation of 10 small amounts of cancer-associated cfdNA. 11 Q. Okay. And these block quotes, these are to 12 the specification of the patent, correct? 13 A. They are. 14 Q. Okay. So what about the claims enable the 15 preparation of small amounts of cancer-associated 16 cfdNA? 17 MS. CORK: Objection. Vague. To the 18 extent they exceed the scope of his report. 19 (Reporter clarification.) 20 THE WITNESS: Well, it's actually pretty 21 much everything in Claim 1 of the '454 patent 22 because the block quotes that I'm providing support 23 for this paragraph are talking about improved 24 analytical methods, improved bioassay methods, 25 improved methods that use a combination of improved

Page 122 1 analytical and bioassay methods. 2 And the point that is being made here is 3 the use of targeted multiplex PCR amplification of 4 10 to 500 target loci that were identified from the 5 whole-genome or whole-exome sequencing of a tumor 6 sample allows for broader identification of SNVs and 7 CNVs, copy number variations, versus looking at 8 what one of the reference calls "hot spot 9 mutations," where you actually know what you are 10 looking for. 11 But the specification is pointing out -- 12 and I think the claimed method practices finding new 13 SNVs that are specific to a patient's cancer. 14 MR. MELCHER: www.LexitasLegal.com/Premier Lexitas 15 Q. So -- so what about -- so cfDNA is 16 challenging to manipulate, or at least it was as of 17 priority date, correct? 18 (Reporter clarification.) 19 A. Right. And I have a footnote citing back 20 to Section 2 of my reply declaration. 21 Q. Okay. So -- and then in Section 2, you -- 22 you referred to a number of these -- these 23 challenges, correct? 24 A. I do. I'll -- everything that's set forth 25 in Section 2 is what I described as the difficulties	Page 124 1 others, but I'm just giving you one example. 2 MR. MELCHER: 3 Q. Sure. I'd like to hear about the others 4 too. 5 A. Sure. So, again, the ability to do Step 1, 6 which is performing whole-exome sequencing and 7 whole-genome sequencing of the tumor sample, allows 8 you to identify patient-specific tumor SNVs. 9 And this is an advantage over the prior art 10 that focused on these hot spot mutations, like the 11 Stroun, S-T-R-O-U-N patent, which I believe is 12 Exhibit 5, and the Goche, G-O-C-H-E, which I believe 13 is Exhibit 6. 14 If I could find that -- where they were 15 looking for known mutations. And what the '454 has 16 recognized is there's lots of other tumor-specific 17 mutations that are missed when you only look for 18 known things. 19 And so an inventive step is doing this 20 whole-genome/whole-exome on a patient's tumor sample 21 to identify patient-specific variants to then 22 monitor when cell-free DNA is isolated from plasma. 23 And then the ability to do these targeted 24 multiplex PCR -- because of all of these 25 improvements in the bioassays that allow the
Page 123 1 and the challenges. 2 Q. Okay. So what about Claim 1 overcomes 3 those challenges? 4 MS. CORK: Objection to the extent it 5 mischaracterizes the scope of his report. 6 THE WITNESS: Well, I'll give you an 7 example because there's a lot of moving parts in 8 Claim 1. 9 But I'll just focus at the end of 10 performing targeted multiplex amplification. And 11 it's where everything is amplified together in the 12 same reaction volume. 13 So the improvements of just that step alone 14 illustrate why Kaper, for example, 2010, would not 15 be successful in using cfDNA because -- because of 16 the small amount of the material, because of the 17 variability of tumor DNA within the material. 18 Being able to do it all in one reaction 19 volume is tremendously advantageous compared to 20 trying to disperse it across multiple reaction 21 wells, where you've introduced the statistical noise 22 and the sampling noise. 23 You create artificial imbalances of alleles 24 and things like that. So that's one of the 25 advantages of the claimed methods. There are	Page 125 1 generation of these loci-specific amplicons that can 2 be sequenced to identify tumor-specific variants 3 that are specific to that patient. 4 And then -- and then the final claim 5 limitation of sequencing having a depth of read of 6 at least 50,000 per target locus allows you now to 7 really improve the sensitivity of finding those 8 patient-specific SNVs. 9 All of that is highly innovative. 10 Q. Anything else? 11 A. I think I captured the main parts here. 12 Q. Okay. So where in Claim 1 is an 13 improvement to a bioassay? 14 MS. CORK: Vague. 15 THE WITNESS: So I would -- one step -- I 16 mean, I could point you to Step 1A, which is 17 performing whole-exome sequencing and whole-genome 18 sequencing of a tumor sample of the subject to 19 identify a plurality of tumor-specific SNVs. I 20 think that's an improvement in the bioassay. 21 That's a starting point -- to then building 22 these -- a test that's specific for that patient 23 involving targeted multiplex amplification of 10 to 24 500 target loci from cell-free DNA that have a 25 defined amplicon link of 50 to 150 bases that are

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1 all amplified in the same reaction volume.

2 So the improvement in the bioassay is doing

3 all of that, where you are not introducing all of

4 this sampling noise. If you were to rely on the old

5 technology, such as in Kaper, of using the Fluidigm

6 system -- so that's one example -- two examples I

7 gave you, actually.

8 MR. MELCHER:

9 **Q. Is there anything else -- any other**

10 **example?**

11 A. Anything else on -- based on what?

12 **Q. Based on the claim, Claim 1.**

13 A. Well, yeah. So there are improved

14 analytical methods that allow you to sequence the

15 amplicons to obtain sequence reads and to detect one

16 or more of the tumor-specific SNV mutations present

17 in the cell-free DNA from the sequence reads where

18 the sequencing has a read depth of at least 50,000

19 per target loci.

20 So, again, the analytical methods allow you

21 to sequence more deeply to increase your sensitivity

22 to find those rare tumor-specific variants in the

23 plasma sample obtained from a cancer patient.

24 **Q. And where is the improved analytical method**

25 **in Claim 1?**

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1 A. Well, I'm reading that from the

2 specification. But to get to the claim that can be

3 practiced having a read depth of 50,000, the patent

4 does explain in great detail a lot of the analytical

5 methods that allow you to get to at least 50,000 per

6 target locus.

7 **Q. Okay. But that's in the specification, not**

8 **in the claim, correct?**

9 A. That's --

10 MS. CORK: Objection. Misstates testimony.

11 Misstates the scope of his report.

12 THE WITNESS: That's true. What I'm doing

13 is reading what is claimed and understanding what is

14 in the specification of how you can achieve what is

15 claimed.

16 MR. MELCHER:

17 **Q. Did Forsheo do whole-exome sequencing or**

18 **whole-genome sequencing of a tumor sample?**

19 A. Do you have Forsheo I could review?

20 **Q. I don't know if I do, actually.**

21 MS. CORK: Calls for speculation.

22 MR. MELCHER:

23 **Q. All right. We'll come back to that.**

24 **So what about the method of Claim 1 enables**

25 **the method to be practiced having a read depth of**

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1 **50,000?**

2 MS. CORK: Objection. Vague. Calls for

3 speculation. To the extent it exceeds the scope of

4 his report.

5 THE WITNESS: I haven't provided any

6 opinions on enablement in my reply declaration. I

7 may in the future, but I haven't done so to date.

8 MR. MELCHER:

9 **Q. Okay. So earlier you said:**

10 **"Well, I'm reading from the**

11 **specification. But to get to the claim**

12 **that can be practiced having a read**

13 **depth of 50,000, the patent does explain**

14 **in great detail a lot of analytical**

15 **methods that allow you to have at least**

16 **50,000 per target locus."**

17 **So I'm asking about that answer -- about**

18 **what allows the claims to be practiced having a read**

19 **depth of 50,000.**

20 MS. CORK: Vague to the extent it

21 mischaracterizes prior testimony and the scope of

22 his report. And compound.

23 THE WITNESS: So I was answering a question

24 that you asked, and I'm trying to remember what

25 paragraph we were talking about.

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1 But it was a block quote from the '454

2 specification where it pointed out improved

3 bioassays and improved analytical assays. And I was

4 making comments based on what was in that block

5 quote as how it pertained to the claim.

6 MR. MELCHER:

7 **Q. Okay. So you are pointing to the block**

8 **quote in the specification, not to the words in the**

9 **claim itself, correct?**

10 (Reporter clarification.)

11 A. I don't understand the question because

12 that's not what you were asking me, and that's not

13 how I answered the question. You were asking -- and

14 I think I'm looking at paragraph 210.

15 In the block quote, how did that pertain to

16 the claimed invention? And I was just describing in

17 the block quote what was innovative is -- are these

18 improved methods, improved analytical methods,

19 improved bioassay methods, improved methods that use

20 a combination of improved analytical and bio.

21 So I was just saying what was described in

22 the block quote and where I thought it appeared in

23 the claim. That was the extent of my answer.

24 **Q. Okay. Let's turn to Exhibit 1, paragraph**

25 **217.**

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1 A. Okay. I'm there, and I'll just take a
2 moment to read through it.
3 Okay. I have reviewed paragraph 217 in my
4 reply declaration.
5 **Q. Okay. So here you state:**
6 "Notably, when performed in
7 combination as recited in the asserted
8 claims of the '035 patent, the claim
9 techniques permit identification of 2 to
10 2,000 SNPs associated with cancer using
11 cfDNA" -- excuse me -- "a DNA source
12 that the art recognizes highly
13 challenging to manipulate successfully."
14 **Do you see that?** www.LexitasLegal.com/Premier Lexitas
15 A. I do, but I think you have the range wrong.
16 It's 25 to 2,000 SNPs.
17 **Q. That's right. Thank you.**
18 **What about the claimed techniques --**
19 **(Reporter clarification.)**
20 **Q. What about the claimed techniques permit**
21 **identification of 25 to 2,000 SNPs associated with**
22 **cancer using cfDNA?**
23 MS. CORK: Objection to the extent it
24 exceeds the scope of his report.
25 THE WITNESS: Sorry. I'm actually looking

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1 at paragraph 216 first because I'm referencing
2 combination. And it's based on the prior paragraph
3 of -- talking about an inventive combination of
4 specific laboratory techniques and therefore. So
5 I'm just taking a moment to review that first.
6 Okay. Could you repeat the question, please.
7 MR. MELCHER:
8 **Q. Sure. What about the claimed techniques**
9 **permit identification of 25 to 2,000 SNPs associated**
10 **with cancer using cfDNA?**
11 MS. CORK: Same objections.
12 THE WITNESS: Well, I'm talking about the
13 combination of the techniques in their order
14 provide -- it's an inventive combination of specific
15 laboratory techniques.
16 So the combination of techniques -- I'm
17 looking at Claim 1 of the '035 patent -- is tagging
18 isolated cell-free DNA with one or more universal
19 tail adapters to generate tailed -- tagged products
20 and so forth.
21 So those -- all of those techniques that
22 are described in the claim in -- in this combination
23 are -- is what is innovative.
24 MR. MELCHER:
25 **Q. Okay. I didn't ask what was innovative,**

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1 **though. I asked what about the claimed techniques**
2 **permit innovation of 2 to 2,000 SNPs associated with**
3 **cancer using cfDNA?**
4 MS. CORK: Same objection. And vague.
5 THE WITNESS: Well, maybe I used
6 "innovative" versus the way you framed it in
7 amplifying 25 to 2,000. But I would come back to
8 the same point.
9 It's the combination of these specific
10 laboratory techniques that create this useful method
11 for generating useful data that employ 25 to 2,000
12 loci associated with cancer.
13 MR. MELCHER:
14 **Q. So you can't point to anything in**
15 **particular? It's just whole claim?**
16 MS. CORK: Objection. Mischaracterizes his
17 report. And to the extent it misstates his
18 testimony. And argumentative.
19 THE WITNESS: I'm happy to do that. So the
20 first step is "tagging isolated cell-free DNA with
21 one or more universal tail adapters to generate
22 tagged products."
23 And then I would go on: "Wherein the
24 isolated" -- "cell-free DNA is isolated from blood
25 sample collected from a subject who is not a

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1 pregnant woman."
2 The second step is "then amplifying those
3 tagged products one or more times to generate a
4 final amplification product, wherein one of the
5 amplification steps comprises targeted amplification
6 of a plurality of single nucleotides polymorphisms
7 (SNP) loci in a single reaction volume, wherein one
8 of the amplifying steps introduce a barcode in one
9 or more sequencing tags."
10 And then the last step in this combination
11 of ordered specific techniques: "Sequencing the
12 plurality of SNP loci on the cell-free DNA by
13 conducting massively parallel sequencing on the
14 final amplification products wherein the plurality
15 of SNIP loci comprises 2 to" -- I'm sorry -- "25 to
16 2,000 loci associated with the cancer."
17 Those are all the specific laboratory
18 techniques in this combination that make it
19 inventive to characterize 25 to 2,000 loci
20 associated with cancer.
21 MR. MELCHER:
22 **Q. Let's turn to -- excuse me.**
23 **Let's turn to Exhibit 1, paragraph 229.**
24 A. Did you say 229?
25 **Q. Yes.**

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1 A. Okay. If I could have a moment to review
2 that. Okay. I have reviewed 229.
3 Q. Okay. So near the end of this paragraph,
4 you state:
5 "In overcoming these technical
6 challenges, the '035 patent teaches that
7 its methods can be used to prepare small
8 amounts of cancer-associated cfDNA,
9 which are challenging to manipulate, for
10 example, because they are fragmented."
11 Do you see that?
12 A. I see that.
13 Q. What about the claimed methods of the '035
14 patent enable these methods to be used to prepare
15 small amounts of cancer-associated cfDNA?
16 MS. CORK: Objection to the extent it
17 exceeds the scope of his report.
18 THE WITNESS: Well, first, the block quote
19 that I'm providing from the specification teaches:
20 "Primer tails may improve the
21 detection of fragmented DNA from
22 universally tagged libraries. If the
23 library tag in the primer tails contain
24 a homologous sequence, hybridization can
25 be improved.

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1 "(For example, melting temperature
2 is lowered.) And primers can be
3 extended if only a portion of the primer
4 target sequence is in the sample DNA
5 fragment."
6 So if you go now to Claim 1 of the '035
7 patent, Step 1 is tagging isolated cell-free DNA
8 with one or more universal tail adapters to generate
9 these tag products.
10 And so the specification is teaching you
11 how to work with small amounts of cancer-associated
12 cfDNA that are fragmented. And this tagging step is
13 one step that is important to improve the method.
14 And then the second step is the --
15 amplifying the tagged products. At the wherein
16 clause, it introduces homologous sequencing, such as
17 barcodes or sequencing tags.
18 So -- so the specification is teaching you
19 the improved method. And that appears in Claim 1 of
20 the '035 patent.
21 MR. MELCHER:
22 Q. So the entirety of this improved method
23 that's described in this specification is also
24 reproduced in the claims?
25 MS. CORK: Objection. Misstates testimony.

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1 THE WITNESS: I didn't say that. The block
2 quote here really deals specifically with tagging
3 and using homologous sequencing.
4 In the claim method, there's also a
5 targeted amplification that this block quote doesn't
6 address. It probably -- it does appear in other
7 places in the specification.
8 So it's just giving an example of how the
9 methods can be improved by tagging and using
10 homologous sequences, but there are other
11 improvements to the method that appear in Claim 1 of
12 the '035 patent.
13 MR. MELCHER:
14 Q. So where does Claim 1 discuss the use of
15 the homologous sequences?
16 MS. CORK: Objection to the extent it
17 exceeds the scope of his report.
18 THE WITNESS: If you look at Step 1A, which
19 is the tagging isolated cell-free DNA with one or
20 more universal tail adapters, those universal tail
21 adapters are analogous to homologous sequences.
22 MR. MELCHER:
23 Q. And is it your testimony that before the
24 '035 patent, no one had ever thought to tag isolated
25 cell-free DNA with universal tail adapters?

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1 MS. CORK: Objection. Mischaracterizes
2 testimony and his report.
3 THE WITNESS: I'm not sure if I talked
4 about that or not, and I don't dispute that
5 individually that step may be in the prior art.
6 I think the point that I'm making here is
7 it's really the combination of these specific
8 laboratory techniques that create this new and
9 useful method for identifying tumor-specific SNVs in
10 cell-free DNA from cancer patients.
11 MR. MELCHER:
12 Q. Okay. Let's look at paragraph 230 of
13 Exhibit 1.
14 A. That's easy. It's the next paragraph.
15 Q. Trying to make it easy for you.
16 A. Okay. I have reviewed paragraph 230 in my
17 reply declaration.
18 Q. Okay. So here you state:
19 "Second, the specific claimed
20 approach recited in the asserted claims
21 of the '035 patent also represents an
22 improvement over prior art techniques
23 because amplifying multiple target loci
24 together, when done successfully, as the
25 '035 patent describes, is efficient and

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1 provides more comprehensive genetic 2 information amplifying only one or a few 3 targets." Do you see that? 4 A. I do see that. 5 Q. So what about the claims of the '035 patent 6 enable amplification of multiple target loci 7 together? 8 MS. CORK: Objection to the extent it 9 exceeds the scope of his report. 10 THE WITNESS: So paragraph 130 now is 11 really talking about the ability to multiplex 12 targeted loci compared to prior art approaches that 13 only did one or a few targets in a reaction. 14 So in the claimed method, this comes into 15 the amplifying the tagged products step where -- and 16 it's that first wherein clause: 17 "One of the amplification steps 18 comprises targeted amplification of a 19 plurality of single nucleotide 20 polymorphisms (SNP) loci in a single 21 reaction volume." 22 So that's specifically what it's telling 23 you there and the improvements and the reasons why 24 there's advantages of doing it that way. And what 25 it does -- it allows a plurality of SNP loci to be	1 MR. MELCHER: 2 Q. Sure. Is it your understanding that a 3 typographical error can form the basis for written 4 description? 5 MS. CORK: Same objection. 6 THE WITNESS: I guess it would depend on 7 the context in which the alleged typographical error 8 appeared in relation to other descriptions in the 9 specification. 10 So I don't know if I can answer that in 11 isolation. I guess I would consider -- because, as 12 I understand it, an inquiry into written description 13 is to look at the four corners of the -- of the 14 patent itself. 15 So I don't know if I could just answer that 16 question in isolation without considering everything 17 else within the specification -- four corners of the 18 specification. 19 MR. MELCHER: 20 Q. So if there was a drafting error in the 21 patent and a word appeared that shouldn't have been 22 there, could that word provide the basis for that 23 description? 24 MS. CORK: Same objection. Lacks 25 foundation.
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1 characterized between 25 and 2,000 loci associated 2 with cancer. 3 MR. MELCHER: 4 Q. Let's turn to paragraph 236 of Exhibit 1. 5 A. Okay. I have reviewed paragraph 236 in my 6 reply declaration. 7 Q. Okay. So it's in the second sentence here. 8 You state: 9 "It is my understanding from counsel 10 that the adequacy of a patent's written 11 description is determined based on the 12 written description within the four 13 corners of the patent and from the 14 perspective of one of ordinary skill in 15 the art." Do you see that? 16 A. I see that. 17 Q. Is it your understanding that a 18 typographical error can provide the basis for 19 written description? 20 MS. CORK: Objection to the extent it 21 exceeds the scope of his report. And calls for 22 speculation. 23 (Reporter clarification.) 24 THE WITNESS: After all of that, can you 25 please repeat the question.	1 THE WITNESS: Well, the word -- 2 MS. CORK: Incomplete hypothetical. 3 THE WITNESS: As I'm understanding your 4 question, I mean, the word appears. It could be 5 debated whether it's a typographical error or not, 6 but I think in this situation -- and we're -- I 7 think we're talking about whole-genome sequencing. 8 I pointed to plenty other disclosures 9 within the specification that even if it was a 10 typographical error, whole-genome sequencing is well 11 described in the specification of the '454 patent. 12 MR. MELCHER: 13 Q. But if it was a typographical error, could 14 that alone form the basis for a description under 15 your understanding of the law? 16 MS. CORK: Same objections. 17 THE WITNESS: Well, I guess I haven't 18 opined on the law as it pertains to a typographical 19 error, so I wouldn't be able to give you an answer 20 to that. But I have read the specification. 21 It's unclear whether it is or isn't a 22 typographical error. But even if it was, there's 23 other places that I point to in the specification 24 that adequately describe whole-genome sequencing. 25 ///

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1 MR. MELCHER:

2 Q. Would a POSA have been able to modify a

3 protocol for whole-genome sequencing to create a

4 protocol for whole-exome sequencing?

5 MS. CORK: Objection to the extent it

6 exceeds the scope of his report. Calls for

7 speculation. Vague.

8 THE WITNESS: It's unclear whether they

9 would modify a protocol, but a person of ordinary

10 skill in the art would understand how to prepare

11 what we call a DNA library that would be composed of

12 only whole-exome sequences that then could be

13 analyzed by a sequencing instrument.

14 MR. MELCHER: www.LexitasLegal.com/Premier Lexitas

15 Q. Is having a protocol for whole-exome

16 sequencing the same thing as having a protocol for

17 whole-genome sequencing?

18 MS. CORK: Same objections.

19 THE WITNESS: In part, yes, and in part,

20 no.

21 MR. MELCHER:

22 Q. Is it possible to do whole-exome sequencing

23 without doing whole genome sequencing?

24 MS. CORK: Same objections.

25 THE WITNESS: Yes, it is possible to do

Page 143

1 whole-exome sequencing without doing whole-genome

2 sequencing.

3 MR. MELCHER:

4 Q. Is it possible to do phasing without doing

5 whole-genome sequencing?

6 MS. CORK: Same objections.

7 THE WITNESS: In my opinion, no.

8 MR. MELCHER:

9 Q. Is it possible to sequence long stretches

10 of DNA on the same chromosome without sequencing an

11 entire genome?

12 MS. CORK: Same objections.

13 THE WITNESS: It is possible. There are

14 techniques that capture either a whole chromosome or

15 parts of a chromosome which could then be sequenced

16 that would not be whole-genome sequencing. But

17 whole genome sequencing is one of the main methods

18 that are used for phasing the genome.

19 MR. MELCHER:

20 Q. Is it possible to do whole-genome

21 sequencing without doing phasing?

22 MS. CORK: Same objection.

23 THE WITNESS: Yes, it is definitely

24 possible. And I actually write about that in my

25 2010 report -- or review.

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1 MR. MELCHER:

2 Q. Is it possible to employ Illumina's

3 molecular technology without performing whole-genome

4 sequencing?

5 MS. CORK: Same objection.

6 THE WITNESS: In what context?

7 MR. MELCHER:

8 Q. Any context.

9 A. -- would you do that?

10 Well, I think it's context specific. I

11 think for human genomes, you wouldn't want to do

12 that. For environmental samples, I guess that would

13 be metagenomics. Whether that constitutes whole

14 genome or not, I'm not sure. So I think it does

15 depend on the context.

16 Q. So you said for human genomes, you wouldn't

17 want to do that. But could you do it is the

18 question.

19 MS. CORK: Same objection.

20 THE WITNESS: Not unless you introduced

21 another step into the workflow. So the molecular

22 technology fragments large pieces of DNA and then

23 aliquots them into different reaction containers and

24 then barcodes them and then sequences those

25 fragments and recreates these long reads.

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1 You would actually have to manipulate the

2 starting material to select for different regions

3 that excluded other parts of the genome. But I

4 haven't seen where the molecular technologies have

5 been used in that way.

6 MR. MELCHER:

7 Q. Is it possible to do long-read sequencing

8 without doing whole-genome sequencing?

9 MS. CORK: Same objection.

10 THE WITNESS: Using the molecular

11 technology? I just explained that.

12 MR. MELCHER:

13 Q. Just any type of long-read sequencing.

14 A. Can you give me an example of what you are

15 thinking as long-read sequencing.

16 Q. Can you give me an example of long-read

17 sequencing other than Illumina's molecular

18 technology?

19 A. There's several single-molecule techniques

20 out there, such as PacBio and Oxford Nanopore. They

21 can do both targeted and whole-genome sequencing.

22 Those platforms can do both techniques.

23 Q. And those are long-read sequencing

24 technologies?

25 A. They are.

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1 Q. Does avoiding allelic bias reduce the 2 number of primer dimers? 3 MS. CORK: Objection to the extent it 4 exceeds the scope of his report. Calls for 5 speculation. 6 THE WITNESS: We have changed gears here. 7 I know I write about both of those in my report. If 8 I can have a moment, I can try and find where I 9 write about that. 10 MR. MELCHER: 11 Q. You might check paragraph 253. 12 A. Okay. Can you -- I reviewed paragraph 253 13 of my reply declaration. Can you repeat the 14 question. 15 Q. Yeah. I'll just point out in the -- so at 16 the beginning -- excuse me. Page 142, in the same 17 paragraph, you write: 18 "The '035 patent also teaches other 19 different methods of improving the 20 quality of amplification results -- for 21 example, by avoiding allelic bias." 22 Do you see that? 23 A. I do see that. 24 Q. Does avoiding allelic bias reduce the 25 number of primer dimers?	1 A. Yes. I actually provide two block quotes. 2 Q. And according to these two block quotes, 3 the maximum allowable amount of primer dimer is 4 60 percent. Is that correct? 5 MS. CORK: Objection to the extent it 6 misstates the report, the patents cited in the 7 report, his testimony. 8 THE WITNESS: I don't think -- I don't 9 think these block quotes are providing a maximum 10 here. I mean, the first block quote starts "In 11 various embodiments." Less than 60 percent. So I 12 think in some examples, these are the ranges that 13 you could expect. 14 In the second block quote, it says "In some 15 embodiments." So, again, I think it's just 16 providing some examples. But I don't think there's 17 any limitation here at all in what's being described 18 in the specification. 19 MR. MELCHER: 20 Q. Is there an amount of primer dimers such 21 that the claimed methods would not function? 22 MS. CORK: Objection to the extent it 23 exceeds the scope of his report. Calls for 24 speculation. 25 THE WITNESS: I'm not sure I have provided
Page 147	Page 149
1 MS. CORK: Objection to the extent it 2 exceeds the scope of his report. Calls for 3 speculation. 4 THE WITNESS: Yeah. I think the patent is 5 treating them as different methods, and that's 6 exactly the sentence that you read. So I don't see 7 where one is necessarily connected to the other, at 8 least in the parts that you have read. 9 MR. MELCHER: 10 Q. I just mean in general. Is -- is a method 11 of reducing allelic bias going to also reduce primer 12 dimers? 13 MS. CORK: Same objections. 14 THE WITNESS: I haven't thought about that. 15 I actually don't know. I somewhat treated them the 16 way the patent treats them, as separate problems. 17 MR. MELCHER: 18 Q. And then to -- turn to paragraph 254. 19 A. Yes. I'm going to just read it. 20 Okay. I have reviewed paragraph 254 of my 21 reply declaration. 22 Q. Okay. So here in paragraph 254, you write: 23 "The Natera patents, therefore, contemplate that 24 primer dimers can be present at some level." And 25 then you provide a block quote. Do you see that?	1 an opinion of how much primer dimer would make the 2 claim not useful, but I -- I do think, because of 3 next-generation sequencing, you could have -- you 4 could have -- you may not want. 5 But you could have a substantial amount of 6 primer dimer and still be able to get enough 7 sequence information of 25 to 2,000 loci to practice 8 the claim. 9 MR. MELCHER: 10 Q. What would be the substantial amount to 11 primer dimer you mentioned as a percentage? 12 MS. CORK: Same objections. 13 THE WITNESS: Oh, I -- I'm not in a 14 position to put a number on it, but it could be -- 15 it could be over 60 percent. It could be. 16 I don't -- but I don't know exactly what's 17 the limit where you would cross over to this 18 threshold of no longer providing useful information 19 regarding the 25 to 2,000 loci in the claimed 20 method. 21 MR. MELCHER: 22 Q. But there is a threshold, though, correct? 23 MS. CORK: Same objections. 24 THE WITNESS: Well, I guess in the extreme 25 case, if you had 100 percent primer dimer and you

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1 had no amplicons that targeted any of the loci, 2 well, I guess that would be a threshold. 3 Because of the amount of information that's 4 produced by next-generation sequencing, even just 5 the small fraction of loci that met the claim 6 language would still produce useful information. 7 MR. MELCHER: So I'm going to mark as 8 Exhibit 10 declaration of Dr. Brian Van Ness in 9 support of NeoGenomics' Laboratories, Inc.'s 10 response in opposition to Natera, Inc.'s motion for 11 preliminary injunction. 12 (Exhibit 10 was marked for identification.) 13 Q. Okay. I -- were you going to take a 14 minute, or are you good? 15 A. I have reviewed -- 16 Q. Oh, perfect. 17 A. -- this declaration. 18 Q. Okay. 19 A. So I don't know where you wanted me to go. 20 Q. Okay. Thank you. If we could take a look 21 at paragraph 112, please. 22 A. Okay. I have reviewed paragraph 112 in the 23 Van Ness responsive declaration. 24 Q. Okay. And this is -- if you turn, this is 25 page 46. If you turn to page 44, this is under the	1 A. Well, I would have to look in my reply 2 report to address that. 3 Q. So you don't remember whether you 4 identified this as an inconsistency or not? 5 MS. CORK: Objection to the extent this 6 line of questioning mischaracterizes his report or 7 testimony. 8 THE WITNESS: Sitting here right now, my 9 reply report is 170 pages. So specifically as -- 10 did I remember whether this was an inconsistency or 11 not, I don't know. 12 It's not a memory test. But what I was 13 asking -- if I had Forshaw in front of me, I could 14 confirm or refute whether Dr. Van Ness is correct or 15 not. 16 MR. MELCHER: 17 Q. But you have no reason to specifically 18 doubt this sentence, correct? 19 MS. CORK: Same objection. 20 THE WITNESS: Well, I see what it says. 21 MR. MELCHER: 22 Q. Isn't it your opinion that NeoGenomics' 23 TAm-Seq test infringes the '454 patent? 24 A. I don't think that's correct. I think my 25 opinion is RaDaR infringes the '454 patent. And
Page 151	Page 153
1 header overview of Forshaw 2012, correct? This 2 paragraph 112, right? 3 A. I see that. 4 Q. And here Dr. Van Ness states in the second 5 sentence of paragraph 112: 6 "At a high level, TAm-Seq 7 accomplishes this by performing 8 whole-genome sequencing of both healthy 9 and tumor tissue and then comparing the 10 sequence data to identify tumor-specific 11 mutations -- in particular, SNVs." 12 Do you see that? 13 A. I see that. 14 Q. Do you have any reason to think 15 Dr. Van Ness was incorrect when he wrote that 16 sentence? 17 MS. CORK: Objection. Speculation. 18 THE WITNESS: I would actually compare it 19 to the Forshaw reference to be able to answer that 20 question. I -- I have found inconsistencies in his 21 report, so it would be something I would want to 22 verify. 23 MR. MELCHER: 24 Q. But this is not an inconsistency that you 25 previously identified, assuming it is?	1 parts of RaDaR can be found in Forshaw, but not 2 everything is found in Forshaw. 3 Q. So it's your opinion that RaDaR does not 4 use TAm-Seq or eTAm-Seq? 5 MS. CORK: Objection to the extent it 6 mischaracterizes his prior testimony or his reports. 7 THE WITNESS: I didn't say that at all. 8 What I said was my opinion is RaDaR infringes the 9 '454 patent, and RaDaR uses some of Forshaw but not 10 everything in Forshaw. 11 MR. MELCHER: 12 Q. Does it use TAm-Seq or eTAm-Seq? 13 MS. CORK: Objection to the extent it 14 mischaracterizes his prior testimony. Exceeds the 15 scope of his reports. Calls for speculation. 16 THE WITNESS: Forshaw does not describe 17 eTAm-Seq. ETAm-Seq came after the Forshaw 18 reference. Forshaw teaches TAm-Seq. 19 MR. MELCHER: 20 Q. Okay. That was not my question at all. My 21 question is does RaDaR use TAm-Seq or eTAm-Seq. My 22 question did not include the word "Forshaw." 23 MS. CORK: Objection. 24 THE WITNESS: So parts of TAm-Seq can be 25 found in eTAm-Seq. There were parts that were taken

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1 out of TAM-Seq to create eTAM-Seq.
 2 Based on the information that I have had --
 3 that I have had the ability to review so far, it's
 4 my opinion that the eTAM-Seq method encompasses what
 5 RaDaR does, but Forshew does not practice eTAM-Seq.
 6 MR. MELCHER:
 7 **Q. But it does practice TAM-Seq?**
 8 A. It does practice TAM-Seq.
 9 **Q. And then the changes between TAM-Seq -- oh,**
 10 **okay. Strike that.**
 11 **And do you have any reason to think that**
 12 **TAM-Seq does not perform whole-genome sequencing of**
 13 **tumor tissue?**
 14 MS. CORK: Objection. Vague.
 15 THE WITNESS: My recollection is it did
 16 either whole genome or whole exome. I would have to
 17 review Forshew to know which one of those two
 18 methods Forshew did on one cancer patient that had
 19 breast cancer.
 20 MR. MELCHER:
 21 **Q. Okay. And -- okay. If we could turn back**
 22 **to Exhibit 1, please, paragraph 270.**
 23 MS. CORK: We have been going about an
 24 hour. If we could take ten minutes, please.
 25 MR. MELCHER: I think we're about at time,

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1 if we just want to plow through.
 2 MS. CORK: Okay.
 3 THE WITNESS: That's fine with me.
 4 MR. MELCHER: We're getting close, I think.
 5 THE WITNESS: That's fine with me.
 6 MR. MELCHER: Okay.
 7 THE WITNESS: Paragraph 270?
 8 MR. MELCHER:
 9 **Q. Yes.**
 10 A. Okay. If I can have a moment.
 11 Okay. I have read the paragraph 270 of my
 12 reply report.
 13 **Q. Okay. So looks like the last sentence**
 14 **here, you state:**
 15 **"While the amplified products of the**
 16 **targeted PCR reaction are further**
 17 **amplified to add sequencing-related**
 18 **sequences (adapters and barcodes), the**
 19 **same sequence generated by the targeted**
 20 **multiplex reaction (50 to 150 base pairs**
 21 **comprising the target loci) is subjected**
 22 **to sequencing, and sequence reads for**
 23 **that sequence are obtained."**
 24 So the same sequence you refer to here,
 25 that's the same sequence targeted by the PCR

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1 amplification, correct?
 2 MS. CORK: Objection.
 3 THE WITNESS: Well, I think that's what I
 4 state. I say "the same sequence generated by the
 5 targeted multiplex reaction."
 6 MR. MELCHER:
 7 **Q. Okay. Thank you. And then if we could**
 8 **turn to paragraphs 307 and 308 of Exhibit 1.**
 9 A. Okay. I have read those two paragraphs in
 10 my reply declaration.
 11 **Q. Okay. So in the -- paragraph 307, you have**
 12 **this block quote. And there's -- excuse me -- an**
 13 **emphasized line that states:**
 14 **"Each amplicon can be designed to**
 15 **amplify sequences of up to 70 base pair**
 16 **length and is designed to contain one**
 17 **base pair that differs between the tumor**
 18 **and somatic genotypes."**
 19 **So what does "up to 70" mean to you?**
 20 MS. CORK: Objection. Vague. To the
 21 extent it exceeds the scope of his report.
 22 THE WITNESS: Well, just reading this block
 23 quote without any other context of this document,
 24 which is an internal Natera document -- if I were
 25 just to interpret this in isolation, up to 70 would

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1 basically be a minimum of 70 base pair length.
 2 MR. MELCHER:
 3 **Q. Up to 70 is a minimum?**
 4 A. Oh, I'm sorry. No. Up to 70 base pair
 5 would be the -- the higher end -- sorry --
 6 **Q. Okay.**
 7 A. -- of the -- the length of the amplicon.
 8 **Q. Long day, I guess.**
 9 A. Yeah.
 10 **Q. About lunchtime.**
 11 **So up to 70 would include 40?**
 12 MS. CORK: Objection to the extent it
 13 exceeds the scope of his report. Calls for
 14 speculation. Lacks foundation.
 15 THE WITNESS: Well, again, so I would have
 16 to -- I'm sure the document has other descriptions
 17 that probably provide the lower end. I mean, in
 18 this block quote, it doesn't have a lower end.
 19 But I think in designing these amplicons
 20 for targeting, you would want to keep it at least
 21 above 50 because the sequencers in general can
 22 sequence 50 bases, 100 bases.
 23 And so not matching the amplicon link with
 24 the performance of the sequencer would be kind of a
 25 waste of performance and resources of the NGS

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1 machine.

2 MR. MELCHER:

3 Q. Okay.

4 A. So I think there's a practical lower limit,

5 I guess is what I'm trying to say, in designing

6 these targeted multiplex PCR loci.

7 Q. Okay. But there's no lower limit described

8 in this block quote, correct?

9 MS. CORK: Objection to the extent it

10 exceeds the scope of his report. Lacks foundation.

11 Mischaracterizes his testimony.

12 THE WITNESS: Yeah. I mean, just in this

13 block quote alone in isolation, I -- I don't see a

14 lower limit, but it is taken from a larger document.

15 And that may actually provide the lower limit. It's

16 just -- I didn't provide it here.

17 MR. MELCHER: Okay. I have no further

18 questions.

19 MS. CORK: All right. Let me check my

20 notes, and I may have some questions for

21 Dr. Metzker. If we could take a ten-minute break.

22 MR. MELCHER: Sure.

23 (Reporter clarification.)

24 THE VIDEOGRAPHER: We are off the record,

25 12:10 p.m.

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1 (Break taken.)

2 THE VIDEOGRAPHER: And we are back on the

3 record at 12:55.

4 EXAMINATION BY MS. CORK

5 MS. CORK:

6 Q. Welcome back, Dr. Metzker.

7 A. Thank you.

8 Q. In your deposition, counsel for NeoGenomics

9 asked you about legal standards relating to the

10 Section 101 patent-eligibility analysis. Do you

11 recall that?

12 A. Yes, I do.

13 Q. In particular, counsel asked you about

14 paragraphs four to six of your declaration and your

15 legal standards section regarding whether the

16 "directed to" analysis involves human effort and

17 intervention. Do you recall that?

18 A. Yes, I do.

19 Q. Can I ask you to go to Exhibit 1, please,

20 your reply declaration.

21 A. Yes. I have that.

22 Q. Can I ask you to go to page 18. And let me

23 know --

24 A. Yes. I'm there.

25 Q. And under the heading -- Roman numeral III,

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1 there's a header "Summary of Opinions." Do you see

2 that?

3 A. Yes, I do.

4 Q. Next page, page 19, there's a subheader for

5 opinions relating to validity. Do you see that?

6 A. I do.

7 Q. And in paragraph 30, in that -- your

8 validity opinions, you state:

9 "The claims are directed to

10 patent-eligible subject matter (methods

11 of sample preparation) and recite

12 specific concrete laboratory steps which

13 generate DNA sequences not found in

14 nature and which require human effort to

15 perform." Do you see that?

16 A. I see that.

17 Q. In this paragraph of your report, you

18 discuss the use of human effort to perform the

19 methods claimed in the Natera patents, true?

20 MR. MELCHER: Objection to form.

21 THE WITNESS: Yes. I do see that in

22 paragraph 30 of my reply declaration.

23 MS. CORK:

24 Q. Did counsel for NeoGenomics point you to

25 this paragraph of your declaration when he was

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1 asking you about the aspect of your

2 patent-eligibility analysis involving what the

3 Natera patent claims are directed to?

4 MR. MELCHER: Objection. Form.

5 THE WITNESS: I don't recall being directed

6 to paragraph 30 of my reply declaration.

7 MS. CORK:

8 Q. Let's go to page 104 of Exhibit 1.

9 A. Sorry. Page 104?

10 Q. Page 104.

11 A. Yes. I'm there.

12 Q. At the top of page 140, it says, under the

13 Heading A: "The '454 patent claims are patent

14 eligible."

15 And then under that is the subheader: "The

16 '454 patent claims are directed to patent-eligible

17 subject matter." Do you see that?

18 A. I do see that.

19 Q. In this section, do you see paragraph 191?

20 A. I do.

21 Q. Paragraph 191 of your reply report,

22 Exhibit 1, states:

23 "In my opinion, the asserted claims

24 of the '454 patent are directed not to a

25 natural phenomenon but rather to an

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1 inventive combination of specific
2 laboratory techniques, each of which
3 requires significant human effort to
4 perform." Do you see that?
5 MR. MELCHER: Objection to form.
6 THE WITNESS: I do see that.
7 MS. CORK:
8 Q. Same section of your declaration at page --
9 sorry -- paragraph 194. Are you there?
10 A. Yes, I'm there.
11 Q. Okay. Paragraph 194 refers to the use of
12 whole-genome sequencing and whole-exome sequencing,
13 as recited in the asserted claims of the '454
14 patent. Do you agree? www.LexitasLegal.com/Premier Lexitas
15 MR. MELCHER: Objection to form.
16 THE WITNESS: I do see that.
17 MS. CORK:
18 Q. Paragraph 194 of Exhibit 1 states: "Both
19 techniques require significant human effort and
20 intervention to achieve." Do you see that?
21 MR. MELCHER: Objection to form.
22 THE WITNESS: I do see that.
23 MS. CORK: Counsel, what is the basis of
24 your form objection?
25 MR. MELCHER: Basis? Objection to form.

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1 MS. CORK: In what way?
2 I'll assume counsel for NeoGenomics is not
3 answering my question as he's been silent for about
4 30 seconds.
5 (Reporter clarification.)
6 (Reporter admonition.)
7 MR. MELCHER: I was reviewing the document
8 in order to answer your question. If you prefer I
9 not answer, we can proceed.
10 MS. CORK: No. Please.
11 MR. MELCHER: Okay. I'll continue
12 reviewing the document.
13 MS. CORK: Okay. All right. I'll withdraw
14 my question to counsel. It's not clear it is being
15 answered.
16 Q. All right. Dr. Metzker, could you go to
17 paragraph 196 of your declaration -- sorry -- 198 of
18 your reply declaration, Exhibit 1.
19 A. Yes. I'm there.
20 Q. Do you see where it says that "The asserted
21 claims of the '454 patent additionally recite a
22 specific protocol for amplifying cfDNA"?
23 And you go onto state that "This step
24 requires one of skill in the art to perform at least
25 five specific activities, each of which requires

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1 significant human effort to design and implement."
2 MR. MELCHER: Objection to form.
3 THE WITNESS: I do see that.
4 MS. CORK:
5 Q. And in the next paragraph, paragraph 199,
6 you state that "Notably, targeted amplification in
7 one reaction volume is one way to amplify DNA (using
8 human effort) but not the only way, as Dr. Van Ness
9 acknowledged in his deposition." Do you see that?
10 MR. MELCHER: Objection to form.
11 THE WITNESS: Yes, I do see that.
12 MS. CORK:
13 Q. In each of these paragraphs of your reply
14 report that I have just reviewed, you discuss the
15 use of human intervention and effort to perform the
16 methods claimed in the '454 patent, true?
17 MR. MELCHER: Objection to form.
18 THE WITNESS: That is correct.
19 MS. CORK:
20 Q. Did you consider human intervention and
21 effort as part of forming your opinions of what the
22 '454 patent claims are directed to?
23 MR. MELCHER: Objection to form.
24 THE WITNESS: Yes, I did.
25 ///

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1 MS. CORK:
2 Q. Did counsel for NeoGenomics point you to
3 these paragraphs of your declaration when he was
4 asking you about what the Natera patent claims are
5 directed to?
6 MR. MELCHER: Objection to form. Beyond
7 the scope.
8 THE WITNESS: I do not believe he pointed
9 me to these paragraphs.
10 MS. CORK:
11 Q. Would you please go to page 118 of your
12 declaration -- reply declaration, Exhibit 1.
13 A. Yes. I'm there.
14 Q. Do you see the header that says "The '035
15 patent is patent eligible" and then the subheader
16 "The '035 patent claims are directed to
17 patent-eligible subject matter"?
18 A. I do.
19 Q. And in that section a few paragraphs down,
20 at paragraph 216, you state:
21 "In my opinion, the asserted claims
22 of the '035 patent are directed not to a
23 natural phenomenon but rather to an
24 inventive combination of specific
25 laboratory techniques, each of which

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1 requires significant human effort to
2 perform and which involve modifying
3 natural occurring products as part of
4 the process."
5 MR. MELCHER: Objection to form. Beyond
6 the scope.
7 MS. CORK:
8 Q. Do you see that?
9 A. I do see that.
10 Q. We jump a couple paragraphs down in the
11 same section, paragraph 219, you state that the
12 first recited step -- first, let me ask you: Are
13 you there?
14 A. Yes, I'm there. I'm sorry.
15 Q. And in paragraph 219 of Exhibit 1, you
16 state that:
17 "The first recited step of the
18 asserted claims of the '035 patent
19 requires performing two different steps,
20 each of which depends upon human
21 intervention and effort."
22 Do you see that?
23 MR. MELCHER: Objection to form. Beyond
24 the scope.
25 THE WITNESS: Yes, I do.

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1 MS. CORK:
2 Q. In the next paragraph in the same section,
3 paragraph 220, you state that:
4 "The asserted claims of the '035
5 patent recite a specific protocol for
6 amplifying cfDNA. This step requires
7 specific technical approaches, each of
8 which require significant human effort
9 to design and implement."
10 Do you see that?
11 MR. MELCHER: Objection to form. Beyond
12 the scope.
13 THE WITNESS: Yes, I do.
14 MS. CORK:
15 Q. In the very next paragraph in the same
16 section, paragraph 221, you state:
17 "The asserted claims of the '035
18 patent recite sequencing the plurality
19 of SNIP, loci, and cfDNA by conducting
20 massively parallel sequencing on the
21 final amplification products.
22 "Like the other recited preparation
23 steps, the massively parallel sequencing
24 step requires significant human effort
25 to implement and does not occur in

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1 nature." Do you see that?
2 MR. MELCHER: Objection to form. Beyond
3 the scope.
4 THE WITNESS: Yes, I do.
5 MS. CORK:
6 Q. In each of these paragraphs of your reply
7 report that I've just read, you discuss the use of
8 human effort and intervention to perform the methods
9 claimed in the '035 patent, true?
10 A. That is correct.
11 Q. Did you consider human intervention and
12 effort as part of forming your opinions of what the
13 '035 patent claims are directed to?
14 MR. MELCHER: Objection to form. Beyond
15 the scope.
16 THE WITNESS: Yes, I did.
17 MS. CORK:
18 Q. Did counsel for NeoGenomics point you to
19 these paragraphs --
20 (Reporter clarification.)
21 (Reporter admonition.)
22 Q. Did counsel for NeoGenomics point you to
23 these paragraphs of your declaration when he was
24 asking you about what the Natera patent claims are
25 directed to?

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1 MR. MELCHER: Objection to form. Beyond
2 the scope.
3 THE WITNESS: No, I do not recall
4 Mr. Melcher pointing me to these paragraphs.
5 MS. CORK:
6 Q. Do you recall counsel for NeoGenomics
7 asking you about Exhibit 8, a paper by Glenn?
8 MR. MELCHER: Objection to form.
9 THE WITNESS: Yes, I do.
10 MS. CORK:
11 Q. Let's go to Exhibit 8, and let me know when
12 you are there.
13 A. Yes. I have Exhibit 8.
14 Q. Do you recall counsel for NeoGenomics
15 asking you about Table 3 of Exhibit 8?
16 A. Yes, I do.
17 Q. Did counsel ask you whether any of the data
18 in Table 3 of Exhibit 8 affect your opinions of
19 whether the '454 patent claims would be obvious over
20 Forshaw?
21 MR. MELCHER: Objection to form.
22 THE WITNESS: No, he did not.
23 MS. CORK:
24 Q. Did counsel ask you whether any of the
25 sequencers listed in Table 3 of Exhibit 8 affect

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1 your opinions of whether the '454 patent claims
2 would be obvious over Forshaw?
3 MR. MELCHER: Objection to form.
4 THE WITNESS: He did not.
5 MS. CORK:
6 Q. Do you recall counsel for NeoGenomics
7 asking you about Exhibit 9, the paper by Kinde,
8 et al.?
9 A. Yes, I do.
10 Q. Can you please go to Exhibit 9.
11 A. I have Exhibit 9.
12 Q. You discuss Exhibit 9 in your analysis of
13 whether the '454 patent claims would be obvious over
14 Forshaw, true?
15 MR. MELCHER: Objection to form.
16 THE WITNESS: I do.
17 MS. CORK:
18 Q. Does your consideration of Exhibit 9 affect
19 your opinions of whether the '454 patent claims
20 would be obvious over Forshaw?
21 MR. MELCHER: Objection to form. And I'll
22 just note for the record that we have been informed
23 that Natera has a hard stop at 1:00 p.m. It is now
24 1:09 p.m.
25 THE WITNESS: Can you repeat the question,

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1 please.
2 MS. CORK:
3 Q. Does your consideration of Exhibit 9 affect
4 your opinions of whether the '454 patent claims
5 would be obvious over Forshaw?
6 MR. MELCHER: Objection to form.
7 THE WITNESS: It does not.
8 MS. CORK:
9 Q. Do any of the references cited in your
10 analysis of Forshaw affect your opinions of whether
11 the '454 patent claims would be obvious over
12 Forshaw?
13 MR. MELCHER: Objection to form.
14 THE WITNESS: They do not.
15 MS. CORK:
16 Q. Did counsel for NeoGenomics ask you whether
17 any of the references cited in your analysis of
18 Forshaw affect your opinions of whether the '454
19 patent claims would be obvious over Forshaw?
20 MR. MELCHER: Objection to form.
21 THE WITNESS: I don't recall being asked
22 those questions.
23 MS. CORK: Nothing further from Natera.
24 MR. MELCHER: Let's see.
25 RE-EXAMINATION BY MR. MELCHER

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1 MR. MELCHER:
2 Q. Let's see. Just a couple questions of
3 recross, I guess.
4 Did you have any discussions with counsel
5 about the substance of your testimony during any of
6 the breaks?
7 A. I did not.
8 MR. MELCHER: No further questions.
9 THE VIDEOGRAPHER: This will conclude
10 today's proceedings in the deposition of Michael
11 Metzker, PhD. We are off the record at 1:10 p.m.
12 (The matter concluded, 1:10 p.m.)
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1 DECLARATION UNDER PENALTY OF PERJURY
2
3 I, MICHAEL METZKER, PhD, do hereby certify
4 under penalty of perjury that I have read the
5 foregoing transcript of my deposition taken on
6 November 14, 2023; that I have made such corrections
7 as appear noted on the Deposition Errata Page,
8 attached hereto, signed by me; that my testimony as
9 contained herein, as corrected, is true and
10 accurate.
11
12 Dated this ____ day of _____,
13 2023.
14
15
16
17 MICHAEL METZKER, PhD
18
19
20
21
22
23
24
25

1 STATE OF CALIFORNIA)
2)
3 COUNTY OF SACRAMENTO)
4 I, TAMMY MOON, CSR No. 13184, Certified
5 Shorthand Reporter, do hereby certify:
6 That prior to being examined, the witness
7 in the foregoing proceedings was by me duly sworn to
8 testify to the truth, the whole truth, and nothing
9 but the truth;
10 That said proceedings were taken by me in
11 shorthand and thereafter transcribed into
12 typewriting under my direction and supervision;
13 That I am neither counsel for, nor related
14 to, any party to said proceedings, nor in any way
15 interested in the outcome thereof.
16 I further certify that I am not a party to
17 any stipulation, if made, that would waive my duties
18 mandated by the Court Reporters Board of California.
19 In witness whereof, I have hereunto
20 subscribed my name.
21 Dated: 15th of November, 2023
22
23
24 Tammy Moon, CSR No. 13184, RDR, CRR
25

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