

VOLUME: I

PAGES: 1 to 113

EXHIBITS: 1 to 4

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.

Petitioner

IPR2022-00817

Patent No. 10,760,127

VS.

UNIVERSITY OF WASHINGTON

Patent Owner

CORRECTED TRANSCRIPT

VIDEOTAPED DEPOSITION OF JOHN

QUACKENBUSH, Ph.D., a witness called on
behalf of the Petitioner, before Jeanette N.
Maracas, Registered Professional Reporter and
Notary Public in and for the Commonwealth of
Massachusetts, at the Offices of Wilson,
Sonsini, Goodrich & Rosati, P.C., One Boston
Place, Boston, Massachusetts, on Monday, May
15, 2023, commencing at 9:04 a.m.

Page 1

1 APPEARANCES:

2
3 WILSON, SONSINI, GOODRICH & ROSATI

By: Jad A. Mills, Esq.

4 701 Fifth Avenue

Seattle, Washington 98104

5 For the Petitioner.

Jmills@wsgr.com

6
7 STERNE, KESSLER, GOLDSTEIN & FOX, PLLC

By: Byron L. Pickard, Esq.

8 By: R. Wilson "Trey" Powers, III, Esq.

1100 New York Avenue, NW

9 Washington, DC 20005

For the Patent Owner.

10 Bpickard@sternekessler.com

Tpowers@sternekessler.com

11
12 Bob Giannini, Videographer.

I N D E X

Testimony of:	Direct	Cross
John Quackenbush, Ph.D		
(by Mr. Pickard)	5	
(by Mr. Mr. Mills)		108

E X H I B I T S

No.	Description	Page
Exhibit 1	Exhibit 20, Declaration of Dr. Quackenbush, TwinStrand vs. Guardiant.	8
Exhibit 2	9/2/22 transcript of videotaped deposition of Dr. Quackenbush.	91
Exhibit 3	12/4/19 Declaration of Dr. Quackenbush.	93
Exhibit 4	4/7/23 Expert Report of Dr. Quackenbush on Invalidity.	100

1 P R O C E E D I N G S 08:46:01

2 VIDEOGRAPHER: Good morning. We 09:03:25

3 are on the record. This is the videographer 09:04:50

4 speaking, Bob Giannini. I'm with the court 09:04:52

5 reporter, Jeanette Maracas, with Veritext. 09:04:55

6 Today's date is May 15, 2023, and the time is 09:04:58

7 9:04 a.m. Eastern Time. We are currently 09:05:01

8 located in the offices of Wilson, Sonsini, 09:05:07

9 Goodrich & Rosati, located at Boston, 09:05:10

10 Massachusetts, to take the video deposition 09:05:12

11 of Dr. John Quackenbush in the matter of 09:05:14

12 Guardant Health versus University of 09:05:17

13 Washington, et al. 09:05:19

14 Will counsel please introduce 09:05:21

15 themselves for the record. 09:05:23

16 MR. PICKARD: On behalf of the 09:05:23

17 patent owner, Byron Pickard and Trey Powers 09:05:25

18 from Sterne Kessler. 09:05:29

19 MR. MILLS: On behalf of the 09:05:31

20 petitioner Guardant Health, Inc., Jad Mills 09:05:32

21 with Wilson Sonsini. 09:05:35

22 JOHN QUACKENBUSH, Ph.D

23 A witness called for examination

24 by counsel for the Petitioner, having been

25 first duly sworn, was examined and testified

1 as follows:

2 DIRECT EXAMINATION

3 BY MR. PICKARD: 09:05:44

4 Q. Good morning, Dr. Quackenbush. 09:05:45

5 A. Good morning. 09:05:48

6 Q. How are you? 09:05:48

7 A. I'm doing well today. 09:05:49

8 Q. Okay. Great. So just some basics. You've 09:05:50

9 been deposed before, correct? 09:05:52

10 A. Yes, I have. 09:05:54

11 Q. So I just have a few sort of baseline 09:05:54

12 principles. I'll ask questions, I'd ask that 09:06:02

13 you allow me to complete the questions and 09:06:04

14 your attorney may or may not have some 09:06:06

15 objections, and if you understand the 09:06:07

16 question, I'd like you to answer to it. If 09:06:10

17 for any reason you don't understand the 09:06:13

18 questions I put to you, will you please let 09:06:14

19 me know? 09:06:14

20 A. I will. 09:06:14

21 Q. Is that fair? 09:06:16

22 A. Yes. 09:06:16

23 Q. And I need you to answer audibly, so head 09:06:16

24 nods and non-verbal responses won't suffice 09:06:19

25 today. Do you understand that? 09:06:21

1 A. I understand that, yes. 09:06:22

2 Q. Okay. And even if your counsel objects, 09:06:23

3 I need you to answer the question unless 09:06:25

4 there's an instruction from him not to 09:06:27

5 provide an answer. Do you understand that? 09:06:31

6 A. I understand that, yes. 09:06:33

7 Q. Is there any reason you can't testify 09:06:33

8 truthfully and accurately today? 09:06:35

9 A. None whatsoever. 09:06:37

10 Q. What, if anything, did you do to prepare 09:06:38

11 for your deposition today? 09:06:41

12 A. I reviewed my rebuttal expert report, I 09:06:42

13 reviewed the report from Dr. Larrea, I 09:06:45

14 reviewed Dr. Satija's report, his deposition 09:06:49

15 transcript. 09:06:54

16 Q. Did you meet with anyone? 09:06:54

17 A. I met with Attorney Mills and Attorney 09:06:56

18 Gerrard from Wilson Sonsini. 09:07:04

19 Q. Anybody else? 09:07:05

20 A. No. 09:07:06

21 Q. All right. Did you see anything during 09:07:07

22 your preparation that refreshed your memory 09:07:09

23 as to anything relevant to this case? 09:07:11

24 A. As I said, I looked at my reports, the other 09:07:14

25 reports, I looked at some of the patents, 09:07:17

1 some of the references, Travers references, 09:07:20
2 other related materials. Things cited in 09:07:24
3 my report are the things I looked at. 09:07:26
4 Q. Did you look at anything that wasn't cited 09:07:28
5 in your rebuttal report in this case? 09:07:30
6 A. To the best of my knowledge, no. 09:07:33
7 Q. You mentioned that you looked at some 09:07:34
8 patents. Were there patents other than the 09:07:37
9 '127 patent that you looked at? 09:07:39
10 A. To the best of my recollection, the '127, 09:07:41
11 there's also the Travers '075 patent 09:07:45
12 application. 09:07:48
13 Q. So just those two? 09:07:49
14 A. To the best of my recollection, yes. 09:07:51
15 Q. Okay. 09:07:52
16 A. Unless there are others that were cited in 09:08:00
17 my report. I don't recall everything that 09:08:00
18 was cited. 09:08:04
19 Q. To the best of your knowledge, all of the 09:08:04
20 documents you looked at were cited in at 09:08:05
21 least one of your reports in this case, 09:08:08
22 correct? 09:08:09
23 A. All of the documents were cited in my 09:08:09
24 rebuttal expert report. 09:08:13
25 MR. PICKARD: Good ahead and mark 09:08:32

Page 8

1 And before I proceed, I'm going to ask 09:12:29
2 for the third time for a copy of my expert 09:12:32
3 report. 09:12:35
4 Q. Your attorney will have an opportunity to 09:12:36
5 do some redirect of you when we're done, so 09:12:39
6 if it's important you look at it, I'm sure 09:12:42
7 he'll show it to you. And I think that's 09:12:44
8 actually the point. We can stipulate that 09:12:45
9 you didn't cite this to the office in any of 09:12:47
10 your reports in this case, okay? 09:12:51
11 A. I would like to check for myself. I'm going 09:12:52
12 to ask for a fourth time for a copy of my 09:12:55
13 expert report. 09:12:57
14 Q. I'd like to draw your -- let me back up. 09:12:58
15 You prepared this report and signed 09:13:03
16 it under oath, correct, this declaration, I 09:13:05
17 should say? 09:13:09
18 A. Yes, but, again, I don't believe this is 09:13:10
19 the topic for our deposition today, and so 09:13:11
20 I'm going to ask for a fifth time for a copy 09:13:14
21 of my expert report. 09:13:17
22 Q. And in preparing and executing the 09:13:19
23 declaration we marked as Quackenbush 1, you 09:13:24
24 did your best to testify as accurately and 09:13:27
25 truthfully, correct? 09:13:30

1 MR. MILLS: Objection to scope. 09:13:31

2 A. Again, this is not the subject of today's 09:13:32

3 deposition, so I'm going to ask for a sixth 09:13:36

4 time for a copy of my expert report, but 09:13:39

5 yes, I did testify accurately and truthfully 09:13:41

6 when I prepared this and signed it. 09:13:46

7 Q. I'd like to turn your attention to Paragraph 09:13:49

8 98 of the Quackenbush 1 exhibit. Let's go 09:13:52

9 back a little bit. If you start at Page 29, 09:14:05

10 30, so it's 29 of your declaration which is 09:14:19

11 Page 30 of the exhibit, do you see that? 09:14:22

12 MR. MILLS: Objection as to scope. 09:14:25

13 Q. Let me know when you're there. 09:14:29

14 A. Yes, I am. 09:14:30

15 Q. There's a heading that says "fragment 09:14:31

16 features and DNA fragment specific 09:14:33

17 information." Do you see that? 09:14:37

18 A. Yes, I do. 09:14:37

19 Q. The phrase "DNA fragment specific 09:14:38

20 information," that's a claim term that 09:14:40

21 appears in the '127 patent, right? 09:14:42

22 A. I'd like to request a copy of my expert 09:14:45

23 report. I'd also like to request a copy 09:14:48

24 of the '127 patent. 09:14:51

25 Q. All right. I've given you the '127 patent, 09:14:54

1 Doctor, which is Exhibit 1001 in this case. 09:14:57

2 So I'll ask the question again. 09:15:05

3 The phrase "DNA fragment specific 09:15:06

4 information," that's a term that appears in 09:15:09

5 the claims of the '127 patent, correct? 09:15:11

6 A. The term "DNA fragment specific information" 09:15:17

7 appears in claim 22 and 26 of the '127 patent 09:16:25

8 as stated in the document you've marked as 09:16:34

9 Exhibit 1. 09:16:37

10 Q. All right. And just so you don't think I'm 09:16:38

11 not playing fairly, Doctor, here's a copy of 09:16:44

12 your report which is Exhibit 1039 in this 09:16:46

13 case. 09:16:50

14 A. Thank you. 09:16:50

15 Q. If you need to look at that to answer any 09:16:51

16 of my questions, that's fine. I just ask 09:16:53

17 that you so state for purposes of the record. 09:16:55

18 Is that fair? 09:16:57

19 A. State that I'm looking at it? 09:17:00

20 Q. Yes. If you need to look at your report in 09:17:01

21 order to respond to any of my questions, I'd 09:17:03

22 like you to just tell me that, okay? Is 09:17:05

23 that fair? 09:17:08

24 A. I will look at my report to answer your 09:17:08

25 questions, yes. 09:17:10

1 Q. All right. Let's stay with Quackenbush 09:17:11
2 Exhibit 1 here. In the paragraphs 90 through 09:17:14
3 98, you provide opinions concerning 09:17:30
4 indefiniteness as to fragment features and 09:17:34
5 DNA fragment specific information, correct? 09:17:38
6 MR. MILLS: Objection to scope. 09:17:40
7 A. So I don't believe this is the subject of 09:17:42
8 our deposition today. I don't believe I 09:17:48
9 addressed this in my rebuttal report, which 09:17:51
10 is the topic of our deposition today. 09:17:54
11 However, looking at the document, the title 09:17:57
12 of the section is fragment features and DNA 09:18:00
13 fragment specific information, and so I 09:18:05
14 believe that I offered opinions about the 09:18:10
15 meaning of those two terms, yes. 09:18:12
16 Q. And the opinion you provided was that the 09:18:14
17 terms were indefinite, correct? 09:18:17
18 MR. MILLS: Objection to scope. 09:18:20
19 A. (Witness examines document) Would you repeat 09:18:21
20 the question, please? 09:22:49
21 MR. PICKARD: Can you read the 09:22:50
22 question back to the witness, please. 09:22:51
23 (Question read) 09:22:52
24 MR. MILLS: Objection to scope. 09:23:06
25 A. So in my expert report, which is the subject 09:23:09

1 of our deposition today, I offered no opinion 09:23:14
2 about definiteness or indefiniteness of 09:23:18
3 any particular terms, to the best of my 09:23:22
4 recollection. In this expert report which 09:23:24
5 was submitted in a different matter for 09:23:29
6 the context of claim construction, as we 09:23:33
7 discussed earlier, I submitted this expert 09:23:37
8 report in which in Paragraph 91 I lay out 09:23:40
9 my interpretation of these terms based on 09:23:48
10 reading the patents, the patent claim 09:23:51
11 history, the prosecution -- excuse me, the 09:23:55
12 prosecution history and with multiple 09:23:57
13 citations to both in which I state in my 09:24:00
14 opinion, the plain and ordinary meaning 09:24:04
15 cannot be determined with sufficient clarity. 09:24:07
16 "For example, do the claimed 09:24:13
17 features and information encompass any or all 09:24:16
18 of the size, specific nucleotide pattern, 09:24:20
19 overall nucleotide composition, nucleotide 09:24:24
20 modification or any other property of the DNA 09:24:29
21 fragment. The patents shed no light on the 09:24:34
22 answer to this answer question." 09:24:37
23 So in this unrelated matter which 09:24:38
24 is not the subject of our deposition today, I 09:24:40
25 did offer that opinion, yes. 09:24:42

1 Q. All right. If you'd turn to Paragraph 98 09:24:43
2 of Quackenbush 1, please, let me know when 09:24:47
3 you're there. 09:24:50
4 A. I'm there, yes. 09:24:51
5 Q. You wrote, "as there's no way to discern 09:24:52
6 from the intrinsic or extrinsic evidence 09:24:55
7 what precisely is encompassed by these 09:24:58
8 phrases, it is my opinion that they are 09:25:01
9 indefinite." Have I read that correctly? 09:25:04
10 MR. MILLS: Objection to scope. 09:25:06
11 A. So as we discussed earlier, the definiteness 09:25:07
12 or indefiniteness arguments made in an expert 09:25:12
13 report I submitted in an unrelated matter 09:25:15
14 are not the subject of our deposition today. 09:25:17
15 Our deposition today is supposed to be about 09:25:21
16 my rebuttal expert report submitted in this 09:25:23
17 IPR matter. 09:25:27
18 However, in the report which you've 09:25:29
19 marked as Exhibit 1, in looking at the terms, 09:25:31
20 fragment features and DNA specific 09:25:35
21 information -- excuse me, only DNA fragment 09:25:38
22 specific information appears in the '127 09:25:41
23 patent. I opined in Paragraph 98, as you 09:25:43
24 read correctly, that as there is no way to 09:25:49
25 discern from the intrinsic or extrinsic 09:25:53

1 evidence what precisely is encompassed by 09:25:57
2 these phrases, it is my opinion that they 09:26:00
3 are indefinite. And as I told you earlier 09:26:02
4 in Paragraph 91, I lay out some of the 09:26:05
5 arguments for this. It is my opinion that 09:26:09
6 the plain and ordinary meaning cannot be 09:26:12
7 determined with sufficient clarity for terms 09:26:14
8 like "DNA fragment specific information." 09:26:17
9 For example, do the claimed features and 09:26:21
10 information encompass any or all of the 09:26:23
11 size, specific nucleotide pattern, overall 09:26:27
12 nucleotide composition, nucleotide 09:26:30
13 modification or any other property of a DNA 09:26:33
14 fragment. The patents shed no light on the 09:26:38
15 answer to this question. And between 09:26:42
16 Paragraphs 91 and 98 that you cited, I lay 09:26:44
17 out some of the arguments that led me to this 09:26:47
18 conclusion, or some of the lines of evidence 09:26:49
19 that led me to this conclusion, including 09:26:51
20 reviewing the specification of the '127 09:26:54
21 patent and the patent prosecution history. 09:26:56
22 Q. Now, again focusing on Paragraph 98, you 09:27:01
23 refer to these phrases. These phrases are 09:27:05
24 "fragment features" and "DNA fragment 09:27:08
25 specific information," correct? 09:27:10

1 MR. MILLS: Objection as to scope. 09:27:11

2 A. Again, this document is not the subject 09:27:13

3 of our deposition today. It's from an 09:27:17

4 unrelated matter. The subject of our 09:27:21

5 deposition today should have been my expert 09:27:23

6 report which was submitted in the context 09:27:25

7 of this IPR matter. 09:27:29

8 However, Paragraph 98, to answer 09:27:32

9 your question, says, "as there is no way to 09:27:34

10 discern the intrinsic or extrinsic evidence 09:27:37

11 what precisely is encompassed by these 09:27:43

12 phrases, it is my opinion that they are 09:27:46

13 indefinite." And the phrases which we are 09:27:48

14 discussing in this section are "fragment 09:27:51

15 features," which does not appear in the 09:27:54

16 '127 patent, and "DNA fragment specific 09:27:56

17 information," which does appear in the '127 09:27:59

18 patent. And as I stated in Paragraph 91, 09:28:02

19 it is my opinion that the plain and ordinary 09:28:06

20 meaning which TwinStrand had asserted should 09:28:09

21 be used for these, to define these terms 09:28:14

22 cannot be determined with sufficient clarity. 09:28:16

23 For example, do the claimed features and 09:28:20

24 information encounter any or all of the size, 09:28:22

25 specific nucleotide pattern, overall 09:28:25

1 nucleotide composition, nucleotide 09:28:28
2 modification or any other property of a 09:28:30
3 DNA fragment. The patents shed no light on 09:28:34
4 the answer to this question, and indeed 09:28:37
5 between Paragraphs 91 and 98 which you cited, 09:28:40
6 I reviewed some of the evidence in the 09:28:43
7 patents themselves and in the patent 09:28:46
8 prosecution history to support the conclusion 09:28:48
9 that these terms in the context of this 09:28:52
10 matter are indefinite. 09:28:54
11 Q. This declaration you provided here which we 09:28:56
12 marked as Quackenbush 1, that was provided 09:29:01
13 in a district court case, correct? 09:29:04
14 MR. MILLS: Objection to scope. 09:29:05
15 A. So as stated on the front page, this was 09:29:08
16 offered, this document was offered during 09:29:29
17 claim construction for TwinStrand 09:29:32
18 Biosciences, Incorporated and the University 09:29:36
19 of Washington, plaintiffs, versus Guardant 09:29:40
20 Health, Incorporated, defendant, in Case No. 09:29:42
21 CA No. 21-1126-VAC-SRF. 09:29:47
22 Q. All right. And, of course, the purpose of 09:29:57
23 today's deposition is to discuss the opinions 09:30:02
24 you provided in an inter-partes review, 09:30:04
25 correct? 09:30:08

1 A. That is correct. 09:30:08

2 Q. You understand that the legal principles 09:30:09

3 governing claim construction are the same 09:30:13

4 in district court as they are in an 09:30:16

5 inter-partes review? 09:30:18

6 A. I'm not an attorney, I'm not a patent 09:30:21

7 attorney. I'm not sure of the breadth and 09:30:23

8 scope of the legal requirements. To the 09:30:26

9 best of my knowledge, I don't believe 09:30:29

10 there's a claim construction hearing that 09:30:30

11 takes place in an IPR. If there was one, 09:30:33

12 I would appreciate it if you could refresh 09:30:37

13 my memory. I don't believe I cited to that 09:30:40

14 within my report which is the subject of 09:30:44

15 our deposition today. 09:30:47

16 Q. Is it your opinion today that the phrase 09:30:49

17 "DNA fragment specific information" as it 09:30:52

18 appears in the '127 patent is indefinite? 09:30:55

19 MR. MILLS: Objection to scope. 09:31:00

20 A. In the context of the opinion I offered in 09:31:03

21 this district court case, these terms I would 09:31:06

22 argue are indefinite given the reasons I 09:31:11

23 laid out here. For example, do the claimed 09:31:15

24 features and information encompass any or 09:31:18

25 all of the size, specific nucleotide pattern, 09:31:22

1 overall nucleotide composition, nucleotide 09:31:25
2 modification or any property of the DNA 09:31:28
3 fragment. The patents shed no light on 09:31:30
4 the answer to that question. 09:31:34
5 However, if we're going to discuss 09:31:35
6 something specifically in the context of 09:31:36
7 this IPR and the '127 patent, I'd prefer 09:31:38
8 not to answer a hypothetical question, but 09:31:41
9 instead provide my best interpretation of 09:31:44
10 those terms in the context of the question 09:31:47
11 you asked. 09:31:49
12 Q. So outside the context of the district court, 09:31:49
13 and let's focus it so it's not hypothetical. 09:31:54
14 In the context of this IPR, do you believe 09:31:56
15 the phrase "DNA fragment specific 09:32:00
16 information" as it appears in the '127 patent 09:32:03
17 is indefinite? 09:32:03
18 MR. MILLS: Objection to scope. 09:32:04
19 A. So I don't believe the object of this IPR 09:32:05
20 and my testimony today is to offer opinions 09:32:10
21 regarding claim construction. I believe 09:32:12
22 your question is rather hypothetical given 09:32:16
23 the fact that we're not discussing this 09:32:19
24 within a specific context, and so I would 09:32:21
25 prefer not to offer an opinion at this time 09:32:24

1 as to the meaning of those terms without a 09:32:27
2 specific example to consider. And, again, 09:32:30
3 I don't believe I offered any opinions about 09:32:35
4 definiteness or indefiniteness in the 09:32:38
5 context of the report which is supposedly 09:32:41
6 the subject of our deposition today. 09:32:42
7 Q. Let me ask you this. Have you reviewed any 09:32:45
8 materials or done any analysis in this case 09:32:49
9 that has caused you to conclude that DNA 09:32:53
10 fragment specific information is anything 09:32:56
11 other than indefinite? 09:32:58
12 MR. MILLS: Objection as to scope. 09:33:02
13 A. So the subject of our deposition today is 09:33:03
14 the report which I submitted. This 09:33:10
15 deposition -- or sorry. This report which 09:33:13
16 I submitted was a response to a report 09:33:16
17 submitted by Dr. Satija and in this report 09:33:22
18 I offered a number of opinions. 09:33:28
19 The Travers publication admittedly 09:33:31
20 discloses amplification followed by 09:33:34
21 sequencing. Amplification followed by 09:33:38
22 sequencing is an important element to 09:33:41
23 discuss. In fact, amplification is something 09:33:44
24 which is important for a variety of reasons, 09:33:45
25 including low sample volume, an interest in 09:33:47

1 increasing the number of reads and depth 09:33:51
2 of coverage or to target specific loci in 09:33:54
3 particular applications. And so Dr. Satija 09:33:58
4 offered opinions about these and I responded 09:34:03
5 to those. 09:34:07
6 Next, Dr. Satija offered opinions 09:34:10
7 about first strand sequence reads as required 09:34:13
8 by claims 1 to 21 and I responded to those, 09:34:17
9 and I don't believe any of Dr. Satija's 09:34:21
10 arguments included discussion of DNA fragment 09:34:24
11 specific information. 09:34:28
12 Next, Dr. Satija offered opinions 09:34:32
13 about grouping in claims 22 to 30 and, to 09:34:36
14 the best of my knowledge, I don't believe 09:34:41
15 Dr. Satija offered opinions as to the meaning 09:34:42
16 of DNA fragment specific information, to 09:34:49
17 which I had to respond, although if my memory 09:34:51
18 is not correct, I'd be happy to have it 09:34:54
19 refreshed and to discuss those terms in 09:34:56
20 context. 09:34:59
21 And then, finally, in terms of 09:35:00
22 direct response, Dr. Satija argued, made 09:35:06
23 arguments about asymmetry of adapters when, 09:35:11
24 in fact, the patent claim language describes 09:35:17
25 asymmetry of adapter DNA molecules in claim 09:35:21

1 19 and then some additional arguments 09:35:21
2 about interoperability and secondary 09:35:24
3 considerations. 09:35:28
4 To the best of my knowledge, I did 09:35:28
5 not need to rely on the term "DNA fragment 09:35:31
6 specific information" and so did not offer 09:35:34
7 an opinion, but I would be happy to discuss 09:35:36
8 it in the context of the arguments laid out 09:35:39
9 in my report. 09:35:42
10 MR. PICKARD: I move to strike as 09:35:44
11 non-responsive. 09:35:45
12 Q. Let's look at the '127 patent, please. 09:35:46
13 MR. MILLS: I oppose the motion. 09:35:49
14 Q. Look at the '127 patent, please. 09:35:50
15 A. Yes. 09:35:52
16 Q. I'd like to focus you on claim 22. You're 09:35:52
17 familiar with that, no doubt? 09:35:56
18 A. Yes, I am. 09:35:57
19 Q. And you've applied some of the prior art to 09:35:58
20 that claim in your opinions in this case, 09:36:01
21 correct? 09:36:02
22 A. Yes. I believe the Tavers (sic) references, 09:36:10
23 including the Tavers (sic) '075 directly 09:36:14
24 anticipates claim 1 of this patent. And 09:36:17
25 since claim 22 mirrors claim 1, I believe 09:36:21

1 MR. MILLS: Objection to scope. 09:43:22

2 A. So I don't believe I made any arguments 09:43:23

3 about obviousness in my rebuttal report which 09:43:28

4 is the subject of my deposition today. 09:43:31

5 However, Dr. Satija argues in his report 09:43:35

6 to which I responded that claims 22 to 23 09:43:39

7 distinguish over Travers in that Travers 09:43:43

8 does not describe, quote, "for at least 09:43:46

9 some of the double-stranded adapter DNA 09:43:48

10 molecules in the library, grouping the 09:43:52

11 strand sequence reads into families based 09:43:55

12 on, No. 1, barcode sequence, and No. 2, DNA 09:43:56

13 fragment specific information." 09:44:00

14 So as I point out, Dr. Satija does 09:44:02

15 not dispute that the '127 patent claims 09:44:05

16 encompass the Travers U-shaped adapters or 09:44:08

17 that those adapters contain barcodes as 09:44:12

18 recited in claims 1 to 22. Dr. Satija, 09:44:17

19 according to Dr. Satija, the Travers 09:44:19

20 publications, while disclosing barcode 09:44:23

21 adapters, do not specifically utilize the 09:44:25

22 barcodes for grouping as recited in claim 09:44:28

23 22. However, as I point out in my report, 09:44:32

24 Dr. Satija's argument is not commensurate 09:44:34

25 with the language of the '127 patent or 09:44:37

1 the guidance in the specification, and I 09:44:39
2 disagree for at least the reasons set forth 09:44:42
3 below. 09:44:44
4 So I provide a number of arguments 09:44:46
5 in here refuting Dr. Satija's claims, 09:44:49
6 statements about the claim 22 of the '127 09:44:54
7 patent, including having to do with the 09:44:58
8 definition of barcodes. But specifically 09:45:02
9 in Paragraph 18 in response to Dr. Satija's 09:45:07
10 argument about grouping, Travers discloses 09:45:13
11 redundantly sequencing both strands of DNA 09:45:16
12 molecules, and I cite to Exhibit 1018 and 09:45:20
13 1021. Travers further describes assembling 09:45:26
14 the sequence data from multiple reads of a 09:45:30
15 given sequence to provide an overall 09:45:32
16 consensus sequence when multiplexing -- well, 09:45:35
17 I won't provide that since that discusses 09:45:38
18 the uses of barcodes. 09:45:42
19 And so clearly, according to 09:45:43
20 Travers, Travers expressly described 09:45:46
21 determining consensus sequences based on 09:45:49
22 assembled or group redundant sequence reads 09:45:52
23 as required by the claims. 09:45:55
24 MR. PICKARD: I move to strike as 09:45:57
25 non-responsive. 09:45:58

1 Q. Doctor, although it was only a couple of 09:45:59
2 questions ago, it was ten minutes ago, so 09:46:03
3 I'll just refresh your memory. 09:46:03
4 You mentioned doing some analysis 09:46:07
5 in which you concluded that the Travers 09:46:09
6 references, one of Travers references 09:46:11
7 anticipates one or more claims of the '127 09:46:13
8 patent. Do you recall that? 09:46:16
9 A. Yes, I do. 09:46:17
10 Q. Is it your opinion in this case that there's 09:46:17
11 an anticipation theory of unpatentability? 09:46:20
12 A. I didn't make that argument in my expert 09:46:25
13 report. In fact, though, if you look at 09:46:28
14 what's claimed, I may have previously laid 09:46:33
15 out that argument. But, again, the subject 09:46:37
16 of our deposition today is to discuss the 09:46:40
17 expert report which I submitted responding 09:46:44
18 to Dr. Satija's statements. 09:46:47
19 Q. So there's no anticipation theory in the 09:46:50
20 two reports you submitted in this case, 09:46:57
21 correct? 09:46:59
22 A. I haven't reviewed my first report. I'm 09:46:59
23 here to discuss this report today. We had a 09:47:02
24 previous deposition on that report and I 09:47:06
25 believe you declined to ask any -- only asked 09:47:12

1 a very small number of questions. I don't 09:47:15
2 believe we discussed that at the time. 09:47:18
3 Q. All right. I show you Exhibit 1002, your 09:47:19
4 opening report in this case. 09:47:23
5 MR. MILLS: I object to the exhibit 09:47:27
6 as to scope. 09:47:29
7 Q. Doctor, did you think that all of the things 09:47:30
8 you said in the various cases about the 09:47:33
9 '127 patent wouldn't be fair game to talk 09:47:35
10 about today? 09:47:37
11 A. My understanding is that the subject of the 09:47:40
12 deposition today is to discuss the report 09:47:43
13 which I submitted which I believe is marked 09:47:47
14 as Exhibit 1039, which is my declaration 09:47:54
15 submitted in response to Dr. Satija's report. 09:48:00
16 Q. All right. If you could, I'd like you to 09:48:04
17 look at -- first of all, you recognize 09:48:06
18 Exhibit 1002 as your opening report in this 09:48:11
19 case, correct? 09:48:13
20 A. I believe so, yes. 09:48:15
21 Q. If you could turn to Page 19, please, let 09:48:26
22 me know when you're there. 09:48:29
23 A. I'm there. 09:48:31
24 Q. Under the heading "Claim Construction" in 09:48:45
25 Paragraph 48, you wrote, "I have been advised 09:48:47

1 term "DNA fragment specific information" 09:56:24
2 which in an unrelated case I had argued that 09:56:27
3 those terms in the context of the '127 patent 09:56:33
4 were indefinite, and laid out the reasons 09:56:37
5 based on the specification of the patent as 09:56:41
6 well as the prosecution history. 09:56:46

7 In the context of interpreting 09:56:48
8 the term "DNA fragment specific information" 09:56:50
9 and looking at the meaning in the report 09:56:54
10 today, I was responding to Dr. Satija's 09:56:58
11 arguments about whether or not grouping could 09:57:04
12 be performed using information that was 09:57:08
13 available, including the barcode sequence 09:57:12
14 and DNA fragment specific information. 09:57:15
15 Whether or not Travers actually defines that 09:57:21
16 term, it's not defined in the '127 patent. 09:57:24
17 However, the ultimate question here is 09:57:30
18 whether or not Travers performed grouping and 09:57:31
19 how Travers does that grouping. 09:57:34

20 Travers, in fact, discloses, and I 09:57:37
21 have this in Paragraph 113 of Exhibit 1002, 09:57:44
22 Travers further discloses grouping of 09:57:52
23 redundant sequence reads. Specifically, 09:57:56
24 Travers describes collectively analyzing 09:57:57
25 multiple reads of the target molecule, 09:58:00

1 describes the use of oligonucleotide tags 09:58:05
2 where barcodes to pool data for analysis 09:58:11
3 and then discloses assembling the sequence 09:58:12
4 reads and analyzing those sequence reads. 09:58:15
5 As you may know, the process of 09:58:18
6 assembly is one of grouping and the barcodes 09:58:19
7 themselves are also used to group reads. 09:58:23
8 So whether or not the term is definite or 09:58:26
9 indefinite in the context of the '127 patent, 09:58:29
10 in fact, Travers discloses grouping sequences 09:58:35
11 using a, one or more barcode sequences in 09:58:39
12 DNA fragment specific information. So at the 09:58:44
13 very least, in the process of assembling 09:58:48
14 sequence, I can interpret Travers as using 09:58:51
15 DNA sequence information from the fragments 09:58:55
16 as DNA fragment specific information. 09:58:58
17 That argument which I lay out in 09:59:02
18 part in my rebuttal report which is the 09:59:05
19 subject of our deposition today, is 09:59:08
20 irrelevant to whether or not the '127 patent 09:59:12
21 is actually definite or indefinite in its 09:59:16
22 description of DNA fragment information. 09:59:19
23 And as we discussed earlier, there are a 09:59:22
24 number of different features of DNA -- a 09:59:24
25 number of different types of DNA fragment 09:59:31

1 specific information that could be 09:59:34
2 interpreted here with no guidance. 09:59:34
3 Nevertheless, Travers does use 09:59:37
4 at least one form of that DNA specific 09:59:39
5 sequence information. Whether or not there 09:59:41
6 are others that Travers could use and whether 09:59:44
7 or not the inventors of the '127 patent 09:59:46
8 are considering other types of information 09:59:49
9 is irrelevant for the analysis provided in 09:59:52
10 my rebuttal report which is the subject of 09:59:55
11 our deposition today. 09:59:58
12 MR. PICKARD: Move to strike as 10:00:00
13 non-responsive. 10:00:01
14 Q. My question is not about DNA fragment 10:00:02
15 specific information. My question is 10:00:06
16 broader. So you can set aside Quackenbush 1 10:00:06
17 for purposes of this question, and it's 10:00:09
18 very simple. 10:00:11
19 In your opening report in Paragraph 10:00:12
20 48, you lay forth some principles which you 10:00:13
21 state that you followed in your analysis, 10:00:15
22 and what I'd like to know is did you follow 10:00:17
23 the same principles in your rebuttal report 10:00:19
24 that you describe here in Paragraph 48 of 10:00:22
25 your opening report? 10:00:24

1 MR. MILLS: I oppose the motion. 10:00:26

2 Objection to form, objection to scope. 10:00:28

3 A. So we've been talking about indefiniteness 10:00:32

4 in claim construction in the context of my 10:00:45

5 opening report which is not the subject 10:00:47

6 of today's deposition. In looking at that 10:00:48

7 opening report, one of the things I offered 10:00:52

8 opinions about was whether or not -- let 10:00:54

9 me start over. In looking at my opening 10:01:02

10 report -- sorry, I'm going to have to look 10:01:06

11 back at this. (Witness examines document) 10:01:17

12 So I was asked whether or not I 10:03:30

13 applied the same principles of claim 10:03:34

14 construction in my rebuttal report, which 10:03:36

15 is the subject of today's deposition, that 10:03:38

16 I had applied in my opening report, which 10:03:42

17 is not the subject of today's deposition. 10:03:46

18 However, in that deposition -- sorry. 10:03:49

19 In that opening report I stated I 10:03:52

20 have been advised that the claims of the 10:03:54

21 '127 patent claim are to be given the plain 10:03:55

22 and ordinary meaning that terms would have 10:03:59

23 to a person of ordinary skill in the art in 10:04:02

24 question at the relevant priority date. I 10:04:05

25 understand that the analysis focuses on how 10:04:08

1 the patentee used the claim terms in the 10:04:09
2 claim specification and prosecution history. 10:04:12
3 To the extent that I needed to construe terms 10:04:17
4 in the context of reaching conclusions 10:04:21
5 presented in my rebuttal report which is 10:04:24
6 the subject of today's deposition, the answer 10:04:25
7 is yes, I applied those same principles. 10:04:29
8 Specifically, when Dr. Satija argues 10:04:32
9 that grouping was not described in the 10:04:37
10 Travers references, I point out in Paragraph 10:04:49
11 18 of my rebuttal report that Travers groups 10:04:54
12 sequences based on the barcode and then 10:04:59
13 assembles the sequences -- or sorry, pools 10:05:01
14 sequences based on the barcode and then 10:05:10
15 assembles them which, in fact, the assembly 10:05:13
16 process is grouping. So my application of 10:05:16
17 those terms is consistent in interpreting 10:05:19
18 Travers. 10:05:22
19 MR. MILLS: We've been going for 10:05:24
20 about an hour. Are we ready for a break? 10:05:25
21 MR. PICKARD: Sure. How long would 10:05:28
22 you like. 10:05:29
23 MR. MILLS: Five minutes, ten 10:05:31
24 minutes? 10:05:32
25 THE WITNESS: Ten minutes. 10:05:32

1 VIDEOGRAPHER: The time is 10:05. 10:05:35
2 We're off the record. 10:05:37
3 (Break taken) 10:05:38
4 VIDEOGRAPHER: The time is 10:18. 10:18:26
5 We're back on the record. 10:18:38
6 BY MR. Pickard: 10:18:39
7 Q. If you'd look back at Quackenbush 1, please, 10:18:40
8 Doctor. 10:18:42
9 A. I'm sorry, that is? 10:18:54
10 Q. The first exhibit you looked at today, right 10:18:55
11 there. 10:18:58
12 A. Yes. 10:18:58
13 Q. Did you review this document that's been 10:18:58
14 marked as Quackenbush 1 in preparing for your 10:19:01
15 deposition today? 10:19:03
16 A. No, I did not. This is a declaration 10:19:06
17 submitted in an unrelated matter and not the 10:19:09
18 subject of our deposition today. 10:19:12
19 Q. Do you know the last time you looked at 10:19:15
20 Quackenbush 1 before today? 10:19:19
21 A. So the document you refer to as Quackenbush 1 10:19:24
22 from an unrelated matter was executed on 10:20:02
23 August 26, 2022, so August 26, 2022, or at 10:20:08
24 some time after. I do not recall. 10:20:18
25 Q. So you believe the district court case 10:20:20

1 between the University of Washington and 10:20:24

2 TwinStrand versus Guardant Health is 10:20:27

3 unrelated to this case, is that right? 10:20:29

4 A. My understanding is the district court 10:20:31

5 case and the inter-partes review are, in 10:20:34

6 fact, distinct matters. They fall under, 10:20:39

7 to the best of my understanding, different 10:20:43

8 jurisdictions. 10:20:44

9 Q. Do you think that, given your view between 10:20:47

10 the separateness of the district court case 10:20:51

11 and this case, that you're allowed to say 10:20:53

12 things in one case that conflict or are 10:20:56

13 inconsistent with things you say in the 10:20:58

14 other? 10:21:00

15 MR. MILLS: Objection to form. 10:21:01

16 A. I believe that each of the documents I've 10:21:08

17 submitted in each of the matters in which 10:21:13

18 I've been involved have been to the best of 10:21:17

19 my ability at the time consistent with my 10:21:20

20 understanding and offered within the context 10:21:23

21 of what I believe are the appropriate 10:21:27

22 definitions in operation at that time. 10:21:30

23 Q. And if there were any inconsistencies, it 10:21:34

24 would be fair for me to ask you about them, 10:21:37

25 right? 10:21:40

1 MR. MILLS: Objection to form. 10:21:40

2 A. Again, the scope of our deposition today 10:21:42

3 is the, marked as Exhibit 1039, which is my 10:21:52

4 declaration offered in response to Dr. 10:22:01

5 Satija's report. 10:22:04

6 Q. And that response analyzes, among other 10:22:05

7 things, the '127 patent, correct? 10:22:09

8 MR. MILLS: Objection to form. 10:22:12

9 A. So the document which is the subject of our 10:22:28

10 deposition today is simply a response to a 10:22:31

11 number of arguments made by Dr. Satija about 10:22:35

12 the '127 patent. Specifically, Dr. Satija 10:22:39

13 offers some opinions about amplification 10:22:45

14 followed by sequencing, to which I respond. 10:22:51

15 Dr. Satija offers opinions about first and 10:22:54

16 second-strand sequence reads as required by 10:22:59

17 claims 1 to 21 of the '127 patent, to which 10:23:03

18 I respond. Dr. Satija offers some opinions 10:23:06

19 about barcodes and groupings, grouping in 10:23:10

20 claims 22 to 30 of the '127 patent, to which 10:23:14

21 I respond. Dr. Satija also offers some 10:23:17

22 opinions about the asymmetry of adapter 10:23:21

23 molecules rather than adapter DNA molecules 10:23:25

24 as required by claim 19, to which I respond. 10:23:30

25 Dr. Satija offers some fallacious arguments 10:23:31

1 about interoperability, to which I respond. 10:23:35

2 Dr. Satija also offers some arguments about 10:23:40

3 secondary considerations in which he refers 10:23:44

4 to articles describing duplex consensus 10:23:47

5 sequencing which is not what is claimed in 10:23:52

6 the '127 patent, to which I respond. 10:23:54

7 Q. Can we at least agree that the rebuttal 10:23:56

8 report which is Exhibit 1039, it relates to 10:23:58

9 the '127 patent? 10:24:03

10 A. The rebuttal report specifically responds 10:24:05

11 to issues raised by Dr. Satija regarding the 10:24:10

12 '127 patent. The issues about which I'm 10:24:15

13 prepared to discuss today are Dr. Satija's 10:24:18

14 arguments about whether or not the Travers 10:24:22

15 publications disclose amplification followed 10:24:26

16 by sequencing, which they do; whether or 10:24:29

17 not the Travers publications describe first 10:24:32

18 and second-strand sequence reads as required 10:24:34

19 by claims one through 21, which they do; 10:24:37

20 whether or not the Travers publications 10:24:41

21 describe grouping as in claims 22 to 30, 10:24:43

22 which, in fact, they do; whether or not the 10:24:45

23 Travers publications describe using the 10:24:48

24 asymmetry of adapter DNA molecules rather 10:24:50

25 than simply adapters which Dr. Satija tries 10:24:55

1 to argue and, in fact, the Travers 10:24:59
2 publications disclose asymmetry of adapter 10:25:01
3 DNA molecules as being useful as required 10:25:07
4 by claim 19; whether or not the Travers 10:25:08
5 publications are really interoperable and 10:25:12
6 whether or not secondary considerations 10:25:17
7 which he offers regarding duplex consensus 10:25:19
8 sequencing have anything to do with the 10:25:23
9 '127 patent, which they do not. 10:25:25
10 Q. Can you give me a yes-or-no answer as to 10:25:27
11 whether the rebuttal report which is 10:25:29
12 Exhibit 1039, in your view, relates to the 10:25:32
13 '127 patent? 10:25:34
14 MR. MILLS: Objection to form, asked 10:25:35
15 and answered. 10:25:37
16 A. So the rebuttal report which is the subject 10:25:37
17 of our deposition today offers my opinions 10:25:40
18 about which I am prepared to testify, 10:25:43
19 including those which encompass my response 10:25:45
20 to Dr. Satija's assertions that the Travers 10:25:50
21 publications do not disclose amplification 10:25:53
22 followed by sequencing, which they do; that 10:25:57
23 the Travers publications do not describe 10:25:59
24 first and second-strand sequence reads as 10:26:01
25 required by claims 1 to 21, which they do; 10:26:04

1 that the Travers publications describe 10:26:06
2 grouping as in claims 22 to 30 of the '127 10:26:09
3 patent, which they do; that the Travers 10:26:13
4 publications describe using adapter, 10:26:15
5 asymmetry of adapter DNA molecules as 10:26:18
6 required by claim 19, which they do, and 10:26:23
7 then additional arguments that Dr. Satija 10:26:24
8 makes about interoperability of the Travers 10:26:27
9 references and secondary considerations 10:26:31
10 which have to do with duplex consensus 10:26:32
11 sequencing rather than the inventions claimed 10:26:36
12 in the '127 patent. 10:26:38
13 Q. So no, you're not able to give me a yes-or-no 10:26:39
14 answer? 10:26:43
15 MR. MILLS: Objection to form. 10:26:43
16 Q. I'm not asking what your answer is. I'm 10:26:44
17 just asking can you give me a yes-or-no 10:26:47
18 answer, and if you can't, I'll move on. 10:26:50
19 So can you give me a yes-or-no answer whether 10:26:52
20 your rebuttal report relates to the '127 10:26:54
21 patent? 10:26:57
22 MR. MILLS: Objection to form. 10:26:58
23 A. So my rebuttal report which I'm prepared to 10:26:58
24 discuss today offers my opinions in response 10:27:01
25 to a limited number of arguments made by 10:27:03

1 Dr. Satija about the '127 patent, including 10:27:06
2 whether or not the Travers publications 10:27:11
3 disclose amplification by sequencing, which 10:27:13
4 they do; whether or not the Travers 10:27:17
5 publications describe first and second-strand 10:27:23
6 sequence reads as required by claims 1 to 21 10:27:26
7 of the '127 patent, which they do; whether 10:27:29
8 or not the Travers publications describe 10:27:32
9 grouping as in claims 22 to 30 of the '127 10:27:34
10 patent, which they do; whether or not the 10:27:38
11 Travers publications describe using the 10:27:40
12 asymmetry of adapter DNA molecules as 10:27:42
13 required by claim 19, which they do, and then 10:27:45
14 additional arguments about interoperability 10:27:48
15 of the Travers publications and secondary 10:27:51
16 considerations in which Dr. Satija describes 10:27:57
17 information or provides information about 10:27:59
18 duplex consensus sequencing which is not 10:28:01
19 claimed in the '127 patent. 10:28:04
20 Q. If you could turn to Paragraph 35 of your 10:28:05
21 rebuttal report, please. There you wrote 10:28:07
22 under oath, "the claims of the '127 patent 10:28:20
23 are so broad as to encompass the prior art, 10:28:22
24 including prior art methods described in 10:28:25
25 the Travers publications," correct? 10:28:27

1 MR. MILLS: Objection to form. 10:28:29

2 A. (Witness examines document) 10:28:30

3 Q. Doctor, why do you need to look at your 10:30:18

4 claim construction report in this unrelated 10:30:21

5 case to answer a question about your rebuttal 10:30:21

6 report? 10:30:21

7 A. So I grabbed the wrong document. 10:30:25

8 Q. I have a very simple question. I just asked 10:30:27

9 you in Paragraph 35 you wrote under oath, 10:30:29

10 "the claims of the '127 patent are so broad 10:30:31

11 as to encompass the prior art, including 10:30:35

12 prior art methods described by the Travers 10:30:37

13 publications." Do you understand my 10:30:40

14 question, Doctor? I'm withdrawing the last 10:30:45

15 question. My question is do you understand 10:30:51

16 the question I had previously posed? 10:30:54

17 A. I believe I understand your question, yes. 10:30:56

18 Q. Okay. The question is simply, you wrote 10:30:58

19 under oath, correct, "the claims of the '127 10:31:00

20 patent are so broad as to encompass the prior 10:31:03

21 art, including prior art methods described 10:31:05

22 by the Travers publication." Isn't that 10:31:08

23 right? 10:31:19

24 A. So you're quoting and you quoted correctly 10:31:19

25 part of Paragraph 35 -- 10:31:25

1 Q. Thank you. That's all I'm asking. 10:31:28

2 A. -- in my rebuttal -- 10:31:28

3 Q. I'll stipulate it's not the entire paragraph. 10:31:31

4 Doctor, you've answered my question. 10:31:32

5 MR. MILLS: Counsel, you need to 10:31:34

6 not interrupt the witness. 10:31:36

7 MR. PICKARD: Your witness is 10:31:36

8 speechfying and not responding to questions, 10:31:38

9 and I -- 10:31:39

10 MR. MILLS: Counsel, the primary 10:31:39

11 rule of the deposition at the very beginning 10:31:41

12 is that you weren't going to talk over one 10:31:42

13 another. You're breaking that rule. 10:31:44

14 MR. PICKARD: That was not the 10:31:46

15 primary instruction. Also, the primary 10:31:46

16 instruction, in fact, was that he would 10:31:48

17 answer the questions posed to him. He's 10:31:49

18 not doing that. 10:31:51

19 MR. MILLS: I disagree with that. 10:31:51

20 MR. Pickard: He has, in fact, 10:31:52

21 answered this question and we're done and 10:31:53

22 moving on. You make your objection 10:31:54

23 MR. MILLS: You need to not 10:31:56

24 interrupt the witness. 10:31:56

25 MR. PICKARD: Don't instruct me. 10:31:56

1 Make your objection and we're moving on. 10:31:57

2 MR. MILLS: You cannot interrupt 10:32:00

3 the witness. You cannot speak over the 10:32:00

4 witness. We can only have one person 10:32:01

5 speaking at a time. 10:32:03

6 MR. PICKARD: I didn't interrupt 10:32:03

7 him. 10:32:04

8 Q. Let's move on to Paragraph 39. The question 10:32:05

9 is -- we've moved on, Doctor. 10:32:11

10 A. The question you asked -- 10:32:13

11 Q. Doctor, there's no question pending, Doctor. 10:32:14

12 A. I'm continuing my answer which you 10:32:18

13 interrupted. 10:32:20

14 Q. If you would look to Paragraph 39. 10:32:21

15 A. -- was on secondary considerations in which 10:32:24

16 Dr. Satija lays out arguments about duplex 10:32:26

17 consensus sequencing, and in Paragraph 35 10:32:29

18 which you did quote correctly, at least 10:32:32

19 part of it, I stated the claims of the '127 10:32:35

20 patent are so broad as to encompass prior 10:32:38

21 art, including prior art methods described 10:32:41

22 by the Travers publication, and then go on 10:32:43

23 to say, "furthermore, I understand the board 10:32:45

24 has found that Kinde, Exhibit 1006, in 10:32:47

25 view of Craig, Exhibit 1038, teaches each 10:32:52

1 limitation of claim 1 of the '127 patent, 10:32:55
2 Guardant Health versus University of 10:32:55
3 Washington." And then I quote the decision, 10:33:00
4 "we find petitioner has shown sufficiently 10:33:05
5 the combination of Kinde and Craig teaches 10:33:08
6 each limitation of claim 1." 10:33:12
7 Q. If you could turn to Paragraph 39, please. 10:33:12
8 Five lines down you wrote under oath there, 10:33:18
9 "however, as I discuss above, the claims of 10:33:20
10 the '127 patent do not require DCS." I read 10:33:22
11 that correctly, right? 10:33:26
12 A. (Witness examines document) You read it 10:33:33
13 correctly. Dr. Satija was inappropriately 10:33:55
14 trying to assert that praise for DCS somehow 10:33:58
15 indicated as a secondary consideration that 10:34:02
16 the '127 patent was -- 10:34:06
17 Q. Thank you. 10:34:11
18 A. -- was... 10:34:13
19 Q. Doctor, I didn't ask why you wrote it. I 10:34:18
20 said those are the words you wrote, right? 10:34:21
21 All right. 10:34:21
22 Given those two statements, is it 10:34:24
23 fair to say you considered the breadth of 10:34:25
24 the claims and what the claims require of 10:34:28
25 the '127 patent in your rebuttal report? 10:34:29

1 A. (Witness examines document) So Dr. Satija 10:34:54
2 had argued that praise, long-felt need and 10:35:03
3 unexpected results associated with duplex 10:35:06
4 consensus sequencing and duplex sequencing 10:35:09
5 provides objective evidence of the 10:35:11
6 non-obviousness of the '127, the claim for 10:35:16
7 the '127 patent. However, as I discuss 10:35:20
8 above, the claims of the '127 patent do not 10:35:24
9 require duplex consensus sequencing. So to 10:35:27
10 the extent that I drew a comparison between 10:35:31
11 duplex consensus sequencing, which is not 10:35:34
12 claimed in the -- it does not appear in the 10:35:37
13 claims of the '127 patent, and the evidence 10:35:41
14 that Dr. Satija offers as evidence of 10:35:45
15 non-obviousness, I analyzed those claims and 10:35:50
16 compared them to what is in the 10:35:55
17 specification, which is something distinct 10:35:56
18 from the claimed invention. 10:35:59
19 MR. PICKARD: Objection, move to 10:36:01
20 strike as non-responsive. 10:36:01
21 Q. Here's my question, Doctor. In preparing 10:36:03
22 the opinions that you stated in your rebuttal 10:36:06
23 report, Exhibit 1039, did you consider how 10:36:08
24 broad the claims of the '127 patent were and 10:36:11
25 what the claims of the '127 patent required? 10:36:13

1 MR. MILLS: Objection to form. 10:36:16

2 A. So the statement you highlighted in Paragraph 10:36:18

3 39 states, "however, as I discuss above, 10:36:22

4 the claims of the '127 patent do not require 10:36:25

5 DCS duplex consensus sequencing." Dr. Satija 10:36:28

6 in his report offered an opinion that 10:36:32

7 because there were papers praising, or at 10:36:36

8 least one paper praising some of the merits 10:36:38

9 of duplex consensus sequencing, this provides 10:36:41

10 objective evidence of the non-obviousness 10:36:46

11 of the claims appearing in the patent. And, 10:36:49

12 in fact, what I did was I drew distinctions 10:36:51

13 between DCS and what's claimed in the claims 10:36:54

14 of the '127 patent. 10:36:58

15 To the extent that I needed to rebut 10:37:00

16 Dr. Satija's arguments as laid out here, I 10:37:03

17 analyzed the claims of the '127 patent and 10:37:07

18 I'm prepared to testify about the opinions I 10:37:10

19 offered in my report. 10:37:12

20 Q. If you could turn back to Quackenbush 10:37:13

21 Exhibit 1, your declaration from the district 10:37:16

22 court case, let me know when you're there. 10:37:19

23 A. I have that, yes. 10:37:29

24 Q. If you turn to Page 21 of your declaration 10:37:30

25 which is Page 22 of the exhibit, there's a 10:37:33

Page 47

1 A. I see where in this unrelated document it 10:39:06
2 says, "substantially identifiable" in the 10:39:09
3 table. 10:39:12
4 Q. And the claim term "substantially 10:39:12
5 identifiable" appears in claim 26 of the 10:39:14
6 '127 patent, correct? 10:39:16
7 A. You're correct, the phrase "substantially 10:39:21
8 identifiable" appears in claim 26 of the 10:39:24
9 '127 patent. 10:39:27
10 Q. Now, if you look in the following pages 10:39:27
11 in Paragraphs 72 to 82, you provide an 10:39:32
12 analysis of the claim terms that appear in 10:39:36
13 that table, correct? 10:39:38
14 MR. MILLS: Objection to scope. 10:39:39
15 A. (Witness examines document) Could you repeat 10:39:40
16 the question, please? 10:44:55
17 Q. Yes. If you look at Paragraphs 72 to 82, 10:44:56
18 you provide an analysis of the terms that 10:45:01
19 appear in the table starting at Page 21 of 10:45:04
20 that exhibit, correct? 10:45:07
21 MR. MILLS: Objection to scope. 10:45:08
22 A. So in the context of this unrelated document 10:45:10
23 from an unrelated matter, in Paragraphs 72 10:45:13
24 to 82, I provide an analysis of the number of 10:45:20
25 terms that appear in the claims of the '127 10:45:24

1 patent and an additional unrelated patent, 10:45:28
2 the '699 patent, including the terms 10:45:33
3 "non-uniquely tagged double-stranded adapter 10:45:40
4 DNA molecules" and I believe the other term 10:45:45
5 was -- 10:45:48
6 Q. "Substantially identifiable." 10:45:50
7 A. "Substantially identifiable," and point out 10:45:53
8 that those terms are not used anywhere in 10:45:56
9 the specification of the '127 patent in the 10:46:01
10 other unrelated patent. Those are not 10:46:07
11 relevant to arguments I believe that Dr. 10:46:11
12 Satija made and that I responded to in my 10:46:15
13 rebuttal report which is the subject of 10:46:18
14 today's deposition. 10:46:20
15 Q. Is it your opinion today that the terms 10:46:20
16 "substantially identifiable" and 10:46:27
17 "non-uniquely tagged double-stranded 10:46:30
18 adapter DNA molecules" as they appear in 10:46:33
19 the '127 patent are indefinite? 10:46:39
20 MR. MILLS: Objection to scope. 10:46:40
21 A. So I don't believe that Dr. Satija made 10:46:41
22 arguments about definiteness or 10:46:43
23 indefiniteness that I responded to in the 10:46:45
24 context of the expert report which is the 10:46:49
25 subject of our deposition today. I believe 10:46:53

1 the only argument Dr. Satija made regarding 10:46:56
2 claims 22 to 30 had to do with grouping 10:47:01
3 which I demonstrate in my report that Travers 10:47:05
4 does through the process of assembly using 10:47:08
5 sequence and barcodes, and whether or not 10:47:11
6 those terms are indefinite or not does not 10:47:16
7 seem relevant to the argument or to the 10:47:21
8 facts about which I am prepared to testify 10:47:25
9 today. 10:47:27
10 MR. PICKARD: Move to strike as 10:47:29
11 non-responsive. 10:47:30
12 MR. MILLS: I oppose. 10:47:31
13 Q. You recently submitted an expert report in 10:47:32
14 the district court case raising a number 10:47:37
15 of invalidity issues as to the '127 patent, 10:47:41
16 correct? 10:47:45
17 MR. MILLS: Objection to form. 10:47:45
18 A. I'll take your word for it. 10:47:47
19 Q. You don't remember doing that? 10:47:48
20 A. I may have, yes. 10:47:50
21 Q. Do you recall taking the position as to 10:47:52
22 the indefiniteness of substantially 10:47:54
23 identifiable -- sorry, substantially 10:47:57
24 identical and non-uniquely tagged 10:48:00
25 double-stranded adapter DNA molecules? 10:48:08

1 MR. MILLS: Objection to scope. 10:48:09

2 A. I did not review unrelated matters in 10:48:10

3 preparation for my deposition today. 10:48:15

4 Q. In preparing for your deposition today, 10:48:19

5 did you review your opening report in this 10:48:21

6 IPR? 10:48:26

7 A. I did not since it's not relevant to the 10:48:26

8 subject of today's deposition. You had an 10:48:29

9 opportunity for a deposition on that report 10:48:32

10 previously, and my understanding was the 10:48:35

11 scope of today's questions would be limited 10:48:37

12 to my rebuttal report. 10:48:39

13 Q. A moment ago you said the '699 patent was 10:48:40

14 unrelated to the '127 patent. You understand 10:48:43

15 that those two patents claim priority to 10:48:47

16 common application? 10:48:52

17 A. If I said that, I misspoke. I meant to say 10:48:54

18 that it was irrelevant to the subject of 10:48:58

19 today's deposition, which is my rebuttal 10:49:02

20 report responding to some of Dr. Satija's 10:49:06

21 arguments about the '127 patent. I believe 10:49:10

22 you are correct that they both trace back to 10:49:12

23 the same priority application. 10:49:18

24 Q. Despite describing the district court case 10:49:19

25 as unrelated, it does involve the '127 patent 10:49:22

1 as this case does, correct? 10:49:25

2 A. The district court case does involve the 10:49:28

3 '127 patent, but the district court case, in 10:49:31

4 my understanding, falls under a separate 10:49:34

5 jurisdiction from the inter-partes review 10:49:36

6 which is carried out by the patent board. 10:49:39

7 Q. Do you understand that the result of this 10:49:42

8 case will have an impact on the district 10:49:44

9 court case? 10:49:48

10 MR. MILLS: Objection to scope, 10:49:49

11 form, calls for legal conclusion. 10:49:52

12 A. I'm not an attorney so I'm not sure exactly 10:49:54

13 what the ramifications are of any decision 10:49:58

14 that's reached here with regard to how that 10:50:02

15 case may be tried or prosecuted. 10:50:07

16 Q. If you don't know what the ramifications 10:50:09

17 are between the two cases, how are you so 10:50:11

18 confident in your ability to describe the 10:50:15

19 two proceedings as being unrelated? 10:50:16

20 MR. MILLS: Objection to form. 10:50:18

21 A. My understanding, and I'm not an attorney 10:50:19

22 or patent agent, is that the processes in 10:50:23

23 district court and the patent board are 10:50:33

24 independent processes. If I'm mistaken, 10:50:37

25 then I stand to be corrected, but my 10:50:41

1 understanding is that they are treated 10:50:44
2 distinctly, viewed distinctly, and if the 10:50:49
3 patent review is a trial, then tried 10:50:53
4 distinctly. 10:51:00
5 Q. Do you understand that the claim construction 10:51:01
6 standards that apply in this case are the 10:51:03
7 same that apply in the district court case? 10:51:04
8 MR. MILLS: Objection to form. 10:51:07
9 A. To the best of my knowledge, claim 10:51:09
10 construction can be applied in both IPR 10:51:11
11 matters and in district court cases. I 10:51:17
12 also understand, although I may be incorrect, 10:51:22
13 that claims construed in the district court 10:51:24
14 case may be construed differently in an IPR 10:51:26
15 matter. 10:51:31
16 Q. You are incorrect, I can tell you that. 10:51:32
17 A. Hence -- 10:51:35
18 Q. Why don't we go to the '127 patent. 10:51:36
19 A. Hence my belief that these are independent 10:51:38
20 matters. 10:51:40
21 MR. MILLS: Counsel, again, please 10:51:41
22 don't interrupt the witness and speak over 10:51:43
23 the witness. We need to have a clear 10:51:44
24 transcript. 10:51:47
25 Q. Can you turn to the '127 patent. 10:51:48

1 A. Certainly. 10:51:50

2 Q. I'd like you to look at claim 22. Are you 10:51:54

3 familiar with this? 10:51:57

4 A. Yes, I am. 10:52:02

5 Q. Actually, shift gears to claim 1. You're 10:52:02

6 familiar with claim 1, right? 10:53:04

7 A. I'm familiar with claim 1 of the '127 patent, 10:53:06

8 yes. 10:53:08

9 Q. I'd like you to focus on Step D for a moment. 10:53:09

10 You'll see Step D has three components, a 10:53:19

11 confirming step, a comparing step and an 10:53:22

12 analyzing step. Do you see that? 10:53:25

13 A. I see those terms appearing in Step D, yes. 10:53:28

14 Q. Do you understand that a claim element 10:53:32

15 may be expressed as a means or step for 10:53:56

16 performing a specified function without the 10:53:59

17 recital of a definite structure or materials 10:54:01

18 for performing the step in the claim 10:54:05

19 language? 10:54:07

20 MR. MILLS: Objection to form. 10:54:07

21 A. (Witness examines document) Could you repeat 10:54:25

22 the question, please? 10:55:41

23 Q. Do you understand that a claim element 10:55:43

24 may be expressed as a means or step for 10:55:46

25 performing a specified function without 10:55:48

1 the recital of a definite structure or 10:55:51
2 materials for performing the step in the 10:55:54
3 claim language? 10:55:57
4 MR. MILLS: Objection to form, as 10:55:58
5 to the scope and to the extent it calls for 10:56:02
6 a legal conclusion. 10:56:04
7 A. So it appears that you're quoting patent 10:56:05
8 law or some other official document. To the 10:56:08
9 best of my knowledge, that does not appear, 10:56:15
10 a statement to that effect does not appear 10:56:16
11 in my report today. And sitting here today, 10:56:18
12 I cannot tell you whether or not what you 10:56:22
13 just said is correct or not. 10:56:25
14 Q. Are you familiar with what is sometimes 10:56:27
15 called a means for, or a step for claim -- 10:56:30
16 sorry, means-plus or step-plus-function 10:56:34
17 claim? 10:56:36
18 MR. MILLS: Objection to form, 10:56:36
19 outside the scope. 10:56:39
20 A. I didn't render an opinion on that in my 10:56:41
21 report which is the subject of our deposition 10:56:44
22 today. Sitting here today, I'm not familiar 10:56:47
23 with that, and I am not a patent agent or 10:56:51
24 patent attorney and I'm not familiar with 10:57:00
25 patent law or all the different types of 10:57:03

1 claims which may be rendered, but that's 10:57:06

2 not something I reviewed in preparation for 10:57:09

3 my deposition today. 10:57:11

4 Q. Let's look at the confirming the presence 10:57:14

5 of at least one sequence read derived from 10:57:16

6 each of the original first and second strands 10:57:20

7 of the adapter DNA molecules. Are you with 10:57:22

8 me? 10:57:27

9 A. Yes, I see that. 10:57:27

10 Q. Do you believe that claim is a 10:57:28

11 means-plus-function or a step-plus-function 10:57:31

12 claim? 10:57:33

13 MR. MILLS: Objection to form, 10:57:34

14 outside the scope. 10:57:36

15 A. So as I stated earlier, I'm not a licensed 10:57:59

16 patent agent, nor am I a patent attorney. 10:58:16

17 I'm not intimately familiar with patent law. 10:58:18

18 I do not know all the different types of 10:58:22

19 claims that might be provided within patents, 10:58:26

20 and the question you asked is outside the 10:58:32

21 scope of my report which is what I'm prepared 10:58:34

22 to testify about today. So sitting here 10:58:37

23 today, I am not in a position to render an 10:58:39

24 opinion about the form of claim 1-D. 10:58:42

25 Q. All right. Now, do you also understand that 10:58:48

1 if a claim is a so-called means-plus-function 10:58:51
2 or step-plus-function, that that claim should 10:58:54
3 be construed to cover the corresponding 10:58:57
4 structure, material or acts described in 10:58:59
5 the specification and equivalents thereof? 10:59:02
6 MR. MILLS: Objection to form, 10:59:04
7 outside the scope and to the extent it calls 10:59:05
8 for a legal conclusion. 10:59:08
9 A. So as I stated earlier, I'm neither a patent 10:59:11
10 attorney, nor a licensed patent agent. I 10:59:16
11 don't believe Dr. Satija offered any opinions 10:59:19
12 about that to which I responded. Given that 10:59:21
13 I'm not familiar with patent law and that 10:59:25
14 it's outside the scope of what we had agreed 10:59:30
15 I would testify to today, namely the 10:59:32
16 arguments that appear in my rebuttal report, 10:59:35
17 I'm not prepared to offer an opinion about 10:59:38
18 that, sitting here today. 10:59:41
19 Q. Sitting here today, as of May 15, 2023, do 10:59:41
20 you know if you've ever reviewed the 10:59:47
21 specification of the '127 patent to determine 10:59:48
22 whether there's any corresponding material, 10:59:51
23 structures or acts for the confirming step of 10:59:54
24 claim 1 of the '127 patent? 10:59:59
25 MR. MILLS: Objection to form, 11:00:01

1 outside the scope. 11:00:02

2 A. So your question involves what I believe 11:00:04

3 are a number of legal terms regarding how 11:00:08

4 patent claims are construed and how they're 11:00:10

5 to be interpreted. To the best of my 11:00:13

6 knowledge, I do not recall offering an 11:00:18

7 opinion on that. I may at some point have 11:00:21

8 examined that, but that is outside the scope 11:00:25

9 of what I'm prepared to testify about today. 11:00:27

10 Q. If you had examined the specification for 11:00:30

11 corresponds, for a structure that corresponds 11:00:33

12 to the confirming step that is structure of 11:00:36

13 material of steps, do you know if you found 11:00:39

14 any in the specification of the '127 patent? 11:00:42

15 MR. MILLS: Objection to form, 11:00:43

16 outside the scope. 11:00:45

17 A. So I don't believe I offered any opinions 11:00:46

18 about that in my rebuttal report, nor do I 11:00:49

19 believe Dr. Satija offered any arguments to 11:00:52

20 which I was asked to respond. So that's 11:00:55

21 outside the scope of what I'm prepared to 11:00:58

22 testify about today. 11:01:01

23 Q. Do you believe you've ever offered an opinion 11:01:01

24 as to whether there's structure or material 11:01:12

25 or acts that correspond to the confirming 11:01:15

1 step of claim 1 of the '127 patent? 11:01:17

2 MR. MILLS: Objection to form, 11:01:20

3 outside the scope. 11:01:22

4 A. So you're using a number of legal terms, 11:01:23

5 and I'm not intimately familiar with those. 11:01:26

6 So as I stated earlier, I'm neither a 11:01:28

7 patent attorney, nor licensed patent agent. 11:01:31

8 I have not reviewed those questions or 11:01:33

9 specifications in the context of what I'm 11:01:37

10 prepared to testify to today which are my 11:01:41

11 responses to a limited series of arguments 11:01:46

12 which I believe were fallaciously offered 11:01:48

13 by Dr. Satija in his report and to which I 11:01:50

14 responded to in my rebuttal report. That's 11:01:54

15 the scope of what I'm prepared to offer 11:01:57

16 opinions about today. 11:01:59

17 Q. Would you agree that the confirming element 11:02:00

18 of claim 1 is a functional step? 11:02:10

19 MR. MILLS: Objection to form and 11:02:14

20 as to scope. 11:02:17

21 A. My interpretation of your question based 11:02:18

22 on the way you're asking it is you're asking 11:02:23

23 me to draw a legal conclusion about roles 11:02:25

24 of different steps in patents. My assumption 11:02:29

25 is that a functional step has precise legal 11:02:31

1 definition. I'm neither a licensed patent 11:02:36
2 agent, nor patent attorney. That is not 11:02:39
3 something I reviewed in preparation for my 11:02:44
4 deposition today, which is my response to 11:02:47
5 Dr. Satija's report, and so I'm not prepared 11:02:49
6 to offer testimony about that. 11:02:55
7 Q. Do you believe that you're qualified to 11:02:56
8 determine whether the confirming step of 11:02:59
9 claim 1 of the '127 patent is a, quote, 11:03:01
10 "functional step"? 11:03:04
11 MR. MILLS: Objection, outside the 11:03:05
12 scope, form. 11:03:08
13 A. I don't know, sitting here today, how one 11:03:09
14 might define that. In the past I may have 11:03:13
15 offered opinions based on a study of what 11:03:18
16 had been disclosed to me, but I have not 11:03:23
17 reviewed the definition of functional claims 11:03:25
18 or functional steps, and so I'm not prepared 11:03:28
19 to offer testimony today about whether or 11:03:31
20 not claims may fall within certain classes or 11:03:35
21 not. 11:03:39
22 Q. Let's look at the comparing step of claim 1 11:03:39
23 of the '127 patent. Do you agree that the 11:03:42
24 comparing step in that claim recites a 11:03:45
25 means-plus-function or step-plus-function 11:03:48

1 limitation? 11:03:52

2 MR. MILLS: Objection to form, 11:03:52

3 outside the scope and to the extent it calls 11:03:54

4 for a legal conclusion. 11:03:58

5 A. As I stated earlier, I am neither a patent 11:04:00

6 agent, nor a licensed patent agent, nor a 11:04:05

7 patent attorney. I'm not familiar with 11:04:09

8 the breadth and depth of patent law, and I 11:04:12

9 have not done such an analysis in preparation 11:04:16

10 for my testimony today which I understood 11:04:18

11 would be limited to my response to Dr. 11:04:22

12 Satija's assertions and which are 11:04:27

13 encapsulated in Exhibit 1039 which should be 11:04:29

14 the subject of our deposition today. 11:04:37

15 Q. Do you believe you're qualified to opine 11:04:40

16 whether the comparing step is a 11:04:45

17 means-plus-function or step-plus-function 11:04:48

18 limitation as it appears in claim 1 of the 11:04:50

19 '127 patent? 11:04:53

20 MR. MILLS: Objection to form, 11:04:54

21 outside the scope. 11:04:56

22 A. So you're asking me a hypothetical question 11:04:59

23 without any context. I believe that should 11:05:02

24 I be provided with sufficient instruction 11:05:06

25 as to the legal meaning of these terms and 11:05:10

1 given sufficient time to review and analyze 11:05:13
2 various lines of evidence, I may be able to 11:05:17
3 arrive at a conclusion. However, that is 11:05:21
4 outside the scope of what I'm prepared to 11:05:25
5 testify about today. 11:05:27
6 Q. Did you at any point review the description 11:05:29
7 of the '127 patent to determine whether there 11:05:35
8 were any materials, structures or acts that 11:05:38
9 correspond to the confirming step of claim 1 11:05:41
10 of the '127 patent? 11:05:44
11 MR. MILLS: Objection to form. 11:05:45
12 Outside the scope. 11:05:47
13 A. So there are a number of legal terms that 11:05:48
14 appear in the question you just asked. In 11:05:51
15 preparation for my report today, I did not 11:05:55
16 review any materials that would allow me to 11:05:57
17 make such a determination. 11:06:00
18 Q. Do you believe you're qualified to review 11:06:01
19 the specification of the '127 patent to 11:06:04
20 determine whether there are any materials, 11:06:06
21 structures or acts that correspond to the 11:06:09
22 comparing step of claim 1 of the '127 patent? 11:06:11
23 MR. MILLS: Objection to form. 11:06:14
24 A. So as I stated earlier, I'm not a licensed 11:06:17
25 patent agent, nor am I a patent attorney. 11:06:20

1 legal definition of what comprises a 11:07:27
2 functional step and I have not reviewed 11:07:30
3 that in preparation for our deposition today 11:07:35
4 since that's outside the scope of the 11:07:39
5 opinions that I offered. 11:07:41
6 Q. Let's turn to the analyzing step of claim 1 11:07:42
7 of the '127 patent. Do you agree that the 11:07:46
8 analyzing step is a means-plus-function or 11:07:51
9 step-plus-function limitation? 11:07:54
10 MR. MILLS: Objection to form, 11:07:56
11 outside the scope and to the extent it calls 11:07:58
12 for a legal conclusion. 11:08:01
13 A. So you've asked me about terms which I 11:08:03
14 understand -- could you repeat the question, 11:08:06
15 please? 11:08:08
16 Q. Yes. Do you agree that the analyzing step 11:08:08
17 of claim 1 of the '127 patent is a 11:08:11
18 means-plus-function or step-plus-function 11:08:13
19 limitation? 11:08:15
20 MR. MILLS: Same objections. 11:08:16
21 A. So you asked me about means-plus-function 11:08:18
22 or step-plus-function claims. To my 11:08:21
23 understanding, those are legal definitions. 11:08:27
24 As I have explained to you numerous times, 11:08:29
25 I'm neither a patent attorney, nor am I a 11:08:32

1 licensed patent agent. I'm not familiar 11:08:35
2 intimately with the breadth and scope of 11:08:39
3 patent law and the way in which different 11:08:43
4 claims may or may not be defined. Sitting 11:08:45
5 here today, that is not something I prepared 11:08:48
6 to offer testimony on since it's outside 11:08:50
7 the scope of what we agreed would be the 11:08:53
8 subject of today's deposition, and so I'm not 11:08:56
9 prepared to offer an opinion as to how 11:09:01
10 various steps of claim 1 may or may not be 11:09:05
11 construed. 11:09:09
12 As I stated earlier, given 11:09:09
13 sufficient legal instruction and time to 11:09:11
14 review the relevant documents, I may or may 11:09:14
15 not be able to arrive at a particular 11:09:18
16 conclusion, but that's not something I'm 11:09:21
17 prepared to do today. 11:09:23
18 Q. All right. Would you agree that the 11:09:25
19 analyzing step of claim 1 of the '127 patent 11:09:28
20 is a functional step? 11:09:32
21 MR. MILLS: Objection to form, 11:09:33
22 outside the scope and to the extent it calls 11:09:35
23 for a legal conclusion. 11:09:38
24 A. So to the best of my understanding, the 11:09:40
25 term, quote, "functional step," unquote, has 11:09:47

1 a legal meaning in the context of patent 11:09:52
2 law. As I have informed you nearly a dozen 11:09:53
3 times, I am neither a licensed patent agent, 11:09:57
4 nor a patent attorney. I'm not intimately 11:10:02
5 familiar with the breadth and scope of 11:10:06
6 patent law, and so sitting here today, I am 11:10:09
7 not prepared to offer an opinion particularly 11:10:15
8 since that is outside the scope of what we 11:10:17
9 had agreed would be the subject of my 11:10:21
10 deposition today, which is my rebuttal report 11:10:24
11 to Dr. Satija, in which I don't believe I 11:10:27
12 offered any opinions regarding the definition 11:10:32
13 of legal terms. 11:10:34
14 As I stated earlier, given 11:10:36
15 sufficient instruction and an opportunity 11:10:38
16 to review the relevant materials offered or 11:10:43
17 provided in the patent, patent prosecution 11:10:48
18 history and whatever other materials I might 11:10:51
19 need to be able to reach a conclusion, I 11:10:54
20 believe I could potentially arrive at a 11:10:57
21 conclusion, but I'm not prepared to do that 11:11:00
22 today. 11:11:02
23 Q. Have you reviewed the specification of the 11:11:03
24 '127 patent to determine whether there's any 11:11:07
25 materials, structures or acts that correspond 11:11:12

1 to the analyzing step of claim 1? 11:11:14

2 MR. MILLS: Objection to form. 11:11:16

3 A. In preparation for my deposition today, I 11:11:19

4 reviewed materials relevant to offering 11:11:22

5 opinions to support my opinions regarding 11:11:27

6 arguments made by Dr. Satija about a variety 11:11:30

7 of different aspects of the '127 patent, 11:11:37

8 including whether or not the Travers 11:11:41

9 publications disclose amplification followed 11:11:52

10 by sequencing in which I offered an opinion 11:11:57

11 that they do, in fact, because amplification 11:11:59

12 is disclosed and amplification steps are 11:12:03

13 incredibly important in a variety of 11:12:06

14 different applications, including limited 11:12:09

15 sample, quantities, increased read depth or 11:12:11

16 the goal of targeting specific regions in a 11:12:16

17 genome. 11:12:20

18 I offered opinions about whether 11:12:21

19 or not the Travers publications disclose or 11:12:22

20 describe first and second-strand sequence 11:12:25

21 reads as required by claims 1 to 21, which 11:12:28

22 they do. I provided opinions about whether 11:12:31

23 or not the Travers publications describe 11:12:35

24 grouping as described in claims 22 to 30, 11:12:37

25 which they do. I also provided opinions 11:12:42

1 about whether or not the Travers publications 11:12:44
2 used the asymmetry of adapter DNA molecules 11:12:49
3 as required by claim 19, which they do, and 11:12:55
4 then disposed of arguments by Dr. Satija 11:12:57
5 about interoperability of the Travers 11:13:00
6 publications and secondary considerations. 11:13:03
7 I did not review the claims of 11:13:05
8 the '127 patent with the goal of offering 11:13:08
9 legal opinions about the meaning of different 11:13:11
10 claim terms or how they might be construed 11:13:15
11 within the legal framework because that's 11:13:18
12 beyond the scope of what I was prepared or 11:13:20
13 asked to testify about today. 11:13:22
14 MR. PICKARD: Move to strike as 11:13:24
15 non-responsive. 11:13:26
16 MR. MILLS: I oppose. 11:13:26
17 Q. Doctor, my question was a little different. 11:13:27
18 My question is not whether you did that 11:13:29
19 in preparation for today's deposition, but 11:13:31
20 have you ever done it, and I'll just rephrase 11:13:33
21 the question. Have you ever analyzed the 11:13:35
22 specification of the '127 patent to determine 11:13:37
23 whether there are any materials, structures 11:13:39
24 or acts that correspond to the analyzing step 11:13:41
25 in claim 1? 11:13:43

1 MR. MILLS: Objection to form. 11:13:44

2 A. So I'm not sure what the terms "materials, 11:13:47

3 structures or acts," sitting here today, mean 11:13:50

4 in the context of a legal framework. At 11:13:53

5 some point in the past I may have received 11:13:58

6 instruction about that and I may have been 11:14:01

7 given sufficient time and access to resources 11:14:03

8 to be able to perform such analysis, but 11:14:07

9 that's outside the scope of what I prepared 11:14:11

10 to testify about today, and to the best of 11:14:14

11 my recollection, I do not recall doing that, 11:14:17

12 although I may have at some point. Again, 11:14:20

13 it's outside the scope of what we had agreed 11:14:24

14 would be the subject of our deposition today. 11:14:27

15 Q. So would you be surprised to learn that 11:14:29

16 as recently as April 7th of this year, you 11:14:50

17 provided opinions that the confirming, 11:14:53

18 comparing and analyzing steps are 11:14:55

19 means-plus-function or step-plus-function 11:14:59

20 limitations? 11:15:02

21 MR. MILLS: Objection to form, as 11:15:03

22 to the scope. 11:15:05

23 A. So I do not recall as of April 7th offering 11:15:05

24 those opinions, although at the time I may 11:15:15

25 have received sufficient instruction as to 11:15:18

1 the meaning of those terms and have been 11:15:21
2 given an opportunity to review relevant 11:15:23
3 documents, including the patent claims and 11:15:27
4 other documents, the patent prosecution 11:15:30
5 history such that I may have rendered 11:15:31
6 opinions about the meaning of those terms. 11:15:35
7 Sitting here today, I do not recall. I 11:15:38
8 did not prepare to offer testimony about 11:15:42
9 that today. 11:15:43
10 Q. Would you be surprised to learn that as 11:15:45
11 recently as April 7, 2023, you opined that 11:15:48
12 the confirming, comparing and analyzing 11:15:54
13 limitations of claim 1 were, quote, 11:15:57
14 "functional steps," close quote? 11:15:59
15 MR. MILLS: Objection to form, 11:16:01
16 outside the scope. 11:16:03
17 A. Sitting here today, I do not recall offering 11:16:04
18 those opinions. That is not something that 11:16:07
19 I reviewed in preparation for my deposition, 11:16:11
20 which was by agreement limited to my expert 11:16:13
21 report, rebuttal report to Dr. Satija's 11:16:20
22 report. However, at the time I may have been 11:16:24
23 given sufficient instruction such that I 11:16:29
24 could analyze -- about the meaning of those 11:16:33
25 terms such that I was in a position to 11:16:35

1 analyze the relevant documents and offer an 11:16:38
2 opinion. However, I do not recall. 11:16:41
3 Q. All right. Would you be surprised to learn 11:16:45
4 that as of April 7, 2023, you had offered 11:16:50
5 opinions that there was no description 11:16:54
6 of corresponding structure of materials, 11:16:58
7 structures or acts corresponding to the 11:17:01
8 confirming, comparing and analyzing 11:17:04
9 limitations of claim 1? 11:17:07
10 MR. MILLS: Objection to form, as 11:17:08
11 to scope. 11:17:11
12 A. You're using a number of legal terms about 11:17:11
13 which I'm not intimately familiar. As of 11:17:14
14 April 7th, I may have been given sufficient 11:17:19
15 instruction about the meaning of those terms 11:17:21
16 and provided sufficient opportunity to review 11:17:24
17 the relevant documents and offer opinions 11:17:28
18 about those terms in the context of the 11:17:32
19 claims. However, that is outside the scope 11:17:37
20 of what I reviewed in preparation for my 11:17:40
21 deposition today which we had agreed would be 11:17:42
22 limited to the rebuttal report I had provided 11:17:45
23 in the context of this IPR matter. 11:17:54
24 Q. Would you be surprised to learn that as 11:17:56
25 recently as April 7, 2023, you had offered 11:18:00

1 opinions that the confirming, comparing and 11:18:03
2 analyzing steps of the '127 patent were 11:18:05
3 indefinite? 11:18:08
4 MR. MILLS: Objection to form, 11:18:09
5 outside the scope. 11:18:11
6 A. Again, that is not something that I have 11:18:12
7 reviewed today. As of April 7th, I may 11:18:17
8 have been given sufficient instruction about 11:18:21
9 the meaning of those terms which I'm not 11:18:22
10 intimately familiar, although I do have some 11:18:26
11 vague understanding as a layman as to their 11:18:32
12 meaning. 11:18:35
13 However, if I had been provided 11:18:36
14 with sufficient legal instruction and given 11:18:39
15 the opportunity to review the relevant 11:18:42
16 documents, I may have arrived at that opinion 11:18:45
17 and offered it as of that date. However, I 11:18:50
18 don't recall specifically doing so because 11:18:54
19 that's not something I reviewed in 11:18:58
20 preparation for my deposition today which, 11:19:00
21 by my understanding, was to be limited to my 11:19:03
22 rebuttal response to Dr. Satija's report 11:19:11
23 offered in this IPR matter. 11:19:14
24 MR. MILLS: Counsel, we've been 11:19:16
25 going for about an hour. Are we ready to 11:19:17

1 take a break? 11:19:19

2 MR. PICKARD: I got like five more 11:19:20

3 minutes to finish up this unit. 11:19:22

4 MR. MILLS: Is that okay with you? 11:19:24

5 THE WITNESS: Sure. 11:19:27

6 Q. You signed your rebuttal report in this case 11:19:27

7 on April 13th, correct, of this year, 2023? 11:19:30

8 A. Yes, I did. 11:19:36

9 Q. And that would have been within a week of 11:19:37

10 April 7th, 2023, correct? 11:19:39

11 A. Six days, yes. 11:19:42

12 Q. And that April 7th date, that's the date 11:19:44

13 you submitted your expert report in the 11:19:47

14 district court case involving the '127 11:19:51

15 patent, right? 11:19:55

16 MR. MILLS: Objection to form, 11:19:56

17 outside the scope. 11:19:57

18 A. The report you provided is actually from 11:19:58

19 August 26, 2022. 11:20:06

20 Q. Actually, that's not a report. That's a 11:20:08

21 declaration. 11:20:11

22 A. Sorry, declaration. 11:20:11

23 Q. I'm talking about the very lengthy expert 11:20:12

24 report you submitted as to the invalidity 11:20:14

25 of the patents-in-suit, including the '127 11:20:17

1 patent which you don't have in front of you. 11:20:19

2 I can tell you you won't find it there. 11:20:21

3 A. Then I can't confirm that because I don't 11:20:23

4 have it in front of me. 11:20:25

5 Q. Okay. Earlier you said that if you had 11:20:26

6 been given sufficient instruction, you might 11:20:39

7 be able to answer the question whether or 11:20:41

8 not the analyzing, comparing and confirming 11:20:43

9 steps were a means-plus-function or 11:20:47

10 step-plus-function claim. So I'm going to 11:20:50

11 give you a little instruction and I want you 11:20:52

12 to tell me if that's sufficient. 11:20:54

13 If you understood that a claim 11:20:56

14 element may be expressed as a means or step 11:20:58

15 for performing a specified function without 11:20:58

16 the recital of a definite structure or 11:21:04

17 materials for performing the step in the 11:21:07

18 claim language and also understood that the 11:21:07

19 claim should be construed to cover the 11:21:09

20 corresponding structure, material or acts 11:21:10

21 described in the specification or equivalents 11:21:12

22 thereof, if you had that understanding, could 11:21:16

23 you tell me whether those limitations were 11:21:17

24 functional steps or means-plus-function, 11:21:21

25 step-plus-function steps? 11:21:24

1 MR. MILLS: Objection to form, 11:21:25
2 outside the scope. 11:21:27
3 A. So since you're asking about a report 11:21:28
4 specifically in which you claim I made 11:21:30
5 certain statements, I would like to review 11:21:33
6 that report before answering. 11:21:35
7 Q. You can't answer that question? You have 11:21:38
8 a premise there. What do you base that 11:21:45
9 premise on? 11:21:47
10 A. Excuse me? 11:21:48
11 Q. You just made a factual assertion that I'm 11:21:49
12 asking you a question based on a report. 11:21:51
13 Where do you get that information from? 11:21:53
14 A. Your previous line of questioning. 11:21:55
15 Q. I'm just asking you if you had been given 11:21:58
16 an instruction that a claim element may be 11:22:00
17 expressed as a step or means for performing 11:22:02
18 a specified function without the recital 11:22:04
19 of a definite structure or materials for 11:22:07
20 performing the step in the claim language, 11:22:09
21 could you tell me whether or not a given 11:22:11
22 claim language particularly confirming, 11:22:13
23 comparing and analyzing fall within the 11:22:16
24 means-plus-function or step-plus-function 11:22:19
25 realm? 11:22:22

1 MR. MILLS: Objection to form 11:22:22

2 outside the scope. 11:22:23

3 A. So you're asking questions about a report 11:22:24

4 that I had submitted, you claim, on 11:22:26

5 April 6th, April 6th -- in April of this 11:22:35

6 year. I've asked to review that, but 11:22:39

7 generally, my answer would be yes, given 11:22:42

8 sufficient legal instruction and if I were 11:22:45

9 confident that the instruction you were 11:22:48

10 giving me was valid and correct, then given 11:22:50

11 access to relevant material and sufficient 11:22:56

12 time to study that material, I believe I 11:22:59

13 could arrive at an opinion. 11:23:03

14 Q. Now, several times today you mentioned an 11:23:06

15 agreement. In fact, you said we agreed to 11:23:09

16 the scope of this deposition. Do you 11:23:12

17 remember that? 11:23:14

18 A. Yes. 11:23:14

19 Q. Who are you referring to when you said "we 11:23:14

20 agreed"? 11:23:17

21 A. I believe that the attorneys for the 11:23:18

22 University of Washington through its center 11:23:23

23 for commercialization in TwinStrand and 11:23:25

24 the attorneys for Guardant Health had an 11:23:31

25 agreement about what the individual 11:23:34

1 depositions would be about. And so when I 11:23:36
2 used "we," I'm referring, of course, to 11:23:40
3 myself and Attorney Mills, who's defending 11:23:44
4 my deposition today, and the attorneys 11:23:49
5 representing TwinStrand. If I misspoke, 11:23:55
6 what I would believe -- what I believe I 11:23:58
7 should have said would be the attorneys 11:23:59
8 representing both groups had agreed about 11:24:02
9 the scope of today's deposition. 11:24:04
10 Q. What was your belief based on? 11:24:08
11 A. My understanding is that the scope of 11:24:13
12 today's deposition regards the document 11:24:17
13 which was offered to you on April 13, 2023 11:24:22
14 in which I responded to Dr. Satija. 11:24:32
15 Q. No, I understand that is your understanding. 11:24:34
16 My question is, you said you had a belief 11:24:37
17 earlier that there was an agreement. What 11:24:38
18 formed the basis for your belief that there 11:24:41
19 was an agreement between my side and Mr. 11:24:43
20 Mills' side? 11:24:47
21 A. My understanding was that the scope of 11:24:51
22 today's deposition was my rebuttal report 11:24:54
23 offered in this IPR matter, and I may have 11:24:59
24 mistakenly believed that the attorneys 11:25:02
25 representing both sides had agreed about the 11:25:06

1 limitations of what the deposition should 11:25:09
2 encompass. 11:25:13
3 Q. Were you ever instructed not to answer 11:25:14
4 questions about the written opinions you 11:25:16
5 provided in the district court case in 11:25:20
6 providing your testimony today? 11:25:23
7 MR. MILLS: I'm going to issue a 11:25:24
8 cautionary instruction here on the basis 11:25:26
9 of attorney-work-product privilege. So to 11:25:27
10 the extent the question calls for the 11:25:30
11 disclosure of the contents of any 11:25:32
12 confidential communications with counsel 11:25:35
13 that do not form a basis for any of your 11:25:37
14 opinions in this case, then I would instruct 11:25:40
15 you not to disclose those confidential 11:25:42
16 communications. 11:25:45
17 MR. PICKARD: It's a weird objection 11:25:46
18 because if you hadn't given that instruction, 11:25:47
19 there would be no basis for interposing it. 11:25:50
20 Q. Are you going to follow your lawyer's advice? 11:25:52
21 A. So I was under the belief that what I was 11:25:56
22 going to be deposed about today was this 11:26:03
23 report which was submitted on April 13th 11:26:06
24 responding to Dr. Satija's report. This is 11:26:13
25 what I'm prepared to answer questions about 11:26:17

1 rules of the PTAB are very clear about the 11:27:23
2 scope of cross-examination. It is for the 11:27:25
3 declaration. It doesn't include talking 11:27:27
4 about things that are not part of this 11:27:30
5 case. So we object to -- 11:27:32
6 MR. PICKARD: So -- 11:27:32
7 MR. MILLS: Just let me finish 11:27:35
8 making my record. So I think very few of 11:27:36
9 the questions today have been within the 11:27:40
10 scope. I think we're approaching a point 11:27:41
11 of wasting time, and so I would ask you 11:27:43
12 during the break to please review your 11:27:46
13 outline to make an evaluation of, if any of 11:27:48
14 the questions that you have actually are 11:27:52
15 about his declaration, to ask those and 11:27:54
16 then wrap up the deposition so that we're 11:27:57
17 not wasting the parties' time. 11:27:59
18 MR. PICKARD: We're not wasting 11:28:00
19 any time here. I'm well-familiar with the 11:28:02
20 scope of today's deposition, and it is more 11:28:02
21 than fair game to explore testimony that 11:28:05
22 the witness has given that is inconsistent 11:28:06
23 with his report, which I've done today. And 11:28:09
24 you're under a duty to tell the board when 11:28:12
25 you think there's a means-plus-function 11:28:12

1 limitation in the claims, and you haven't 11:28:14
2 done that. So why don't you think about how 11:28:15
3 you're going to fix that. 11:28:18
4 MR. MILLS: So we disagree with 11:28:19
5 you. I think we've each made a record. We 11:28:21
6 can go off the record. 11:28:22
7 MR. PICKARD: Thanks. 11:28:22
8 VIDEOGRAPHER: The time is 11:28. 11:28:23
9 We're off the record. 11:28:25
10 (Break taken) 11:28:26
11 VIDEOGRAPHER: The time 11:49. We 11:48:57
12 are back on the record. 11:49:09
13 BY MR. PICKARD: 11:49:11
14 Q. Dr. Quackenbush, could you please turn to 11:49:11
15 the '127 patent. 11:49:14
16 A. I have it. 11:49:15
17 Q. So looking at those three final steps, 11:49:16
18 confirming, comparing and analyzing as they 11:49:22
19 appear in claim 1, can you tell me today, 11:49:24
20 in your view, whether or not those, any of 11:49:26
21 those steps qualify as means-plus-function 11:49:29
22 or step-plus-function limitations? 11:49:32
23 MR. MILLS: Objection to form, 11:49:34
24 outside the scope, asked and answered. 11:49:35
25 A. So as I mentioned earlier, I'm neither a 11:49:39

1 licensed patent attorney, nor a licensed 11:49:44
2 patent agent. You're asking me to draw 11:49:46
3 legal conclusions about certain claim 11:49:50
4 elements that are beyond the scope of what 11:49:54
5 I'm prepared to talk about today and what 11:49:56
6 I reviewed in preparation for today's 11:49:59
7 documentation, and so at this moment in time, 11:50:02
8 I'm not prepared to offer such opinion. 11:50:05
9 However, given sufficient 11:50:08
10 instruction and time to review, instruction 11:50:10
11 as to the definition of those terms and legal 11:50:13
12 context, and given time to review relevant 11:50:16
13 materials, I believe I may be able to arrive 11:50:19
14 at such an opinion. 11:50:22
15 Q. Looking at those three limitations again, 11:50:24
16 confirming, comparing and analyzing 11:50:28
17 limitations in claim 1, can you tell me 11:50:30
18 whether, in your view, those limitations 11:50:33
19 are indefinite? 11:50:37
20 MR. MILLS: Objection to form, 11:50:38
21 outside the scope and asked and answered. 11:50:40
22 A. So I don't believe Dr. Satija offered 11:50:44
23 opinions about indefiniteness to which I 11:50:48
24 responded. I cannot find any of those in 11:50:51
25 the report which my understanding was the 11:50:55

1 subject of our deposition today. I have 11:50:58
2 not reviewed those claim elements with the 11:51:02
3 goal of offering opinions today about 11:51:04
4 indefiniteness. 11:51:07
5 My understanding is that 11:51:09
6 "indefiniteness" is a legal term and that 11:51:10
7 given sufficient instruction as to the 11:51:13
8 meaning of "indefiniteness" and time to 11:51:17
9 review the relevant documents, I believe 11:51:20
10 I could offer an opinion, but I'm not 11:51:23
11 prepared to offer an opinion today within 11:51:25
12 the context of what appears in my report. 11:51:29
13 Q. Doctor, I know I asked you earlier, but I 11:51:32
14 don't think the record is very clear. Have 11:51:36
15 you been instructed by anyone to not answer 11:51:38
16 questions concerning the opinions you 11:51:40
17 provided in the district court case that 11:51:42
18 involves the '127 patent? 11:51:45
19 MR. MILLS: Objection to form, asked 11:51:46
20 and answered. 11:51:48
21 A. I have been instructed that today's 11:51:49
22 deposition was on subject matter which is 11:51:54
23 included in my rebuttal report which was 11:51:58
24 submitted on April 13th, 2023, and that is 11:52:02
25 the subject matter about which I'm prepared 11:52:09

1 to offer testimony today. 11:52:11

2 MR. PICKARD: I move to strike as 11:52:14

3 non-responsive. 11:52:15

4 MR. MILLS: Opposed. 11:52:16

5 Q. I understand that you believe today is 11:52:17

6 strictly limited to your rebuttal report, 11:52:19

7 but my question is different and is simply, 11:52:21

8 has anyone instructed you not to answer 11:52:23

9 questions about the opinions you have 11:52:26

10 provided in the district court case 11:52:27

11 concerning the '127 patent? 11:52:29

12 MR. MILLS: Objection to form, asked 11:52:30

13 and answered. 11:52:32

14 A. So my understanding is that the scope of our 11:52:33

15 deposition today was the material covered 11:52:37

16 in my rebuttal report which was submitted on 11:52:41

17 April 13, 2023 in this IPR matter and that 11:52:47

18 is what I'm prepared to answer questions 11:52:52

19 about today. 11:52:54

20 Q. In preparing for your deposition, did any 11:52:55

21 of the attorneys instruct you not to answer 11:52:59

22 questions about the opinions you have 11:53:00

23 provided in the district court case? 11:53:02

24 MR. MILLS: Objection to form, asked 11:53:04

25 and answered. 11:53:06

1 A. So in preparation for my deposition today, 11:53:06
2 the attorneys told me that the subject of 11:53:11
3 this deposition would be my rebuttal report 11:53:17
4 offered in the context of the IPR matter, 11:53:22
5 and that is what I'm prepared to offer 11:53:25
6 testimony about today. 11:53:28
7 MR. PICKARD: Again, move to strike 11:53:30
8 as non-responsive. 11:53:31
9 MR. MILLS: I oppose. 11:53:32
10 Q. It's a very simple question. Were you 11:53:33
11 given an instruction not to talk about these 11:53:35
12 other opinions that you provided in the 11:53:39
13 district court case that relate to the '127 11:53:39
14 patent? 11:53:41
15 MR. MILLS: Objection to form, asked 11:53:41
16 and answered. 11:53:42
17 A. So as I told you earlier, my understanding 11:53:43
18 based on what the attorneys informed me of 11:53:45
19 over the weekend when we were preparing is 11:53:49
20 that the scope of today's deposition would 11:53:52
21 be my rebuttal report which was offered in 11:53:56
22 this IPR matter, not irrelevant matters 11:53:58
23 appearing in other courts. And so I did not 11:54:02
24 prepare to offer opinions about anything 11:54:05
25 other than my rebuttal report in which I 11:54:07

1 respond to Dr. Satija's assertions regarding 11:54:12
2 whether the Travers publications disclose 11:54:17
3 amplification followed by sequencing which, 11:54:20
4 as I've told you previously, they do, 11:54:23
5 whether the Travers publications describe 11:54:26
6 first and second-strand sequence reads as 11:54:28
7 required by claims 1 to 21, which I've 11:54:30
8 informed you they do, whether the Travers 11:54:33
9 publications describe grouping as in claims 11:54:36
10 22 to 30, which we've discussed earlier and 11:54:42
11 I informed you they do in part because 11:54:45
12 consensus sequences are produced which is a 11:54:49
13 form of grouping, whether or not the Travers 11:54:52
14 publications describe using the asymmetry 11:54:55
15 of adapter DNA molecules as required by claim 11:54:58
16 19 rather than the argument put forth by 11:55:03
17 Dr. Satija regarding only the adapters, not 11:55:05
18 the adapter DNA molecules, in which he's 11:55:10
19 incorrect, whether Dr. Satija's opinions 11:55:14
20 about interoperability of the various Travers 11:55:17
21 publications in which he presents a number 11:55:19
22 of meritless arguments and secondary 11:55:22
23 considerations which we discussed earlier 11:55:25
24 regarding publications, something called 11:55:27
25 duplex consensus sequencing which is not 11:55:32

1 represented in the claims of the '127 patent, 11:55:35
2 and that is what I'm prepared to offer 11:55:37
3 opinions about today. 11:55:39
4 Q. Thank you. So I appreciate that you've 11:55:40
5 shared with me what your understanding of 11:55:43
6 the scope of today's depositions is and what 11:55:45
7 you're prepared to testify to. My question, 11:55:48
8 frankly, is not designed to elicit either 11:55:51
9 of those facts. My question is very simple 11:55:54
10 and that is, did anyone instruct you not to 11:55:57
11 answer questions concerning the opinions 11:55:59
12 you offered in the district court about the 11:56:00
13 '127 patent? 11:56:02
14 MR. MILLS: Objection to form, asked 11:56:03
15 and answered. 11:56:05
16 A. So my understanding in preparing for the 11:56:07
17 deposition today was that the questions 11:56:09
18 would be about my rebuttal report which I 11:56:11
19 submitted on April 8th, 2023, in which I 11:56:15
20 responded to various arguments about the 11:56:20
21 '127 patent offered in this IPR matter, 11:56:24
22 including opinions offered by Dr. Satija 11:56:30
23 regarding whether or not the Travers 11:56:33
24 publications disclose amplification followed 11:56:35
25 by sequencing, which they do, whether the 11:56:38

1 Travers publications describe first and 11:56:42
2 second-strand sequence reads as required by 11:56:45
3 claims 1 to 21 of the '127 patent, which 11:56:47
4 they do, whether the Travers publications 11:56:52
5 describe grouping as in claims 22 to 30 11:56:54
6 which we had discussed earlier in which I 11:56:57
7 provided an explanation that centers around 11:57:01
8 assembly, whether or not the Travers 11:57:05
9 publications disclose using the asymmetry 11:57:09
10 of adapter DNA molecules as required by 11:57:12
11 claim 19, which they do, which was offered 11:57:17
12 in response to an argument from Dr. Satija 11:57:20
13 which ignored the DNA molecules, opinions 11:57:23
14 about interoperability, arguments presented 11:57:26
15 by Dr. Satija regarding the Travers 11:57:30
16 publications and secondary considerations 11:57:31
17 offered by Dr. Satija regarding duplex 11:57:36
18 consensus sequencing which has nothing to 11:57:39
19 do with the claims of the '127 patent, and 11:57:41
20 that is what I have prepared to offer 11:57:44
21 testimony about today. 11:57:46
22 Q. All right. 11:57:47
23 MR. PICKARD: Again, I'll move to 11:57:48
24 strike as non-responsive. 11:57:49
25 MR. MILLS: Oppose. 11:57:50

1 MR. PICKARD: Jad, I'll tell you, 11:57:52
2 I don't think your witness is doing you any 11:57:54
3 favors here. I think, given the nature of 11:57:56
4 your objections, you agree I'm entitled to 11:58:00
5 an answer. I suspect that the answer will 11:58:02
6 reveal that nothing improper happened here, 11:58:03
7 but I've got a witness who won't answer the 11:58:04
8 question. So if you want to talk to him 11:58:07
9 off the record at the next break, I'm not 11:58:09
10 going to hold that against you, I want to 11:58:09
11 get an answer. Otherwise, I think I'm going 11:58:12
12 to go to the board and force an answer 11:58:14
13 because it would be entirely improper for 11:58:17
14 you to instruct the witness not to answer 11:58:17
15 questions about relevant topics. I'll let 11:58:20
16 you make that decision on the next break. 11:58:21
17 MR. MILLS: Do you want to excuse 11:58:23
18 the witness and we can talk about this? 11:58:24
19 MR. PICKARD: No. I'm going to keep 11:58:27
20 asking questions and you can talk to him at 11:58:27
21 the break. 11:58:28
22 MR. MILLS: Okay. I just want 11:58:28
23 to note in one of the answers there's a 11:58:29
24 reference to an April 8th declaration. I 11:58:31
25 think that was in reference to April 13. 11:58:34

1 THE WITNESS: I'm sorry, I misspoke. 11:58:38
2 It was April 13. 11:58:40
3 MR. PICKARD: I'm sure in one of his 11:58:44
4 multiple filibusters he got the right date. 11:58:45
5 Let's mark another exhibit. This 11:58:49
6 is Quackenbush 2, please. 11:58:52
7 (Exhibit 2 marked for 11:58:53
8 identification.) 11:58:54
9 MR. MILLS: I object to Exhibit 2 11:59:12
10 as outside the scope. I also object to it 11:59:19
11 as hearsay. 11:59:23
12 Q. Alrighty. Dr. Quackenbush, you've got 11:59:26
13 Exhibit 2 in front of you, Quackenbush 2? 11:59:29
14 A. Yes, I do. 11:59:31
15 Q. If you look at the cover page, you'll see 11:59:32
16 it has the caption of the district court 11:59:34
17 case. Do you see that? 11:59:35
18 A. Yes, I do. 11:59:38
19 Q. Beneath that it says, "Videotaped Deposition 11:59:40
20 of John Quackenbush, Ph.D." That's you, 11:59:43
21 right? 11:59:46
22 A. Yes, it is. 11:59:46
23 Q. And it references a Friday, September 9, 2022 11:59:47
24 date, correct? 11:59:51
25 A. Yes, it does. 11:59:52

1 Q. And you recall I deposed you on that date in 11:59:52
2 Boston? Look at Page 2, it has appearances. 11:59:55
3 A. Yes, I see your name mentioned. 12:00:02
4 Q. Okay. And you recognize this transcript as 12:00:04
5 a record of the testimony you gave that day, 12:00:07
6 correct? 12:00:09
7 A. I believe it is. I will take your word for 12:00:10
8 it. 12:00:13
9 Q. And you were sworn under oath when you gave 12:00:13
10 this testimony, correct? 12:00:16
11 A. Yes, I was. 12:00:17
12 Q. And given that, you would have done your 12:00:18
13 best to testify truthfully and accurately, 12:00:19
14 correct? 12:00:22
15 A. That is correct. 12:00:22
16 Q. You were represented by counsel at this 12:00:22
17 deposition, correct? 12:00:24
18 A. Yes, attorneys from the law firm DLA Piper. 12:00:25
19 Q. And they were free to make objections as 12:00:30
20 was appropriate, correct? 12:00:32
21 A. I believe they were, yes. 12:00:35
22 Q. And after the deposition, you were given a 12:00:36
23 copy of this and given an opportunity to 12:00:38
24 correct any errors in the transcript, 12:00:40
25 correct? 12:00:43

1 A. Yes, I believe I was. 12:00:44

2 Q. In fact, you did correct some errors in the 12:00:46

3 transcript, is that right? 12:00:48

4 A. As many as I could find at the time. There 12:00:50

5 may be others. 12:00:55

6 MR. PICKARD: Mark that as 3. 12:01:03

7 (Exhibit 3 marked for 12:01:08

8 identification.) 12:01:09

9 MR. MILLS: I object to Quackenbush 12:01:22

10 3 as outside the scope and hearsay. 12:01:23

11 Q. Okay. Dr. Quackenbush, do you recognize 12:01:26

12 Quackenbush Exhibit 3 as a declaration you 12:01:30

13 submitted in an IPR numbered IPR 2019-00652? 12:01:33

14 A. (Witness examines document) So this is the 12:02:05

15 declaration I submitted on December 4th, 12:04:23

16 2019, in an IPR, IPR No. 2019-00652 regarding 12:04:29

17 the Patent 9,834,822 and this was a matter 12:04:38

18 involving Foundation Medicine and Guardant 12:04:45

19 Health. 12:04:49

20 Q. If you look at the last page, it has your 12:04:49

21 signature, right? 12:04:51

22 A. Yes, it does. 12:04:52

23 Q. So the statements contained in this document 12:04:53

24 were made under penalty of perjury, is that 12:04:56

25 right? 12:04:58

1 A. Yes, they were. 12:04:59

2 Q. And so you did your best to be truthful and 12:04:59

3 accurate in what you set forth in this 12:05:01

4 document? 12:05:03

5 A. Yes, I did. 12:05:03

6 Q. If you look at Paragraph 13 on Page 4 of 12:05:04

7 this exhibit, do you see there's mention of 12:05:08

8 a disclosure of U.S. Patent No. 9,752,188? 12:05:14

9 A. Hold on, please. 12:05:19

10 Q. The Schmitt patent. 12:05:23

11 A. Which paragraph? 12:05:23

12 Q. Paragraph 13 starting three lines down, you 12:05:25

13 see there's mention of the disclosure of 12:05:31

14 US Patent No. 9,752,188. Do you see that? 12:05:35

15 A. Yes, I do. 12:05:36

16 Q. And the '188 patent is related by priority 12:05:36

17 to the '127 patent, right? 12:05:40

18 MR. MILLS: Objection to form, 12:05:42

19 outside the scope. 12:05:43

20 A. Sitting here today, with the declaration 12:05:44

21 that I submitted in December 2019, I do not 12:05:53

22 recall the specifics of the '188 patent, 12:06:04

23 nor do I recall its history. 12:06:11

24 Q. If you could take the '127 patent out, 12:06:13

25 please. 12:06:30

1 A. I have it. 12:06:30

2 Q. If you turn to the second page, you'll see 12:06:31

3 a heading, "Related US Application Data"? 12:06:36

4 A. I have it. 12:06:44

5 Q. Do you see there's a reference to the '188 12:06:45

6 patent there? 12:06:48

7 MR. MILLS: Objection to scope. 12:07:08

8 A. I see a reference in the '127 patent to a 12:07:16

9 patent numbered 9,752,188. 12:07:29

10 Q. And that's the same number that appears on 12:07:34

11 the report, declaration that we've marked as 12:07:38

12 Quackenbush 3, correct? 12:07:41

13 MR. MILLS: Objection to scope. 12:07:43

14 A. The number appearing in the related US 12:07:45

15 application data, 9,752,188, is indeed the 12:07:55

16 number referred to in Paragraph 13 of a 12:08:00

17 declaration I submitted in 2019 in an 12:08:06

18 unrelated matter before the patent review 12:08:11

19 board. 12:08:15

20 Q. Do you believe that the opinions you provided 12:08:15

21 in the district court case involving the 12:08:20

22 '127 patent are irrelevant to the opinions 12:08:22

23 you provided in this IPR? 12:08:24

24 MR. MILLS: Objection to form. 12:08:26

25 A. So that's a vague question. In both cases 12:08:28

1 I am offering opinions on the '127 patent. 12:08:34

2 In my understanding, those two matters are 12:08:43

3 independent matters which are going to be 12:08:46

4 adjudicated separately. 12:08:50

5 To the best of my understanding, 12:08:53

6 a decision in one may or may not affect 12:08:54

7 others, but to the best of my knowledge, 12:08:59

8 they are separate, separate legal 12:09:04

9 proceedings. 12:09:10

10 Q. Did you do your best to make sure that 12:09:10

11 the opinions you provided in the district 12:09:14

12 court case concerning the '127 patent were 12:09:16

13 consistent with those provided in this 12:09:18

14 case concerning the '127 patent? 12:09:19

15 MR. MILLS: Objection to form, 12:09:22

16 outside the scope. 12:09:23

17 A. To the best of my knowledge, the opinions 12:09:25

18 I've provided are consistent. The opinions 12:09:30

19 reflect my understanding at the time I 12:09:34

20 submitted different declarations. The 12:09:37

21 opinions also reflect the state at which an 12:09:41

22 individual case is in the process. 12:09:44

23 For example, I understand that at 12:09:47

24 the time of claim construction, an expert 12:09:50

25 such as myself is given an opportunity to 12:09:54

1 offer opinions in a civil case. I also 12:09:56
2 understand once the court has construed 12:10:01
3 claims, my role as an expert is to interpret 12:10:04
4 the claims in the context of the claim 12:10:08
5 construction offered by the court 12:10:13
6 irrespective of what my earlier opinions 12:10:16
7 might have been. And so at each stage I 12:10:19
8 offer opinions that I believe are consistent 12:10:25
9 with my understanding of the requirements 12:10:27
10 provided in the context of each individual 12:10:30
11 legal proceeding and my understanding of 12:10:33
12 what is represented in the patents, the 12:10:37
13 prosecution history and other documents given 12:10:39
14 the understanding of one of ordinary skill 12:10:43
15 in the art. 12:10:45
16 MR. PICKARD: Jad, I propose a 12:10:56
17 relatively short break for lunch so we can 12:10:58
18 get organized and wrap things up pretty 12:11:00
19 quickly afterwards. If you want to excuse 12:11:03
20 Dr. Quackenbush and say something on the 12:11:05
21 record, that would be fine. You mentioned 12:11:08
22 earlier that you might want to do that. 12:11:11
23 MR. MILLS: You're thinking that you 12:11:12
24 may be -- 12:11:13
25 MR. PICKARD: Break now because 12:11:13

1	AFTERNOON SESSION	12:47:45
2	VIDEOGRAPHER: The time is 12:58.	12:55:00
3	We're back on the record.	12:58:46
4	BY MR. PICKARD:	12:58:48
5	Q. Welcome back, Dr. Quackenbush.	12:58:48
6	A. Thank you.	12:58:50
7	Q. Try this one more time. So as part of your	12:58:51
8	preparation for today's deposition, did	12:58:57
9	anyone instruct you not to answer questions	12:58:58
10	about the opinions you provided in the	12:59:00
11	district court that relate to the '127	12:59:03
12	patent?	12:59:04
13	MR. MILLS: Objection to form,	12:59:05
14	scope, asked and answered.	12:59:07
15	A. So to the best of my understanding, I was	12:59:08
16	brought here today to offer testimony about	12:59:15
17	the declaration that I submitted in the	12:59:19
18	rebuttal to Dr. Satija's declaration and	12:59:24
19	that was the scope of what I was prepared to	12:59:27
20	testify about today and that is what I'm	12:59:29
21	prepared to testify about today. That's what	12:59:32
22	I prepared to testify about.	12:59:35
23	MR. PICKARD: I move to strike again	12:59:38
24	as non-responsive. I'd really like to avoid	12:59:39
25	going to the board on this, but apparently	12:59:43

1 MR. MILLS: Objection to scope. 01:00:52

2 A. I have no reason to doubt that. It very 01:00:54

3 well may be. Before answering detailed 01:01:01

4 questions, I'd actually like to have a 01:01:06

5 copy of the entire report so I'm sure I'm 01:01:07

6 answering questions in the right context. 01:01:09

7 However, I'm not prepared to offer 01:01:11

8 testimony on this today. I'm only prepared 01:01:13

9 to offer testimony on the subject matter 01:01:16

10 covered in my expert declaration that was 01:01:18

11 submitted in this IPR matter. 01:01:21

12 Q. I'd like to direct you to Paragraph 40, 01:01:23

13 please. Let me know when you're there. 01:01:26

14 A. I'm there. 01:01:35

15 Q. Okay. In Paragraph 40 you wrote, "I 01:01:35

16 understand that a claim element may be 01:01:38

17 expressed as a means or step for performing 01:01:40

18 a specified function without the recital 01:01:43

19 of a definite structure or materials for 01:01:45

20 performing the step in the claim language 01:01:47

21 and the claim should be construed to cover 01:01:51

22 the corresponding structure, material or 01:01:52

23 acts described in the specification and 01:01:55

24 equivalents thereof. I understand that where 01:01:58

25 a patent does not disclose a corresponding 01:02:00

1 definite structure or materials for 01:02:03

2 performing the steps, the claims may be 01:02:05

3 invalid for indefiniteness." Did I read 01:02:08

4 that correctly? 01:02:12

5 MR. MILLS: Objection to scope. 01:02:13

6 A. (Witness examines document) Although this 01:02:24

7 document is outside the scope of what I'm 01:03:17

8 prepared about to testify about today and 01:03:19

9 represents a declaration submitted in a 01:03:22

10 separate legal matter, you did read that 01:03:24

11 paragraph correctly. 01:03:28

12 Q. Okay. Now, if you could turn to Paragraph 01:03:29

13 293 on the following page. 01:03:32

14 A. I see it. 01:03:36

15 Q. It appears beneath the heading 01:03:37

16 "Indefiniteness" and you wrote, "the method 01:03:39

17 claimed by the '127 patent includes 01:03:43

18 functional steps, for example, the 01:03:46

19 'confirming,' 'comparing' and 'analyzing' 01:03:48

20 steps of claim 1. The specification of the 01:03:54

21 '127 patent does not disclose a corresponding 01:03:57

22 structure or steps. Thus, it is my opinion 01:04:00

23 that the claims are invalid for 01:04:03

24 indefiniteness." Did I read that correctly? 01:04:05

25 MR. MILLS: Objection to scope. 01:04:08

1 pairing single-strand consensus sequences 01:07:34
2 with their strand-mate. The code provided 01:07:36
3 in Figure 10 discloses selecting 01:07:37
4 single-strand consensus sequences based on 01:07:39
5 a stringent filter and forming duplex 01:07:42
6 consensus sequences from the filter 01:07:47
7 single-strand consensus sequences. The 01:07:48
8 filtering step retains pairs of single-strand 01:07:50
9 consensus sequences that have an exact 01:07:55
10 complementary match in the SMI sequences. 01:07:56
11 Figure 10 further describes forming duplex 01:07:59
12 consensus sequences from the filtered 01:08:02
13 single-strand consensus sequences. Duplex 01:08:06
14 consensus sequences include nucleotides 01:08:09
15 that perfectly agree between a pair of 01:08:10
16 single-strand consensus sequences. When a 01:08:15
17 pair of single-strand consensus sequences 01:08:15
18 do not agree and is included, this code 01:08:18
19 describes an operation on single-strand 01:08:21
20 consensus sequences which are distinct from 01:08:23
21 the sequence reads and so do not correspond 01:08:28
22 to the confirming, comparing and analyzing 01:08:29
23 steps of claim 1. And my understanding of 01:08:31
24 this at the time I wrote it, now that I've 01:08:35
25 had the opportunity to refresh my memory of 01:08:37

1 at least a limited portion of this, is that 01:08:39
2 the method claimed by the '127 patent 01:08:45
3 includes functional steps, for example, the 01:08:48
4 confirming, comparing and analyzing steps 01:08:50
5 in claim 1. The specification of the '127 01:08:53
6 patent does not disclose a corresponding 01:08:56
7 structure of the steps, thus, it is my 01:08:58
8 opinion that the claims are invalid for 01:09:01
9 indefiniteness. 01:09:04
10 Q. Why don't you take a look at the '127 patent 01:09:06
11 for a moment. 01:09:09
12 A. Certainly. 01:09:11
13 Q. Look again at claim 1, Dr. Quackenbush. Do 01:09:16
14 you agree that the confirming, comparing 01:09:28
15 and analyzing steps as recited there are 01:09:29
16 means-plus-function or step-plus-function 01:09:33
17 claims? 01:09:35
18 MR. MILLS: Objection to form, 01:09:36
19 outside the scope. 01:09:37
20 A. (Witness examines document) Could you repeat 01:09:38
21 the question, please? 01:10:18
22 Q. Sure. Looking at claim 1 on the '127 01:10:19
23 patent, do you believe that the comparing, 01:10:24
24 analyzing and confirming steps qualify as 01:10:27
25 means-plus-function or step-plus-function 01:10:34

1 functional steps, for example, confirming, 01:12:06
2 comparing and analyzing steps of claim 1 01:12:09
3 and that the specification does not disclose 01:12:12
4 corresponding structure or steps. Thus, it 01:12:15
5 was my opinion that the claims were invalid 01:12:19
6 for indefiniteness. 01:12:21
7 I can tell you that, sitting here 01:12:23
8 today, based on what I've had the opportunity 01:12:24
9 to read today and based on my ability to 01:12:26
10 confirm or to remind myself what I had 01:12:33
11 written more than a month ago, there is no 01:12:38
12 disclosure that I was able to find in the 01:12:44
13 '127 patent that describes these various 01:12:46
14 steps, operating on sequence reads, rather, 01:12:51
15 the Figure 10, which I believe TwinStrand 01:12:56
16 has pointed to, does not analyze sequence 01:13:00
17 reads, but analyzes consensus sequences. 01:13:03
18 So to the best of my understanding, 01:13:06
19 those steps are not defined in the 01:13:08
20 specification of the '127 patent, and so 01:13:12
21 without a definition of those steps, my 01:13:15
22 understanding as a layman is that it renders 01:13:17
23 them indefinite. 01:13:20
24 MR. PICKARD: I'll pass the witness. 01:13:26
25 MR. MILLS: Let's take a break. 01:13:27

1 VIDEOGRAPHER: The time is 1:13. 01:13:29
2 We're off the record. 01:13:38
3 (Break taken) 01:13:40
4 VIDEOGRAPHER: The time is 1:33. 01:33:02
5 We're back on the record. 01:33:26
6 CROSS EXAMINATION 01:33:26
7 BY MR. MILLS: 01:33:26
8 Q. Dr. Quackenbush, do you recall being asked 01:33:27
9 questions during your cross-examination 01:33:29
10 about whether or not the claims of the 01:33:31
11 '127 patent encompassed amplification and 01:33:34
12 sequencing as disclosed by the Travers 01:33:38
13 references? 01:33:40
14 MR. PICKARD: Objection to scope. 01:33:41
15 A. Yes, I recall that. 01:33:42
16 Q. Do you stand by that testimony? 01:33:46
17 A. Yes, I do. 01:33:48
18 Q. Why do you stand by that testimony? 01:33:49
19 A. The specification of the '127 patent 01:33:51
20 explicitly calls out the Travers references 01:33:56
21 as an embodiment of claim 1 and the claims 01:33:58
22 in the '127 patent. And in the expert report 01:34:03
23 I filed in the context of the '127 patent, I 01:34:09
24 lay out the arguments by which I believe the 01:34:12
25 Travers references render claim 1 and 01:34:17

1 the pending claims and other claims in the 01:34:21
2 '127 patent at the very least obvious, if 01:34:24
3 not fully anticipatory. 01:34:28
4 MR. MILLS: Thank you. No further 01:34:30
5 questions. 01:34:32
6 MR. PICKARD: I have no questions. 01:34:32
7 MR. MILLS: The deposition is over. 01:34:40
8 VIDEOGRAPHER: The time is 1:34. 01:34:41
9 We're off the record. 01:34:43
10 (Whereupon the deposition was 01:34:45
11 concluded at 1:34 p.m.)
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1 COMMONWEALTH OF MASSACHUSETTS)
2 SUFFOLK, SS.)
3
4

5 I, Jeanette Maracas, Registered
6 Professional Reporter and Notary Public in
7 and for the Commonwealth of Massachusetts, do
8 hereby certify that there came before me on
9 the 15th day of May, 2023, at 9:04 a.m., the
10 person hereinbefore named, who was by me duly
11 sworn to testify to the truth and nothing but
12 the truth of his knowledge touching and
concerning the matters in controversy in this
cause; that he was thereupon examined upon
his oath, and his examination reduced to
typewriting under my direction; and that the
deposition is a true record of the testimony
given by the witness.

13 I further certify that I am neither
14 attorney or counsel for, nor related to or
15 employed by, any attorney or counsel employed
16 by the parties hereto or financially
17 interested in the action.

18 In witness whereof, I have hereunto
19 set my hand this 16th day of May, 2023.

20 

21 Notary Public
22 My commission expires 7/29/27
23
24
25

1 Jad A. Mills

2 Jmills@wsgr.com

3 May 19, 2023

4 RE: GUARDANT HEALTH, INC. v. UNIVERSITY OF WASHINGTON

5 5/15/2023, John Quackenbush PhD (#5919924)

6 The above-referenced transcript is available for
7 review.

8 Within the applicable timeframe, the witness should
9 read the testimony to verify its accuracy. If there are
10 any changes, the witness should note those with the
11 reason, on the attached Errata Sheet.

12 The witness should sign the Acknowledgment of
13 Deponent and Errata and return to the deposing attorney.
14 Copies should be sent to all counsel, and to Veritext at
15 clientservices-yom@veritext.com

16
17 Return completed errata within 30 days from
18 receipt of testimony.

19 If the witness fails to do so within the time
20 allotted, the transcript may be used as if signed.

21
22 Yours,

23 Veritext Legal Solutions
24
25

1 GUARDANT HEALTH, INC. v. UNIVERSITY OF WASHINGTON

2 John Quackenbush PhD (#5919924)

3 E R R A T A S H E E T

4 PAGE _____ LINE _____ CHANGE _____

5
6 REASON _____

7 PAGE _____ LINE _____ CHANGE _____

8
9 REASON _____

10 PAGE _____ LINE _____ CHANGE _____

11
12 REASON _____

13 PAGE _____ LINE _____ CHANGE _____

14
15 REASON _____

16 PAGE _____ LINE _____ CHANGE _____

17
18 REASON _____

19 PAGE _____ LINE _____ CHANGE _____

20
21 REASON _____

22
23 _____

24 John Quackenbush PhD Date

1 GUARDANT HEALTH, INC. v. UNIVERSITY OF WASHINGTON

2 John Quackenbush PhD(#5919924)

3 ACKNOWLEDGEMENT OF DEPONENT

4 I, John Quackenbush PhD, do hereby declare that I
5 have read the foregoing transcript, I have made any
6 corrections, additions, or changes I deemed necessary as
7 noted above to be appended hereto, and that the same is
8 a true, correct and complete transcript of the testimony
9 given by me.

10
11 _____
12 John Quackenbush PhD Date

13 *If notary is required

14 SUBSCRIBED AND SWORN TO BEFORE ME THIS
15 _____ DAY OF _____, 20____.

16
17
18 _____
19 NOTARY PUBLIC
20
21
22
23
24
25

[& - 20005]

&	10,287,631 9:11	25:25 26:6	103:20,23,24
& 1:20 2:3,7 4:9	10,689,699 9:11	27:7 28:9 29:1	105:2,5,10,22
0	10,752,951 9:12	30:3,16 31:9	106:13,25
063 9:15	10,760,127 1:8	31:20 32:7	107:13,20
075 7:11 23:23	9:13	33:21 37:7,12	108:11,19,22
1	10,801,063 9:15	37:17,20 38:6	108:23 109:2
1 1:1,2 3:9 8:1	10,889,858 9:15	38:9,12 39:9	12:11 98:9
8:2,8 10:23	100 3:15	39:13 40:2,12	12:58 99:2
11:8 12:9 13:2	1001 12:1	40:20 41:1,7,9	13 78:13 85:17
15:2,19 18:12	1002 28:3,18	41:19,22 42:10	90:25 91:2
22:8 23:24,25	30:21	42:19 44:19	94:6,12 95:16
25:12,18 32:16	1006 44:24	45:1,10,16,25	13th 74:7 79:23
35:7,14,20,21	1018 26:12	46:6,7,8,13,24	84:24
37:17 39:25	1021 26:13	46:25 47:4,14	15 1:22 4:6
41:6 45:1,6	1038 44:25	47:17 48:17,20	58:19
47:21 55:5,6,7	1039 12:12	49:6,9,25 50:9	15th 110:6
57:24 58:24	28:14 37:3	50:19 51:15	16th 110:16
60:1,18 61:9	38:8 39:12	52:14,21,25	18 26:9 34:11
61:22 62:18	46:23 62:13	53:3 54:18,25	188 94:16,22
63:9,22 64:15	108 3:4	55:7 58:21,24	95:5
65:6,17 66:10	10:05 35:1	59:14 60:1	19 23:1 28:21
66:19 68:1,21	10:18 35:4	61:9,23 62:19	37:24 39:4
69:25 71:13	11,118,221 9:16	63:7,10,19,22	40:6 41:13
72:9 82:19	11,149,306 9:17	64:15 65:7,17	69:3 87:16
83:17 87:7	1100 2:8	66:19 67:24	89:11 111:3
89:3 102:20	113 1:1 30:21	68:7 69:8,22	1:13 108:1
103:23 104:23	11:28 82:8	73:2 74:14,25	1:33 108:4
105:5,13,22	11:49 82:11	82:15 84:18	1:34 109:8,11
106:15 107:2	12/4/19 3:13	85:11 86:13	2
108:21,25	127 7:9,10 9:13	88:1,13,21	2 3:11 9:5,6
10 103:20,24	11:21,24,25	89:3,19 94:17	25:12 91:6,7,9
104:3,11	12:5,7 15:22	94:24 95:8,22	91:13,13 92:2
107:15	16:20 17:16,17	96:1,12,14	20 3:9 113:15
	19:18 20:7,16	99:11 100:25	20005 2:9
	23:12,14 25:15	102:17,21	

[2019 - actually]

2019 93:16 94:21 95:17 2019-00652 93:13,16 2022 35:23,23 74:19 91:23 2023 1:22 4:6 58:19 71:11 72:4,25 74:7 74:10 78:13 84:24 85:17 88:19 100:13 110:6,16 111:3 21 22:8 37:17 38:19 39:25 41:6 47:24 49:19 68:21 87:7 89:3 21-1126 18:21 21498 110:19 22 12:7 22:13 23:16,25 24:2 24:11,13,15,19 24:25 25:6,18 25:23 26:6 37:20 38:21 40:2 41:9 47:25 51:2 55:2 68:24 87:10 89:5 221 9:16 23 25:6 26 12:7 35:23 35:23 48:16,20 49:5,8 74:19	29 11:9,10 293 102:13 3 3 3:13 93:6,7 93:10,12 95:12 30 11:10,11 22:13 37:20 38:21 40:2 41:9 51:2 68:24 87:10 89:5 111:17 306 9:17 34 8:17,21,23 35 41:20 42:9 42:25 44:17 39 44:8,14 45:7 47:3 392 106:23 4 4 1:2 3:14 94:6 100:4,5 4/7/23 3:14 40 101:12,15 48 28:25 29:11 32:20,24 4th 93:15 5 5 3:4 5/15/2023 111:5 5919924 111:5 112:2 113:2	6 631 9:11 699 9:11 50:2 52:13 6th 77:5,5 7 7 71:11 72:4,25 100:13 7/29/27 110:20 701 2:4 72 49:11,17,23 7th 70:16,23 72:14 73:7 74:10,12 8 8 3:10 82 49:11,17,24 858 9:16 8th 88:19 90:24 9 9 91:23 9,752,188 94:8 94:14 95:9,15 9,834,822 93:17 9/2/22 3:11 90 13:2 91 3:12 14:8 16:4,16 17:18 18:5 93 3:13 951 9:12 98 11:8 13:3 15:1,23 16:16 16:22 17:8	18:5 98104 2:4 9:04 1:22 4:7 110:6 a a.m. 1:22 4:7 110:6 ability 36:19 53:18 107:9 able 40:13 63:2 66:15 67:19 70:8 75:7 83:13 107:12 above 45:9 46:8 47:3 111:6 113:7 access 70:7 77:11 accuracy 111:9 accurate 94:3 accurately 6:8 10:24 11:5 92:13 acknowledge... 113:3 acknowledg... 111:12 action 110:14 acts 58:4,23 59:25 63:8,21 67:25 69:24 70:3 72:7 75:20 101:23 actually 10:8 30:15 31:21
--	--	--	---

[actually - appearing]

55:5 74:18,20 81:14 101:4 adapter 22:25 25:9 37:22,23 38:24 39:2 40:4,5 41:12 48:11,19 50:3 50:18 51:25 57:7 69:2 87:15,18 89:10 adapters 22:23 25:16,17,21 38:25 87:17 additional 23:1 40:7 41:14 50:1 80:16 additions 113:6 address 64:9 addressed 13:9 adjudicated 96:4 admittedly 21:19 advice 79:20 advised 28:25 33:20 affect 96:6 afternoon 99:1 agent 53:22 56:23 57:16 58:10 60:7 61:2 62:6,6 63:25 64:22 66:1 67:3 83:2 106:9	ago 27:2,2 52:13 103:4 107:11 agree 38:7 60:17 61:23 64:14 65:7,16 66:18 90:4 104:15,18 105:14 agreed 58:14 66:7 67:9 70:13 72:21 77:15,20 78:8 78:25 agreement 71:20 77:15,25 78:17,19 ahead 7:25 80:17 al 4:13 allotted 111:20 allow 5:13 63:16 64:9 allowed 36:11 alrighty 8:7 91:12 amplification 21:20,21,23 37:13 38:15 39:21 41:3 68:9,11,12 87:3 88:24 108:11 analysis 21:8 24:12,18,24	27:4 31:2 32:9 32:21 33:25 49:12,18,24 62:9 70:8 analyze 63:1 71:24 72:1 107:16 analyzed 46:15 47:17 69:21 analyzes 37:6 107:17 analyzing 30:24 31:4 55:12 65:6,8 65:16 66:19 68:1 69:24 70:18 71:12 72:8 73:2 75:8 76:23 82:18 83:16 102:19 103:21 104:22 105:4,15,24 106:17 107:2 answer 5:16,23 6:3,5 12:15,24 14:22,22 16:15 17:8 18:4 20:4 20:8 34:6 39:10 40:14,16 40:18,19 42:5 43:17 44:12 75:7 76:7 77:7 79:3,25 80:10 84:15 85:8,18 85:21 88:11	90:5,5,7,11,12 90:14 99:9 answered 39:15 43:4,21 82:24 83:21 84:20 85:13,25 86:16 88:15 99:14 answering 76:6 101:3,6 answers 90:23 anticipate 24:1 anticipates 23:24 27:7 anticipation 27:11,19 anticipatory 109:3 anybody 6:19 apparently 99:25 appeal 1:4 appear 17:15 17:17 46:12 49:12,19,25 50:18 56:9,10 58:16 63:14 82:19 appearances 2:1 92:2 appearing 47:11 55:13 86:23 95:14 103:19
--	---	--	--

[appears - attorneys]

appears 11:21 12:4,7 15:22 19:18 20:16 48:16,20 49:5 49:8 56:7 62:18 84:12 95:10 102:15	77:5,5,5 78:13 79:23 84:24 85:17 88:19 90:24,25 91:2 100:13 argue 19:22 39:1	arrived 73:16 art 23:19 24:17 24:23 29:4 33:23 41:23,24 42:11,12,21,21 44:21,21 64:3 97:15	89:8 assert 45:14 asserted 9:14 9:18 17:20 assertion 76:11 assertions 39:20 62:12 87:1
appended 113:7	argued 22:22 30:2 46:2	articles 38:4	associated 46:3 106:11
applicable 111:8	argues 25:5 34:8	aside 32:16	assumption 60:24
application 7:12 34:16 52:16,23 95:3 95:15	argument 25:24 26:10 27:12,15 31:17 51:1,7 87:16 89:12	asked 20:11 27:25 33:12 39:14 42:8 44:10 57:20 59:20 63:14 64:20 65:13,21 69:13 77:6 80:4 82:24 83:21 84:13,19 85:12,24 86:15 88:14 99:14 108:8	asymmetry 22:23,25 37:22 38:24 39:2 40:5 41:12 69:2 87:14 89:9
applications 22:3 68:14	arguments 15:12 16:5,17 22:10,23 23:1 23:8 25:2 26:4 30:11 37:11,25 38:2,14 40:7 40:25 41:14 44:16 47:16 50:11,22 52:21 58:16 59:19 60:11 68:6 69:4 87:22 88:20 89:14 103:18 108:24	asking 40:16,17 43:1 60:22,22 62:22 76:3,12 76:15 77:3 83:2 90:20	attached 111:11
applied 23:19 29:23 33:13,16 34:7 54:10	30:11 37:11,25 38:2,14 40:7 40:25 41:14 44:16 47:16 50:11,22 52:21 58:16 59:19 60:11 68:6 69:4 87:22 88:20 89:14 103:18 108:24	aspects 68:7	attention 9:6 11:7
apply 29:13,21 54:6,7	40:25 41:14 44:16 47:16 50:11,22 52:21 58:16 59:19 60:11 68:6 69:4 87:22 88:20 89:14 103:18 108:24	assembled 26:22	attorney 5:14 6:17,17 10:4 19:6,7 53:12 53:21 56:24 57:16 58:10 60:7 61:2 62:7 63:25 64:23 65:25 67:4 78:3 79:9 83:1 106:10 110:13 110:13 111:13
applying 24:17 24:23	arrive 63:3 64:8 66:15 67:20 77:13 83:13	assembles 34:13,15	attorneys 77:21 77:24 78:4,7
appreciate 19:12 88:4		assembling 26:13 31:3,13	
approaching 81:10		assembly 31:6 34:15 51:4	
appropriate 36:21 80:9 92:20			
april 70:16,23 71:11 72:4,14 72:25 73:7 74:7,10,12			

[attorneys - case]

78:24 85:21 86:2,18 92:18 audibly 5:23 august 35:23 35:23 74:19 available 30:13 111:6 avenue 2:4,8 avoid 99:24	basis 8:6 78:18 79:8,13,19 bears 100:20 beginning 43:11 behalf 1:16 4:16,19 belief 54:19 78:10,16,18 79:21 believe 8:14,14 8:24 9:21,22 10:18 13:7,8 13:14 19:9,13 20:14,19,21 21:3 22:9,14 23:22,25 25:2 27:25 28:2,13 28:20 35:25 36:16,21 42:17 50:4,11,21,25 52:21 57:10 58:11 59:2,17 59:19,23 60:12 61:7 62:15,23 63:18 64:2,7 64:20 67:11,20 77:12,21 78:6 78:6 83:13,22 84:9 85:5 92:7 92:21 93:1 95:20 97:8 103:22 105:23 107:15 108:24	believed 78:24 beneath 91:19 102:15 best 7:6,10,14 7:19 10:24 14:3 19:9 20:9 22:14 23:4 36:7,18 54:9 56:9 59:5 66:24 70:10 80:7 92:13 94:2 96:5,7,10 96:17 99:15 107:18 beyond 69:12 83:4 biosciences 18:18 bit 11:9 100:2 board 1:4 44:23 53:6,23 81:24 90:12 95:19 99:25 bob 2:12 4:4 boston 1:20,21 4:9 92:2 bpickard 2:10 breadth 19:7 45:23 62:8 64:24 66:2 67:5 break 34:20 35:3 74:1 80:17,18 81:12 82:10 90:9,16	90:21 97:17,25 98:3,11 107:25 108:3 breaking 43:13 broad 41:23 42:10,20 44:20 46:24 broader 32:16 brought 99:16 byron 2:7 4:17
b			c
b 3:6 back 10:14 11:9 13:22 33:11 35:5,7 47:20 52:22 82:12 99:3,5 103:23 108:5 barcode 25:12 25:20 30:13 31:11 34:12,14 barcodes 25:17 25:22 26:8,18 31:2,6 37:19 51:5 base 76:8 based 14:9 25:11 26:21 30:5 34:12,14 60:21 61:15 76:12 78:10 86:18 104:4 107:8,9 baseline 5:11 basics 5:8			c 4:1 106:15,16 ca 18:21 called 1:15 4:23 56:15 58:1 87:24 calls 53:11 56:5 58:7 62:3 64:18 65:11 66:22 79:10 108:20 caption 91:16 carried 53:6 case 6:23 7:5 7:21 10:10 12:1,13 18:13 18:20 19:21 21:8 23:20 24:12 27:10,20 28:4,19 29:16 29:23 30:2 35:25 36:3,5 36:10,11,12 42:5 47:22 51:14 52:24

[case - commensurate]

53:1,2,3,8,9,15 54:6,7,14 74:6 74:14 79:5,14 81:5 84:17 85:10,23 86:13 91:17 95:21 96:12,14,22 97:1 100:13,25 103:9 cases 28:8 53:17 54:11 80:7 95:25 cause 110:9 caused 21:9 cautionary 79:8 center 77:22 centers 89:7 certain 9:10 61:20 76:5 83:3 certainly 55:1 105:12 certify 110:6,12 change 112:4,7 112:10,13,16 112:19 changes 111:10 113:6 characterized 106:7 check 10:11 citations 14:13 cite 10:9 26:12	cited 7:2,4,16 7:18,20,23 8:15,24 9:23 9:24 16:16 18:5 19:13 24:3 civil 97:1 claim 8:11 9:10 11:20 12:7 14:6,10 18:17 19:3,10 20:21 22:24,25 23:16 23:20,24,25,25 24:2,11,13,15 24:19,25 25:22 26:6 28:24 29:14,21 33:4 33:13,21 34:1 34:2 37:24 39:4 40:6 41:13 42:4 45:1,6 46:6 48:10,16,20,22 49:4,5,8,12 52:15 54:5,9 55:2,5,6,7,14 55:18,23 56:3 56:15,17 57:10 57:12,24 58:1 58:2,24 60:1 60:18 61:9,22 61:24 62:18 63:9,22 64:15 65:6,17 66:10 66:19 68:1	69:3,10,25 71:13 72:9 75:10,13,18,19 76:4,16,20,22 77:4 82:19 83:3,17 84:2 87:15 89:11 96:24 97:4 101:16,20,21 102:20 103:23 104:23 105:5 105:13,22 106:15 107:2 108:21,25 claimed 14:16 16:9 17:23 19:23 27:14 38:5 40:11 41:19 46:12,18 47:13 102:17 105:2 106:25 claims 12:5 22:8,13 25:6 25:15,18 26:5 26:23 27:7 29:1 33:20 37:17,20 38:19 38:21 39:25 40:2 41:6,9,22 42:10,19 44:19 45:9,24,24 46:8,13,15,24 46:25 47:4,11 47:13,17 49:25 51:2 54:13	57:1,19 59:4 61:17,20 65:22 66:4 68:21,24 69:7 71:3 72:19 82:1 87:7,9 88:1 89:3,5,19 97:3 97:4 102:2,23 105:8,17 106:1 106:7,13 107:5 108:10,21 109:1,1 clarity 14:15 16:7 17:22 classes 61:20 classifications 106:6 clear 54:23 81:1 84:14 clearly 26:19 clientservices 111:15 close 71:14 98:1 code 103:19,25 104:2,18 collectively 9:13,17 30:24 colloquy 80:25 combination 45:5 commencing 1:22 commensurate 25:24
---	---	--	---

[commercialization - continuing]

commercializ... 77:23	composition 14:19 16:12	73:1 75:8	18:17 19:3,10
commission 110:20	18:1 20:1	76:22 82:18	20:21 28:24
common 52:16	comprises 65:1	83:16 102:19	29:14,21 33:4
commonwealth 1:18 110:1,5	concerning 8:11 13:3	104:22 105:4	33:14 42:4
communicati... 79:12,16	84:16 85:11	105:14,24	54:5,10 96:24
companion 100:12	88:11 96:12,14	107:1	97:5
compared 46:16	110:8	conflict 36:12	construe 34:3
comparing 55:11 61:22,24	conclude 21:9	consensus 26:16,21 38:4	construed 54:13,14 58:3
62:16 63:22	concluded 27:5	39:7 40:10	59:4 66:11
64:14 70:18	109:11	41:18 44:17	69:10 75:19
71:12 72:8	conclusion 16:18,19 18:8	46:4,9,11 47:5	97:2 101:21
73:1 75:8	53:11 56:6	47:9 87:12,25	contain 25:17
76:23 82:18	58:8 60:23	89:18 104:1,4	contained 93:23
83:16 102:19	62:4 63:3 64:8	104:6,7,9,12,13	contents 79:11
104:22 105:4	64:19 65:12	104:14,16,17	context 14:6
105:14,23	66:16,23 67:19	104:20 107:17	17:6 18:9
107:2	67:21	consider 21:2	19:20 20:6,10
comparison 46:10	conclusions 34:4 83:3	24:19,24 46:23	20:12,14,24
complementary 104:10	confident 53:18	consideration 45:15	21:5 22:20
complete 5:13	77:9	considerations 23:3 38:3 39:6	23:8 30:3,7
113:8	confidential 79:12,15	40:9 41:16	31:9 33:4 34:4
completed 111:17	100:11	44:15 69:6	36:20 49:22
components 55:10	confirm 75:3	87:23 89:16	50:24 60:9
	107:10	considered 45:23	62:23 64:1,12
	confirming 55:11 57:4	considering 32:8	67:1 70:4
	58:23 59:12,25	consistent 34:17 36:19	72:18,23 83:12
	60:17 61:8	96:13,18 97:8	84:12 86:4
	63:9 70:17	construction 8:12 9:9 14:6	97:4,10 101:6
	71:12 72:8		103:13,14
			106:22 108:23
			continuing 44:12

[controversy - definition]

controversy 110:8 copies 111:14 copy 8:16 9:2 10:2,12,20 11:4,22,23 12:11 92:23 100:11 101:5 106:20 correct 5:9 7:22 8:21 10:16,25 12:5 13:5,17 16:25 18:13,25 19:1 22:18 23:21 24:14 27:21 28:19 29:5 37:7 41:25 42:19 48:17,18 49:6,7,13,20 51:16 52:22 53:1 56:13 74:7,10 77:10 91:24 92:6,10 92:14,15,17,20 92:24,25 93:2 95:12 113:8 corrected 1:13 53:25 corrections 113:6 correctly 9:21 15:9,24 29:12 42:24 44:18 45:11,13 102:4	102:11,24 correspond 59:25 63:9,21 67:25 69:24 104:21 corresponding 58:3,22 72:6,7 75:20 101:22 101:25 102:21 105:6 107:4 corresponds 59:11,11 counsel 4:14,24 6:2 43:5,10 54:21 73:24 79:12 80:15 92:16 110:13 110:13 111:14 couple 27:1 course 18:22 78:2 court 4:4 8:11 18:13 19:4,21 20:12 35:25 36:4,10 47:22 51:14 52:24 53:2,3,9,23 54:7,11,13 74:14 79:5 80:6 84:17 85:10,23 86:13 88:12 91:16 95:21 96:12 97:2,5 99:11 100:13,24	courts 86:23 cover 58:3 75:19 91:15 100:16,20 101:21 coverage 22:2 covered 85:15 101:10 craig 44:25 45:5 cross 3:2 81:2 108:6,9 currently 4:7 d d 3:1 4:1 55:9 55:10,13 57:24 106:15,17 data 26:14 31:2 95:3,15 date 4:6 29:5 33:24 73:17 74:12,12 91:4 91:24 92:1 112:24 113:12 day 92:5 110:6 110:16 113:15 days 74:11 111:17 dc 2:9 dcs 45:10,14 47:5,13 december 93:15 94:21 decision 45:3 53:13 90:16	96:6 declaration 3:9 3:13 8:10,18 8:19 9:4 10:16 10:23 11:10 18:11 28:14 35:16 37:4 47:21,24 74:21 74:22 81:3,15 90:24 93:12,15 94:20 95:11,17 99:17,18 101:10 102:9 declarations 96:20 declare 113:4 declined 27:25 deemed 113:6 defendant 18:20 defending 78:3 define 17:21 61:14 defined 30:16 66:4 107:19 defines 30:15 definite 31:8,21 55:17 56:1 75:16 76:19 101:19 102:1 definiteness 14:2 15:11 21:4 50:22 definition 26:8 61:1,17 65:1
---	--	---	---

[definition - discussed]

67:12 83:11 107:21 definitions 36:22 64:2 65:23 demonstrate 51:3 deponent 111:13 113:3 deposed 5:9 29:12 79:22 92:1 deposing 111:13 deposition 1:14 3:11 4:10 6:11 6:14 9:25 10:19 11:3 13:8,10 14:1 14:24 15:14,15 17:3,5 18:23 19:15 21:6,13 21:15 25:4 27:16,24 28:12 29:10 31:19 32:11 33:6,15 33:17,18 34:6 35:15,18 37:2 37:10 39:17 43:11 50:14,25 52:3,4,8,9,19 56:21 57:3 61:4 62:14 64:13 65:3 66:8 67:10	68:3 69:19 70:14 71:19 72:21 73:20 77:16 78:4,9 78:12,22 79:1 80:3,13 81:16 81:20 84:1,22 85:15,20 86:1 86:3,20 88:17 91:19 92:17,22 99:8 103:5,7 103:11 109:7 109:10 110:10 depositions 78:1 88:6 depth 22:1 62:8 64:24 68:15 derived 57:5 describe 25:8 32:24 38:17,21 38:23 39:23 40:1,4 41:5,8 41:11 53:18 68:20,23 87:5 87:9,14 89:1,5 described 26:20 34:9 41:24 42:12,21 44:21 58:4 68:24 75:21 101:23 describes 22:24 26:13 30:24 31:1 41:16 104:11,19	107:13 describing 38:4 52:24 description 3:8 31:22 63:6 72:5 designed 88:8 despite 52:24 detailed 101:3 determination 63:17 determine 58:21 61:8 63:7,20 67:24 69:22 determined 14:15 16:7 17:22 determining 26:21 different 14:5 31:24,25 36:7 56:25 57:18 60:24 66:3 68:7,14 69:9 69:17 85:7 96:20 differently 54:14 difficult 103:2 103:14 direct 3:2 5:2 9:5 22:22 101:12	direction 110:10 directly 23:23 24:1 disagree 26:2 43:19 82:4 discern 15:5,25 17:10 disclose 38:15 39:2,21 41:3 68:9,19 79:15 87:2 88:24 89:9 101:25 102:21 105:6 107:3 disclosed 61:16 68:12 108:12 discloses 21:20 26:10 30:20,22 31:3,10 104:3 disclosing 25:20 disclosure 79:11 94:8,13 107:12 discuss 18:23 20:5 21:23 22:19 23:7 27:16,23 28:12 38:13 40:24 45:9 46:7 47:3 discussed 14:7 15:11 28:2 31:23 87:10,23 89:6
---	--	---	---

[discusses - earlier]

discusses 26:17	17:16 18:3	documentation	58:11 59:19
discussing	19:17 20:2,15	83:7	60:13 61:5
17:14 20:23	21:9 22:10,16	documents	62:11 67:11
29:25	22:25 23:5	7:20,23 8:5	68:6 69:4
discussion	25:9,12 26:11	36:16 66:14	71:21 73:22
22:10 106:15	30:1,8,14	71:3,4 72:1,17	78:14 79:24
disposed 69:4	31:12,15,16,22	73:16 84:9	82:14 83:22
dispute 25:15	31:24,25 32:4	97:13	87:1,17,19
distinct 36:6	32:14 37:23	doing 5:7 24:12	88:22 89:12,15
46:17 104:20	38:24 39:3	27:4 43:18	89:17 91:12
distinctions	40:5 41:12	51:19 70:11	93:11 97:20
47:12	48:11,19 50:4	73:18 90:2	99:5,18 100:9
distinctly 54:2	50:18 51:25	double 25:9	105:13 108:8
54:2,4	57:7 69:2	48:11,19 50:3	draw 10:14
distinguish	87:15,18 89:10	50:17 51:25	60:23 83:2
25:7	89:13	doubt 23:17	drew 46:10
district 8:10	doctor 12:1,11	101:2	47:12
18:13 19:4,21	27:1 28:7 35:8	dozen 67:2	duly 4:25 110:7
20:12 35:25	42:3,14 43:4	dr 3:9,12,13,15	duplex 38:4
36:4,10 47:21	44:9,11,11	4:11 5:4 6:13	39:7 40:10
51:14 52:24	45:19 46:21	6:14 8:7 21:17	41:18 44:16
53:2,3,8,23	69:17 84:13	22:3,6,9,12,15	46:3,4,9,11
54:7,11,13	document 12:8	22:22 25:5,14	47:5,9 87:25
74:14 79:5	13:11,19 17:2	25:18,19,24	89:17 104:5,11
80:6 84:17	18:16 24:21	26:5,9 27:18	104:13
85:10,23 86:13	29:17,19 33:11	28:15 30:10	duty 81:24
88:12 91:16	35:13,21 37:9	34:8 37:4,11	e
95:21 96:11	42:2,7 45:12	37:12,15,18,21	e 3:1,6 4:1,1
99:11 100:13	46:1 49:1,15	37:25 38:2,11	112:3,3,3
100:24	49:22 55:21	38:13,25 39:20	earlier 9:22
dla 92:18	56:8 78:12	40:7 41:1,16	14:7 15:11
dna 11:16,19	93:14,23 94:4	44:16 45:13	16:3 31:23
12:3,6 13:5,12	102:6,7 103:1	46:1,14 47:5	57:15 58:9
14:20 15:20,21	105:20 106:18	47:16 50:11,21	60:6 62:5
16:8,13,24	106:21	51:1 52:20	63:24 66:12

[earlier - extrinsic]

67:14 75:5 78:17 82:25 84:13 86:17 87:10,23 89:6 97:6,22 98:1 eastern 4:7 effect 56:10 either 88:8 electronic 8:23 100:18 element 21:22 55:14,23 60:17 75:14 76:16 101:16 elements 83:4 84:2 elicit 88:8 embodiment 108:21 employed 110:13,13 encapsulated 62:13 encompass 14:17 16:10 19:24 25:16 39:19 41:23 42:11,20 44:20 79:2 encompassed 15:7 16:1 17:11 108:11 encounter 17:24	engage 80:25 entire 43:3 101:5 106:21 entirely 90:13 entitled 90:4 equivalents 58:5 75:21 101:24 errata 111:11 111:13,17 errors 92:24 93:2 esq 2:3,7,8 et 4:13 evaluation 81:13 evidence 15:6 16:1,18 17:10 18:6 46:5,13 46:14 47:10 63:2 64:7 exact 104:9 exactly 24:16 53:12 examination 4:23 5:2 81:2 108:6,9 110:9 examined 4:25 59:8,10 110:9 examines 13:19 24:21 29:17,19 33:11 42:2 45:12 46:1 49:15 55:21 93:14 102:6	103:1 105:20 example 14:16 16:9 17:23 19:23 21:2 24:18 96:23 102:18 105:3 107:1 excerpted 100:10 excerpts 106:19 excuse 14:11 15:21 76:10 80:18,23 90:17 97:19 executed 35:22 executing 10:22 exhausted 80:15 exhibit 3:9,9,11 3:13,14 8:2,8 9:5 11:8,11 12:1,9,12 13:2 15:19 26:12 28:3,5,14,18 30:21 35:10 37:3 38:8 39:12 44:24,25 46:23 47:21,25 49:20 62:13 91:5,7,9,13 93:7,12 94:7 100:5,7	exhibits 1:2 expert 3:14 6:12 7:24 8:25 9:9,24 10:2,13 10:21 11:4,22 13:25 14:4,7 15:12,16 17:5 27:12,17 50:24 51:13 71:20 74:13,23 96:24 97:3 100:12,23 101:10 108:22 expires 110:20 explained 64:21 65:24 explanation 89:7 explicitly 108:20 explore 81:21 expressed 55:15,24 75:14 76:17 101:17 expressly 26:20 extent 34:3 46:10 47:15 56:5 58:7 62:3 64:18 65:11 66:22 79:10 80:1 extrinsic 15:6 15:25 17:10
---	--	--	---

[fact - fragment]

f	families 25:11	five 34:23 45:8	71:15 72:10
fact 9:23 20:23	favors 90:3	74:2	73:4 74:16
21:23 22:24	features 11:16	fix 82:3	76:1 77:1
27:13 30:20	13:4,12 14:17	focus 20:13	79:13 82:23
31:10 34:15	15:20 16:9,24	23:16 55:9	83:20 84:19
36:6 38:22	17:15,23 19:24	focuses 33:25	85:12,24 86:15
39:1 43:16,20	31:24	focusing 16:22	87:13 88:14
47:12 68:11	felt 46:2	24:10	94:18 95:24
77:15 93:2	fifth 2:4 10:20	follow 32:22	96:15 99:13
100:20 103:24	figure 103:20	79:20	105:18 106:2
106:24	103:24 104:3	followed 21:20	formed 78:18
facts 51:8 88:9	104:11 107:15	21:21 32:21	forming 104:5
factual 76:11	filed 108:23	37:14 38:15	104:11
fails 111:19	filibusters 91:4	39:22 68:9	forth 26:2
fair 5:21 12:18	filter 104:5,6	87:3 88:24	32:20 87:16
12:23 28:9	filtered 104:12	following 49:10	94:3
36:24 45:23	filtering 104:8	102:13	found 44:24
81:21	final 82:17	follows 5:1	59:13
fairly 12:11	finally 22:21	force 90:12	foundation
fall 36:6 61:20	financially	foregoing	93:18
76:23	110:14	113:5	fourth 10:12
fallacious	find 45:4 75:2	form 29:18,24	fox 2:7
37:25	83:24 93:4	32:4 33:2	fragment 11:15
fallaciously	107:12	36:15 37:1,8	11:16,19 12:3
60:12	fine 12:16	39:14 40:15,22	12:6 13:4,5,12
falls 53:4	97:21	42:1 47:1	13:13 14:21
familiar 23:17	finish 74:3 81:7	51:17 53:11,20	15:20,21 16:8
55:3,6,7 56:14	firm 92:18	54:8 55:20	16:14,24,24
56:22,24 57:17	first 4:25 9:3	56:4,18 57:13	17:14,16 18:3
58:13 60:5	22:7 27:22	57:24 58:6,25	19:17 20:3,15
62:7 64:23	28:17 35:10	59:15 60:2,19	21:10 22:10,16
66:1 67:5	37:15 38:17	61:12 62:2,20	23:5 25:13
72:13 73:10	39:24 41:5	63:11,23 64:17	30:1,8,14
81:19 106:5,10	57:6 68:20	65:10 66:21	31:12,16,22,25
	87:6 89:1	68:2 70:1,21	32:14

[fragments - health]

fragments 31:15	104:11 109:4 110:12	86:11 90:3 92:12,22,23	34:16 37:19 38:21 40:2
framework 69:11 70:4	furthermore 44:23	96:25 97:13 110:11 113:9	41:9 51:2 68:24 87:9,13 89:5
frankly 88:8	g	giving 77:10	groupings 37:19
free 92:19	g 4:1	go 11:8 44:22	groups 34:11 78:8
friday 91:23	game 28:9	48:21 54:18	guardant 1:6 4:12,20 9:8,8 9:18 18:19 36:2 45:2 77:24 93:18 111:4 112:1 113:1
front 8:18	81:21	80:17 82:6	guardiant 3:10
18:15 75:1,4	gather 24:11	90:12 98:6	guidance 26:1 32:2
91:13 100:10	gears 55:5	goal 68:16 69:8 84:3	guidelines 64:5
full 24:13,16,19	100:2	going 8:4 10:1	h
24:24 106:22	generally 77:7	10:11,20 11:3	h 3:6 112:3
fully 109:3	generating 106:16	20:5 33:10	hand 110:16
function 55:16	genome 68:17	34:19 43:12	happened 90:6
55:25 56:16	gerrard 6:18	73:25 75:10	happy 22:18 23:7
57:11,11 58:1	getting 98:1	79:7,20,22	he'll 10:7
58:2 61:25,25	giannini 2:12	80:2,23 82:3	head 5:23
62:17,17 65:8	4:4	90:10,11,19	heading 11:15 28:24 48:3 95:3 102:15
65:9,18,18,21	give 39:10	96:3 99:25	health 1:6 4:12 4:20 9:8 18:20 36:2 45:2 77:24 93:19
65:22 70:19,19	40:13,17,19	100:1	
75:9,10,15,24	75:11	goldstein 2:7	
75:25 76:18,24	given 11:25	good 4:2 5:4,5 7:25 98:4	
76:24 81:25	19:22 20:22	goodrich 1:20 2:3 4:9	
82:21,22	26:15 29:2	governing 19:3	
101:18 105:16	33:21 36:9	grabbed 42:7	
105:16,25,25	45:22 58:12	great 5:8	
functional	63:1 64:6	group 26:22 31:7	
60:18,25 61:10	66:12 67:14	grouping 22:13 25:10,22 26:10 30:11,18,19,22 31:6,10 34:9	
61:17,18 64:15	70:7 71:2,23		
65:2 66:20,25	72:14 73:8,14		
71:14 75:24	75:6 76:15,21		
102:18 105:3	77:7,10 79:18		
107:1	80:8 81:22		
further 9:1	83:9,12 84:7		
26:13 30:22			

[health - interoperability]

111:4 112:1 113:1 hearing 19:10 hearsay 8:6 91:11 93:10 hereinbefore 110:7 hereto 110:14 113:7 hereunto 110:16 highlighted 47:2 history 14:11 14:12 16:21 18:8 30:6 34:2 67:18 71:5 94:23 97:13 hold 90:10 94:9 hour 34:20 73:25 hypothetical 20:8,13,22 62:22	iii 2:8 impact 53:8 important 10:6 21:22,24 68:13 improper 90:6 90:13 inappropriate 80:8 inappropriately 45:13 include 81:3 104:14 106:15 included 22:10 84:23 103:12 103:20 104:18 includes 102:17 105:3 106:25 including 16:19 21:25 23:23 26:7 30:13 39:19 41:1,24 42:11,21 44:21 50:2 68:8,14 71:3 74:25 80:6 88:22 inconsistencies 36:23 inconsistent 36:13 81:22 incorporated 18:18,20 incorrect 54:12 54:16 87:19 increased 68:15	increasing 22:1 incredibly 68:13 indefinite 13:17 15:9 16:3 17:13 18:10 19:18,22 20:17 21:11 30:4 31:9,21 50:19 51:6 73:3 83:19 107:23 indefiniteness 13:4 14:2 15:12 21:4 33:3 50:23 51:22 83:23 84:4,6,8 102:3 102:16,24 103:17 105:9 indefinitenss 107:6 independent 53:24 54:19 96:3 indicated 45:15 individual 77:25 96:22 97:10 information 11:17,20 12:4 12:6 13:5,13 14:17 15:21,22 16:8,10,25 17:17,24 19:17	19:24 20:16 21:10 22:11,16 23:6 25:13 30:1,8,12,14 31:12,15,16,22 32:1,5,8,15 41:17,17 76:13 informed 67:2 86:18 87:8,11 106:8 instruct 43:25 79:14 85:21 88:10 90:14 99:9 instructed 79:3 84:15,21 85:8 instruction 6:4 43:15,16 62:24 64:4 66:13 67:15 70:6,25 71:23 72:15 73:8,14 75:6 75:11 76:16 77:8,9 79:8,18 83:10,10 84:7 86:11 inter 18:24 19:5 36:5 53:5 interest 21:25 interested 110:14 interoperability 23:2 38:1 40:8 41:14 69:5 87:20 89:14
i			
identical 51:24 identifiable 48:5,23 49:2,5 49:8 50:6,7,16 51:23 identification 8:3 91:8 93:8 100:6 ignored 89:13			

[interoperable - legal]

interoperable 39:5	inventors 32:7	jmills 2:5 111:2	language 22:24
interposing 79:19	involve 52:25	john 1:14 3:3	25:25 55:19
interpret 31:14	53:2	4:11,22 91:20	56:3 75:18
97:3 103:14	involved 36:18	111:5 112:2,24	76:20,22
interpretation	involves 59:2	113:2,4,12	101:20 103:23
14:9 20:9	84:18	jurisdiction	larrea 6:13
60:21	involving 74:14	53:5	law 56:8,25
interpreted	93:18 95:21	jurisdictions	57:17 58:13
32:2 59:5	100:25	36:8	62:8 64:24
interpreting	ipr 15:17 17:7	k	66:3 67:2,6
30:7 34:17	19:11 20:7,14	keep 90:19	92:18
interrupt 43:6	20:19 52:6	kessler 2:7 4:18	lawyer's 79:20
43:24 44:2,6	54:10,14 72:23	kinde 44:24	lay 14:8 16:4
54:22	73:23 78:23	45:5	16:16 31:17
interrupted	85:17 86:4,22	know 5:19	32:20 106:24
44:13	88:21 93:13,13	11:13 15:2	108:24
intimately	93:16,16 95:23	28:22 31:5	layman 73:11
57:17 60:5	101:11 103:9	32:22 35:19	107:22
66:2 67:4	ipr2022-00817	47:22 53:16	lays 44:16
72:13 73:10	1:7	57:18 58:20	learn 70:15
106:4,10	irrelevant	59:13 61:13	71:10 72:3,24
intrinsic 15:6	31:20 32:9	64:25 84:13	leave 80:20
15:25 17:10	52:18 86:22	101:13	led 16:17,19
introduce 4:14	95:22	knowledge 7:6	legal 19:2,8
invalid 102:3	irrespective	7:19 19:9	53:11 56:6
102:23 105:8	97:6	22:14 23:4	58:8 59:3 60:4
107:5	issue 79:7	54:9 56:9 59:6	60:23,25 62:4
invalidity 3:15	issues 8:11	96:7,17 110:8	62:25 63:13
51:15 74:24	38:11,12 51:15	l	64:4,19 65:1
invention 46:18	j	l 2:7	65:12,23 66:13
inventions	jad 2:3 4:20	laid 19:23 23:8	66:23 67:1,13
40:11	90:1 97:16	27:14 29:15	69:9,11 70:4
	111:1	30:4 47:16	72:12 73:14
	jeanette 1:16		77:8 83:3,11
	4:5 110:4		84:6 96:8

[legal - meaning]

97:11 102:10 103:10 111:23 lengthy 48:1 74:23 library 25:10 licensed 57:15 58:10 60:7 61:1 62:6 63:24 64:22 66:1 67:3 83:1 83:1 106:9 light 14:21 16:14 18:3 20:3 limitation 45:1 45:6 62:1,18 65:9,19 82:1 limitations 70:20 71:13 72:9 75:23 79:1 82:22 83:15,17,18 limited 40:25 52:11 60:11 62:11 68:14 71:20 72:22 73:21 85:6 105:1 line 48:7 76:14 112:4,7,10,13 112:16,19 lines 16:18 45:8 63:2 64:7 94:12	little 11:9 69:17 75:11 100:2 located 4:8,9 loci 22:2 lodge 8:4 long 34:21 46:2 look 7:4 8:8 10:6 12:15,20 12:24 23:12,14 27:13 28:17 33:10 35:7 42:3 44:14 48:9 49:10,17 55:2 57:4 61:22 91:15 92:2 93:20 94:6 100:13 103:16,22 105:10,13 looked 6:24,25 7:3,7,9,20 35:10,19 looking 12:19 13:11 15:19 30:9 33:6,9 82:17 83:15 105:22 low 21:25 lunch 97:17 98:11 m made 15:12 22:22 25:2 37:11 40:25 50:12,21 51:1	68:6 76:4,11 82:5 93:24 103:15 113:5 make 24:9 27:12 43:22 44:1 63:17 80:19,24 81:13 90:16 92:19 96:10 makes 40:8 making 81:8 maracas 1:17 4:5 110:4 mark 7:25 91:5 93:6 100:3 marked 8:2 10:23 12:8 15:19 18:12 28:13 35:14 37:3 91:7 93:7 95:11 100:5 massachusetts 1:19,21 4:10 110:1,5 match 104:10 mate 104:2 material 58:4 58:22 59:13,24 75:20 77:11,12 85:15 101:22 materials 7:2 21:8 55:17 56:2 63:8,16 63:20 67:16,18 67:25 68:4	69:23 70:2 72:6 75:17 76:19 80:11 83:13 101:19 102:1 matter 4:11 14:5,23 15:13 15:17 17:4,7 18:10 35:17,22 49:23 54:15 64:1 72:23 73:23 78:23 80:14 84:22,25 85:17 86:4,22 88:21 93:17 95:18 101:9,11 102:10 103:7 103:10 matters 36:6,17 52:2 54:11,20 80:6 86:22 96:2,3 110:8 mean 24:5,16 64:5 70:3 100:16 meaning 13:15 14:14 16:6 17:20 21:1 22:15 29:2,25 30:9 33:22 62:25 67:1 69:9 71:1,6,24 72:15 73:9,12 84:8
---	--	--	--

[means - need]

means 55:15,24 56:15,16 57:11 58:1 61:25 62:17 65:8,18 65:21 70:19 75:9,14,24 76:17,24 81:25 82:21 101:17 105:16,25 meant 52:17 medicine 93:18 meet 6:16 64:2 memory 6:22 19:13 22:17 27:3 104:25 mention 94:7 94:13 mentioned 7:7 27:4 77:14 82:25 92:3 97:21 meritless 87:22 merits 47:8 met 6:17 method 102:16 105:2 106:24 methods 41:24 42:12,21 44:21 103:21 mills 2:3 3:4 4:19,20 6:17 8:4,13,22 9:20 11:1,12 13:6 13:18,24 15:10 17:1 18:14	19:19 20:18 21:12 23:13 24:20 25:1 28:5 29:6,18 29:24 33:1 34:19,23 36:15 37:1,8 39:14 40:15,22 42:1 43:5,10,19,23 44:2 47:1 48:6 48:13,25 49:14 49:21 50:20 51:12,17 52:1 53:10,20 54:8 54:21 55:20 56:4,18 57:13 58:6,25 59:15 60:2,19 61:11 62:2,20 63:11 63:23 64:17 65:10,20 66:21 68:2 69:16 70:1,21 71:15 72:10 73:4,24 74:4,16 76:1 77:1 78:3,20 79:7 80:15,22 81:7 82:4,23 83:20 84:19 85:4,12,24 86:9,15 88:14 89:25 90:17,22 91:9 93:9 94:18 95:7,13 95:24 96:15	97:23 98:6 99:13 100:7 101:1 102:5,25 105:18 106:2 107:25 108:7 109:4,7 111:1 minutes 27:2 34:23,24,25 74:3 mirrors 23:25 misspoke 52:17 78:5 91:1 mistaken 53:24 mistakenly 78:24 mistakes 24:9 modification 14:20 16:13 18:2 20:2 molecule 30:25 molecules 22:25 25:10 26:12 37:23,23 38:24 39:3 40:5 41:12 48:11,19 50:4 50:18 51:25 57:7 69:2 87:15,18 89:10 89:13 moment 8:7 52:13 55:9 83:7 105:11 monday 1:21	month 103:4 107:11 morning 4:2 5:4,5 motion 23:13 33:1 move 23:10 26:24 32:12 40:18 44:8 46:19 51:10 69:14 85:2 86:7 89:23 99:23 moved 44:9 moving 43:22 44:1 multiple 14:12 26:14 30:25 91:4 106:8 multiplexing 26:16
n			
n 1:16 3:1 4:1 name 92:3 named 110:7 nature 90:3 nearly 67:2 necessary 113:6 need 5:23 6:3 12:15,20 23:5 42:3 43:5,23 46:2 54:23 67:19			

[needed - offers]

needed 34:3 47:15 neither 58:9 60:6 61:1 62:5 65:25 67:3 82:25 106:9 110:12 nevertheless 32:3 new 2:8 nods 5:24 non 5:24 23:11 26:25 32:13 46:6,15,20 47:10 48:3,10 48:18 50:3,17 51:11,24 69:15 85:3 86:8 89:24 99:24 100:11 nos 9:10,15 notary 1:18 110:5,20 113:13,19 note 90:23 111:10 noted 113:7 nuances 106:11 nucleotide 14:18,19,19 16:11,12,12 17:25 18:1,1 19:25 20:1,1 nucleotides 104:14	number 21:18 22:1 26:4 28:1 31:24,25 37:11 40:25 49:24 51:14 59:3 60:4 63:13 72:12 80:4 87:21 95:10,14 95:16 numbered 9:6 93:13 95:9 numerous 64:21 65:24 nw 2:8	42:1 43:22 44:1 46:19 47:1 48:6,13 48:25 49:14,21 50:20 51:17 52:1 53:10,20 54:8 55:20 56:4,18 57:13 58:6,25 59:15 60:2,19 61:11 62:2,20 63:11 63:23 64:17 65:10 66:21 68:2 70:1,21 71:15 72:10 73:4 74:16 76:1 77:1 79:17 82:23 83:20 84:19 85:12,24 86:15 88:14 94:18 95:7,13,24 96:15 99:13 101:1 102:5,25 105:18 106:2 108:14 objections 5:15 8:5 65:20 90:4 92:19 objective 46:5 47:10 objects 6:2 obvious 109:2 obviousness 24:18,23 25:3	46:6,15 47:10 offer 9:8 14:25 20:20,25 23:6 58:17 60:15 61:6,19 64:11 66:6,9 67:7 71:8 72:1,17 83:8 84:10,11 85:1 86:5,24 88:2 89:20 97:1,8 99:16 101:7,9 offered 13:14 14:1 18:16,16 19:20 21:3,18 22:4,6,12,15 33:7 36:20 37:4 47:6,19 58:11 59:17,19 59:23 60:12 61:15 65:5 67:12,16 68:10 68:18 72:4,25 73:17,23 78:13 78:23 83:22 86:4,21 88:12 88:21,22 89:11 89:17 97:5 offering 59:6 68:4 69:8 70:23 71:17 84:3 96:1 offers 37:13,15 37:18,21,25 38:2 39:7,17
--	---	--	---

[offers - paragraph]

40:24 46:14 office 1:3 10:9 offices 1:19 4:8 official 56:8 okay 5:8 6:2 7:15 10:10 12:22 24:9 42:18 74:4 75:5 90:22 92:4 93:11 98:6,8 101:15 102:12 oligonucleoti... 31:1 once 97:2 opening 28:4 28:18 29:10,16 29:23 32:19,25 33:5,7,9,16,19 52:5 operating 107:14 operation 36:22 104:19 opine 62:15 opined 15:23 71:11 opinion 9:9 13:16 14:1,14 14:25 15:8 16:2,5 17:12 17:19 19:16,20 20:25 23:7 27:10 47:6 50:15 56:20	57:24 58:17 59:7,23 66:9 67:7 68:10 72:2 73:16 77:13 83:8,14 84:10,11 102:22 103:2 105:8 107:5 opinions 13:3 13:14 18:23 20:20 21:3,18 22:4,6,12,15 23:20 33:8 37:13,15,18,22 39:17 40:24 46:22 47:18 58:11 59:17 60:16 61:15 65:5 67:12 68:5,5,18,22,25 69:9 70:17,24 71:6,18 72:5 72:17 73:1 79:4,14 83:23 84:3,16 85:9 85:22 86:12,24 87:19 88:3,11 88:22 89:13 95:20,22 96:1 96:11,17,18,21 97:1,6,8 99:10 opportunity 10:4 52:9 67:15 71:2 72:16 73:15	92:23 96:25 98:2 104:25 107:8 oppose 23:13 33:1 51:12 69:16 86:9 89:25 opposed 85:4 order 12:21 ordinary 14:14 16:6 17:19 29:2,3 33:22 33:23 64:3 97:14 organized 97:18 original 57:6 outline 81:13 outside 20:12 29:8,8 56:19 57:14,20 58:7 58:14 59:1,8 59:16,21 60:3 61:11 62:3,21 63:4,12 64:18 65:4,11 66:6 66:22 67:8 70:9,13 71:16 72:19 73:5 74:17 76:2 77:2 80:13 82:24 83:21 91:10 93:10 94:19 96:16 100:8 102:7	103:6 105:19 overall 14:19 16:11 17:25 20:1 26:15 owner 1:11 2:9 4:17
			<p style="text-align: center;">p</p> <p>p 4:1 p.c. 1:20 p.m. 109:11 page 3:8 8:17 8:21,23 9:4,4 11:9,11 18:15 28:21 47:24,25 48:21 49:19 91:15 92:2 93:20 94:6 95:2 100:14,16 100:17,20 102:13 112:4,7 112:10,13,16 112:19 pages 1:1 49:10 103:12,13 pair 104:15,17 pairing 104:1 pairs 104:8 paper 47:8 papers 47:7 paragraph 9:6 11:7 14:8 15:1 15:23 16:4,22 17:8,18 26:9 28:25 29:11 30:21 32:19,24</p>

[paragraph - phrases]

34:10 41:20 42:9,25 43:3 44:8,14,17 45:7 47:2 94:6 94:11,12 95:16 101:12,15 102:11,12 106:23 paragraphs 13:2 16:16 18:5 49:11,17 49:23 part 31:18 42:25 44:19 81:4 87:11 99:7 100:23 106:18 partes 18:24 19:5 36:5 53:5 particular 14:3 22:3 66:15 particularly 67:7 76:22 parties 81:17 110:14 pass 107:24 past 61:14 70:5 patent 1:3,4,8 1:11 2:9 4:17 7:9,11 9:10,11 9:12,12,13,14 9:15,16,16,17 11:21,24,25 12:5,7 14:10 15:23 16:21,21	17:16,18 18:7 19:6,18 20:7 20:16 22:24 23:12,14,24 25:15,25 26:7 27:8 28:9 29:1 30:3,5,16 31:9 31:20 32:7 33:21 37:7,12 37:17,20 38:6 38:9,12 39:9 39:13 40:3,12 40:21 41:1,7 41:10,19,22 42:10,20 44:20 45:1,10,16,25 46:7,8,13,24,25 47:4,11,14,17 48:17,20 49:6 49:9 50:1,1,2,9 50:10,19 51:15 52:13,14,21,25 53:3,6,22,23 54:3,18,25 55:7 56:7,23 56:24,25 57:16 57:16,17 58:9 58:10,13,21,24 59:4,14 60:1,7 60:7 61:1,2,9 61:23 62:5,6,7 62:8,19 63:7 63:10,19,22,25 63:25 64:15,22 64:23,24 65:7	65:17,25 66:1 66:3,19 67:1,3 67:4,6,17,17,24 68:7 69:8,22 71:3,4 73:2 74:15 75:1 82:15 83:1,2 84:18 85:11 86:14 88:1,13 88:21 89:3,19 93:17 94:8,10 94:14,16,17,22 94:24 95:6,8,9 95:18,22 96:1 96:12,14 99:12 100:25 101:25 102:17,21 103:20,24,25 105:2,6,10,23 106:7,9,9,13,25 107:13,20 108:11,19,22 108:23 109:2 patentee 34:1 patents 6:25 7:8,8 9:14,18 14:10,21 16:14 18:3,7 20:3 52:15 57:19 60:24 74:25 97:12 pattern 14:18 16:11 17:25 19:25	penalty 93:24 pending 44:11 109:1 perfectly 104:15 perform 70:8 performed 30:12,18 performing 55:16,18,25 56:2 75:15,17 76:17,20 101:17,20 102:2 perjury 93:24 person 29:3 33:23 44:4 64:2 110:7 petitioner 1:6 1:16 2:5 4:20 4:24 45:4 ph.d 3:3 4:22 ph.d. 1:15 91:20 phd 111:5 112:2,24 113:2 113:4,12 phrase 11:19 12:3 19:16 20:15 48:16,18 49:7 phrases 15:8 16:2,23,23 17:12,13
--	--	---	--

[pickard - proceed]

pickard 2:7 3:4 4:16,17 5:3 7:25 13:21 23:10 26:24 32:12 34:21 35:6 43:7,14 43:20,25 44:6 46:19 51:10 69:14 74:2 79:17 80:21 81:6,18 82:7 82:13 85:2 86:7 89:23 90:1,19 91:3 93:6 97:16,25 98:8 99:4,23 100:3 107:24 108:14 109:6	82:14 91:6 94:9,25 100:4 101:13 105:21 pllc 2:7 plus 56:16,16 57:11,11 58:1 58:2 61:25,25 62:17,17 65:8 65:9,18,18,21 65:22 70:19,19 75:9,10,24,25 76:24,24 81:25 82:21,22 105:16,16,25 105:25 point 10:8 25:14,23 34:10 50:7 59:7 63:6 70:5,12 81:10 pointed 107:16 pointing 48:14 pool 31:2 pools 34:13 portion 105:1 posed 42:16 43:17 position 51:21 57:23 71:25 possible 8:15 potentially 64:8 67:20 powers 2:8 4:17 praise 45:14 46:2	praising 47:7,8 precise 60:25 precisely 15:7 16:1 17:11 prefer 20:7,25 premise 76:8,9 preparation 6:22 52:3 57:2 61:3 62:9 63:15 65:3 68:3 69:19 71:19 72:20 73:20 83:6 86:1 99:8 103:5 prepare 6:10 71:8 86:24 prepared 10:15 11:6 38:13 39:18 40:23 47:18 51:8 57:21 58:17 59:9,21 60:10 60:15 61:5,18 63:4 64:11 66:5,9,17 67:7 67:21 69:12 70:9 79:25 80:9 83:5,8 84:11,25 85:18 86:5 88:2,7 89:20 99:19,21 99:22 101:7,8 102:8	preparing 10:22 35:14 46:21 52:4 85:20 86:19 88:16 presence 57:4 presented 34:5 89:14 103:18 presents 87:21 pretty 97:18 previous 27:24 76:14 previously 27:14 29:12 42:16 52:10 87:4 primary 43:10 43:15,15 principles 5:12 19:2 29:14,22 32:20,23 33:13 34:7 prior 23:19 24:17,23 41:23 41:24 42:11,12 42:20,21 44:20 44:21 priority 29:5 33:24 52:15,23 94:16 privilege 79:9 procedures 80:12 proceed 10:1
---	---	--	--

[proceeding - quoting]

proceeding 97:11	73:13 74:18 79:5 84:17	q	44:10,11 46:21 49:16 55:22
proceedings 53:19 96:9	85:10,23 86:12 89:7 95:20,23	quackenbush 1:15 3:3,9,12 3:13,15 4:11 4:22 5:4 8:1,7 8:8 10:23 11:8 13:1 15:2 18:12 32:16 35:7,14,20,21 47:20 82:14 91:6,12,13,20 93:9,11,12 95:12 97:20 99:5 100:4,9 105:13 108:8 111:5 112:2,24 113:2,4,12	57:20 59:2 60:21 62:22 63:14 64:9,21 65:14 69:17,18 69:21 75:7 76:7,12 78:16 79:10 85:7 86:10 88:7,9 90:8 95:25 103:16 105:21
process 31:5,13 34:16 51:4 96:22	96:11,13,18 97:10 99:10 104:2 106:18		
processes 53:22 53:24	provides 41:17 46:5 47:9		
produced 87:12	providing 79:6 ptab 81:1		
product 79:9	public 1:18 110:5,20 113:19		
professional 1:17 110:5			questioning 29:7 76:14
property 14:20 16:13 18:2 20:2	publication 21:19 42:22 44:22		questions 5:12 5:13,18 12:16 12:21,25 27:2 28:1 43:8,17 52:11 60:8 77:3 79:4,25 80:5 81:9,14 84:16 85:9,18 85:22 88:11,17 90:15,20 99:9 101:4,6 108:9 109:5,6
propose 97:16	publications 25:20 38:15,17 38:20,23 39:2 39:5,21,23 40:1,4 41:2,5,8 41:11,15,25 42:13 68:9,19 68:23 69:1,6 87:2,5,9,14,21 87:24 88:24 89:1,4,9,16	qualified 61:7 62:15 63:18	
prosecuted 53:15		qualify 82:21 105:24	
prosecution 14:11,12 16:21 18:8 30:6 34:2 67:17 71:4 97:13		quantities 68:15	
provide 6:5 13:3 20:9 26:4 26:15,17 49:11 49:18,24	purpose 18:22 purposes 12:17 32:17	question 5:16 6:3 8:9 12:2 13:20,22,23 14:22 16:15 17:9 18:4 20:4 20:8,10,22 24:22 29:4,20 30:17 32:14,15 32:17 33:24 42:5,8,14,15,15 42:16,17,18 43:4,21 44:8	quickly 97:19 quote 25:8 44:18 45:3 61:9 66:25 71:13,14
provided 13:16 18:11,12,24 32:9 57:19 62:24 64:3 67:17 68:22,25 70:17 72:16,22	put 5:18 87:16 python 103:25		quoted 42:24 quoting 42:24 56:7

[r - regarding]

r	really 39:5 99:24	73:18 92:1 94:22,23 103:17 108:8 108:15	redundant 26:22 30:23
r 2:8 4:1 112:3 112:3	realm 76:25		redundantly 26:11
raised 38:11	reason 5:17 6:7 101:2 111:11 112:6,9,12,15 112:18,21	receipt 111:18	refer 16:23 35:21 106:23
raising 51:14		received 70:5 70:25	reference 90:24 90:25 95:5,8
ramifications 53:13,16	reasons 19:22 21:24 26:2 30:4	recently 51:13 70:16 71:11 72:25	referenced 111:6
rather 20:22 37:23 38:24 40:11 87:16 107:14	rebut 47:15	recital 55:17 56:1 75:16 76:18 101:18	references 7:1 7:1 23:22 24:1 24:3 27:6,6 34:10 40:9 91:23 108:13 108:20,25
reach 67:19	rebuttal 6:12 7:5,24 9:24 13:9 15:16 25:3 29:15,22 31:18 32:10,23 33:14 34:5,11 38:7,10 39:11 39:16 40:20,23 41:21 42:5 43:2 45:25 46:22 50:13 52:12,19 58:16 59:18 60:14 67:10 71:21 72:22 73:22 74:6 78:22 84:23 85:6,16 86:3,21,25 88:18 99:18 103:8	recited 25:18 25:22 105:15	referred 95:16
reached 53:14		recites 61:24	referring 48:8 77:19 78:2 106:14
reaching 34:4		recognize 8:9 8:19 28:17 92:4 93:11 100:14,23	refers 38:3
read 9:21 13:21 13:23 15:9,24 24:12,15 29:10 45:10,12 57:5 68:15 102:3,10 102:24 106:21 107:9 111:9 113:5		recollection 7:10,14 14:4 70:11	reflect 96:19,21
reading 14:10		record 4:3,15 12:17 35:2,5 80:19,22,24 81:8 82:5,6,9 82:12 84:14 90:9 92:5 97:21 98:7,10 99:3 108:2,5 109:9 110:10	refresh 19:12 27:3 104:25
reads 22:1,7 25:11 26:14,22 30:23,25 31:4 31:4,7 37:16 38:18 39:24 41:6 68:21 87:6 89:2 103:22 104:21 106:16,17 107:14,17	recall 7:17 27:8 35:24 51:21 59:6 70:11,23 71:7,17 72:2	redirect 10:5	refreshed 6:22 22:19
ready 34:20 73:25		reduced 110:9	refuting 26:5
			regard 53:14
			regarding 20:21 38:11 39:7 51:1 59:3 67:12 68:5 87:1,17,24 88:23 89:15,17 93:16

[regards - response]

regards 78:12	rephrase 69:20	71:21,21,22	require 45:10
regions 68:16	report 3:14	72:22 73:22	45:24 46:9
registered 1:17	6:12,13,14 7:3	74:6,13,18,20	47:4
110:4	7:5,17,24 8:15	74:24 76:3,6	required 22:7
relate 86:13	8:16,25 9:2,24	76:12 77:3	26:23 37:16,24
99:11	10:3,13,15,21	78:22 79:23,24	38:18 39:3,25
related 7:2	11:4,23 12:12	81:23 83:25	40:6 41:6,13
94:16 95:3,14	12:20,24 13:9	84:12,23 85:6	46:25 68:21
110:13	13:25 14:4,8	85:16 86:3,21	69:3 87:7,15
relates 38:8	15:13,16,18	86:25 88:18	89:2,10 113:13
39:12 40:20	17:6 19:14	95:11 100:12	requirements
relatively 97:17	21:5,14,15,16	100:24 101:5	19:8 97:9
relevant 6:23	21:17 23:9	103:3,8,11	resources 70:7
29:4 33:24	24:4 25:3,5,23	106:23 108:22	respond 12:21
50:11 51:7	27:13,17,22,23	reporter 1:17	22:17 37:14,18
52:7 66:14	27:24 28:4,12	4:5 110:5	37:21,24 38:1
67:16 68:4	28:15,18 29:7	reports 6:24,25	38:6 59:20
71:2 72:1,17	29:11,15,16,22	7:21 10:10	87:1
73:15 77:11	29:23 30:9	27:20	responded 22:4
80:11 83:12	31:18 32:10,19	represent	22:8 25:6
84:9 90:15	32:23,25 33:5	100:9	50:12,23 58:12
rely 23:5	33:7,10,14,16	represented	60:14 78:14
remember	33:19 34:5,11	88:1 92:16	83:24 88:20
51:19 77:17	37:5 38:8,10	97:12	responding
remind 107:10	39:11,16 40:20	representing	27:17 30:10
render 56:20	40:23 41:21	78:5,8,25	43:8 52:20
57:23 103:2	42:4,6 45:25	represents	79:24
108:25	46:23 47:6,19	102:9	responds 38:10
rendered 57:1	48:7,15 50:13	request 11:22	response 21:16
71:5	50:24 51:3,13	11:23	22:22 26:9
renders 107:22	52:5,9,12,20	requested	28:15 37:4,6
repeat 13:19	56:11,21 57:21	80:16 106:19	37:10 39:19
24:21 29:19	58:16 59:18	requesting	40:24 61:4
49:15 55:21	60:13,14 61:5	106:20	62:11 73:22
65:14 105:20	63:15 67:10		89:12

[responses - second]

responses 5:24 60:11 responsive 23:11 26:25 32:13 46:20 51:11 69:15 85:3 86:8 89:24 99:24 result 53:7 results 46:3 retained 9:7 retains 104:8 return 111:13 111:17 reveal 90:6 review 18:24 19:5 35:13 36:5 52:2,5 53:5 54:3 63:1 63:6,16,18 64:6 66:14 67:16 69:7 71:2 72:16 73:15 76:5 77:6 80:10 81:12 83:10,12 84:9 95:18 103:4 111:7 reviewed 6:12 6:13,14 18:6 21:7 27:22 57:2 58:20 60:8 61:3,17 65:2 67:23 68:4 71:19	72:20 73:7,19 83:6 84:2 reviewing 16:20 right 6:21 8:17 9:3,19 11:21 11:25 12:10 13:1 15:1 18:22 28:3,16 35:10 36:3,25 42:23 45:11,20 45:21 55:6 57:25 66:18 72:3 74:15 89:22 91:4,21 93:3,21,25 94:17 100:2,21 101:6 role 97:3 roles 60:23 room 80:20 rosati 1:20 2:3 4:9 row 48:9,22 rule 43:11,13 rules 81:1 s s 3:6 4:1 112:3 sample 21:25 68:15 satija 21:17 22:3,6,12,15,22 25:5,14,18,19 34:8 37:11,12 37:15,18,21,25	38:2,11,25 40:7 41:1,16 44:16 45:13 46:1,14 47:5 50:12,21 51:1 58:11 59:19 60:13 67:11 68:6 69:4 78:14 83:22 87:17 88:22 89:12,15,17 satija's 6:14 22:9 25:24 26:5,9 27:18 28:15 30:10 37:5 38:13 39:20 47:16 52:20 61:5 62:12 71:21 73:22 79:24 87:1,19 99:18 says 11:15 17:9 48:3 49:2 91:19 schmitt 94:10 scope 8:6,13,22 9:20 11:1,12 13:6,18,24 15:10 17:1 18:14 19:8,19 20:18 21:12 24:13,16,19,20 24:24 25:1 28:6 29:6,8,9 33:2 37:2 48:6	48:13,25 49:14 49:21 50:20 52:1,11 53:10 56:5,19 57:14 57:21 58:7,14 59:1,8,16,21 60:3,15,20 61:12 62:3,21 63:4,12 64:18 65:4,11 66:2,7 66:22 67:5,8 69:12 70:9,13 70:22 71:16 72:11,19 73:5 74:17 76:2 77:2,16 78:9 78:11,21 80:13 81:2,10,20 82:24 83:4,21 85:14 86:20 88:6 91:10 93:10 94:19 95:7,13 96:16 99:14,19 100:8 101:1 102:5,7 102:25 103:6 105:19 106:3 108:14 seattle 2:4 second 37:16 38:18 39:24 41:5 48:9,22 57:6 68:20 87:6 89:2 95:2
---	---	--	--

[secondary - specific]

secondary 23:2 38:3 39:6 40:9 41:15 44:15 45:15 69:6 87:22 89:16 section 13:12 17:14 106:22 see 6:21 8:20 11:11,17 48:5 48:7,12,14,23 49:1 55:10,12 55:13 57:9 91:15,17 92:3 94:7,13,14 95:2,5,8 102:14 seem 51:7 selecting 104:3 sent 111:14 separate 53:4 80:12 96:8,8 102:10 103:10 separately 96:4 separateness 36:10 september 91:23 sequence 22:7 25:11,12 26:14 26:15,16,22 30:13,23 31:3 31:4,14,15 32:5 37:16 38:18 39:24 41:6 51:5 57:5	68:20 87:6 89:2 103:21,22 104:21 106:16 106:17 107:14 107:16 sequences 26:21 31:10,11 34:12,13,14 87:12 103:21 104:1,4,6,7,9 104:10,12,13 104:14,16,17 104:20 107:17 sequencing 21:21,22 26:11 37:14 38:5,16 39:8,22 40:11 41:3,18 44:17 46:4,4,9,11 47:5,9 68:10 87:3,25 88:25 89:18 108:12 series 60:11 session 99:1 set 26:2 32:16 94:3 110:16 several 77:14 shaped 25:16 shared 88:5 shed 14:21 16:14 18:3 20:3 sheet 111:11 shift 55:5 100:2	short 97:17 show 10:7 28:3 shown 45:4 sic 23:22,23 24:1 side 78:19,20 sides 78:25 sign 111:12 signature 8:20 8:23 93:21 100:15,19,21 110:19 signed 8:20 10:15 11:6 74:6 111:20 similar 24:9 simple 32:18 42:8 86:10 88:9 simply 37:10 38:25 42:18 85:7 single 104:1,4,7 104:8,13,16,17 104:19 sitting 56:11,22 57:22 58:18,19 61:13 64:10,25 66:4 67:6 70:3 71:7,17 94:20 103:17 106:4 107:7 six 74:11 sixth 11:3	size 14:18 16:11 17:24 19:25 skill 29:4 33:23 64:3 97:14 small 28:1 smi 104:10 software 103:19 solutions 111:23 sonsini 1:20 2:3 4:8,21 6:18 sorry 21:15 33:10,18 34:13 35:9 51:23 56:16 74:22 91:1 103:11 sort 5:11 speak 44:3 54:22 speaking 4:4 44:5 specific 11:16 11:19 12:3,6 13:5,13 14:18 15:20,22 16:8 16:11,25 17:16 17:25 19:17,25 20:15,24 21:2 21:10 22:2,11 22:16 23:6 25:13 30:1,8 30:14 31:12,16 32:1,4,15
--	---	--	--

[specific - subject]

68:16 specifically 20:6 25:21 26:8 30:23 34:8 37:12 38:10 73:18 76:4 103:8 106:14 specification 16:20 26:1 30:5 34:2 46:17 50:9 58:5,21 59:10 59:14 63:19 67:23 69:22 75:21 101:23 102:20 105:5 107:3,20 108:19 specifications 60:9 specifics 94:22 specified 55:16 55:25 75:15 76:18 101:18 speechfying 43:8 srf 18:21 ss 110:2 stage 97:7 stand 53:25 108:16,18 standards 54:6 start 11:9 33:9	starting 49:19 94:12 starts 9:4 state 12:17,19 14:13 32:21 96:21 stated 9:22 12:8 17:18 18:15 33:19 44:19 46:22 57:15 58:9 60:6 62:5 63:24 66:12 67:14 statement 47:2 56:10 80:19 103:15 statements 26:6 27:18 45:22 76:5 93:23 states 1:3 47:3 stay 13:1 80:22 step 55:9,10,11 55:11,12,13,15 55:18,24 56:2 56:15,16 57:11 58:2,23 59:12 60:1,18,25 61:8,10,22,24 61:25 62:16,17 63:9,22 64:14 64:16 65:2,6,8 65:9,16,18,22 66:19,20,25	68:1 69:24 70:19 75:10,14 75:17,25 76:17 76:20,24 82:22 101:17,20 104:8 105:16 105:25 106:15 106:16,17 steps 59:13 60:24 61:18 66:10 68:12 70:18 71:14 73:2 75:9,24 75:25 82:17,21 102:2,18,20,22 104:23 105:3,4 105:7,15,24 106:5,6 107:1 107:2,4,14,19 107:21 sterne 2:7 4:18 sternekessler.... 2:10,10 stipulate 10:8 43:3 strand 22:7 25:11 37:16 38:18 39:24 41:5 68:20 87:6 89:2 104:1,2,4,7,8 104:13,16,17 104:19 stranded 25:9 48:11,19 50:3	50:17 51:25 strands 26:11 57:6 streamline 98:3 strictly 85:6 strike 23:10 26:24 32:12 46:20 51:10 69:14 85:2 86:7 89:24 99:23 stringent 104:5 structure 55:17 56:1 58:4 59:11,12,24 72:6 75:16,20 76:19 101:19 101:22 102:1 102:22 105:7 107:4 structures 58:23 63:8,21 67:25 69:23 70:3 72:7 study 61:15 77:12 subject 9:25 11:2 13:7,25 14:24 15:14 17:2,4 19:14 21:6,13 25:4 27:15 28:11 29:9 31:19 32:10 33:5,15 33:17 34:6
---	---	--	--

[subject - testimony]

35:18 37:9	67:15 70:7,25	51:24	50:4 66:25
39:16 50:13,25	71:23 72:14,16	tags 31:1	84:6
52:8,18 56:21	73:8,14 75:6	take 4:10 8:7	terms 9:10
62:14 66:8	75:12 77:8,11	51:18 74:1	13:15,17 14:3
67:9 70:14	83:9 84:7	80:17 92:7	14:9 15:19
80:2,14 84:1	sufficiently	94:24 98:2	16:7 17:21
84:22,25 86:2	45:4 48:4	105:10 107:25	18:9 19:21
101:9 103:7	suffolk 110:2	taken 35:3	20:10 21:1
submit 103:11	suggested 98:2	82:10 103:13	22:19,21 29:3
submitted 8:10	suit 74:25	108:3	30:3 33:22
14:5,7 15:13	support 18:8	takes 19:11	34:1,3,17 48:5
15:16 17:6	68:5	talk 28:9 43:12	49:12,18,25
21:14,16,17	supposed 15:15	83:5 86:11	50:2,8,15 51:6
27:17,20 28:13	supposedly	90:8,18,20	55:13 59:3
28:15 35:17	21:5	talking 33:3	60:4 62:25
36:17 51:13	sure 9:23 10:6	74:23 81:3	63:13 64:5
74:13,24 77:4	19:7 24:16	target 22:2	65:13 67:13
79:23 84:24	34:21 53:12	30:25	69:10 70:2
85:16 88:19	70:2 74:5	targeting 68:16	71:1,6,25
93:13,15 94:21	80:21 91:3	tavers 23:22,23	72:12,15,18
95:17 96:20	96:10 101:5	24:1,6	73:9 83:11
99:17 100:12	105:22	teaches 44:25	testified 4:25
100:24 101:11	surprised	45:5	testify 6:7 8:25
102:9 103:3,9	70:15 71:10	tell 12:22 54:16	9:1 10:24 11:5
subscribed	72:3,24	56:12 75:2,12	39:18 47:18
113:14	suspect 90:5	75:23 76:21	51:8 57:22
substantially	sworn 4:25	81:24 82:19	58:15 59:9,22
48:4,23 49:2,4	92:9 110:7	83:17 90:1	60:10 63:5
49:7 50:6,7,16	113:14	107:7	69:13 70:10
51:22,23	t	ten 27:2 34:23	88:7 92:13
suffice 5:24	t 3:6 112:3,3	34:25	99:20,21,22
sufficient 14:15	table 48:1,8	term 11:20	102:8 110:7
16:7 17:22	49:3,13,19	12:4,6 23:5	testimony 3:2
62:24 63:1	tagged 48:10	30:1,8,16 31:8	20:20 61:6,19
64:4,6 66:13	48:19 50:3,17	48:10,22 49:4	62:10 64:12

[testimony - travers]

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

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EXHIBIT 20



**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

TWINSTRAND BIOSCIENCES, INC. &
UNIVERSITY OF WASHINGTON,

Plaintiffs,

v.

GUARDANT HEALTH, INC.,

Defendant.

C.A. No. 21-1126-VAC-SRF

JURY TRIAL DEMANDED

**DECLARATION OF JOHN QUACKENBUSH PH.D. IN SUPPORT OF
DEFENDANT GUARDANT HEALTH, INC.'S ANSWERING CLAIM
CONSTRUCTION BRIEF**

I, John Quackenbush, declare as follows:

1. I have been retained by Counsel on behalf of Guardant Health, Inc. to provide opinions in this matter related to my experience and expertise. My opinions are based on my skills, knowledge, training, education, and experience in matters of this nature, and my examination of the materials utilized in preparing this report.

2. I have been retained by Guardant Health, Inc. ("Guardant") to offer an expert opinion on the construction of certain claim terms in U.S. Patent Nos. 10,287,631 ('631 Patent), 10,689,699 ('699 Patent), 10,752,951 ('951 Patent), and 10,760,127 ('127 Patent), (collectively, "TwinStrand Asserted Patents") and U.S. Patent Nos. 10,801,063 (the "'063 patent"), 10,889,858 (the "'858 patent"), 11,118,221 (the "'221 patent"), 11,149,306 (the "'306 patent"), (collectively, "Guardant Asserted Patents"). Collectively, I refer to the "TwinStrand Asserted Patents" and the "Guardant Asserted Patents" as the "Asserted Patents."

3. I receive \$750 per hour for my services. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

4. In preparing this declaration, I have reviewed the Asserted Patents and their file histories, the constructions proposed by the parties, and any other documents referenced in this Declaration.

5. In forming the opinions expressed in this declaration, I relied upon my education and experience in the relevant field of the art and have considered the viewpoint of a person having ordinary skill in the relevant art as of March 20, 2012, for the TwinStrand Asserted Patents for the Guardant Asserted Patents December 28, 2013.

II. QUALIFICATIONS

6. In forming the opinions expressed in this declaration, I relied upon my education and experience in the relevant field of the art and have considered the viewpoint of a person having ordinary skill in the relevant art ("POSITA"). A copy of my *Curriculum Vitae*, attached as Ex. A, contains further details on my education, experience, publications, and other qualifications to render an expert opinion in this matter. Below I have summarized those qualifications, as well as any other background and expertise relevant to the technical issues in this case.

7. I am a Henry Pickering Walcott Professor of Computational Biology and Bioinformatics and Chair of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health. I am the founding Director and current co-Director of the MS Program in Computational Biology and Quantitative Genetics, Director of the Big Data to Knowledge Training Program, and co-Director of the Cancer Genomics Training Program. I hold appointments as Professor of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute and at the Channing Division of Network Medicine of Brigham and Women's Hospital.

8. In addition to my academic appointments, I co-founded Genospace LLC. Genospace produces software solutions to operationalize precision medicine through the integration of clinical and genomic data and its presentation to clinical and research users in an intuitive format. Genospace was purchased by Hospital Corporation of America in January of 2017.

9. In addition to my academic and research responsibilities, over the years I have taken significant regional and national research leadership responsibilities. I have served on the Scientific Advisory Board of the St. Jude's Children's Research Hospital and the Board of Scientific Counselors of the Environmental Protection Agency. I have also served on numerous scientific review panels for the National Institutes of Health, the National Science Foundation, the Department of Energy, the National Aeronautics and Space Administration, the Wellcome Trust, Genome British Columbia, Genome Canada, the National Sciences and Engineering Council of Canada, and the European Union. And I have served on numerous study panels for the National Research Council, the National Academy of Sciences, and the Institute of Medicine.

10. I have presented more than 300 talks, courses, and workshops since joining the Harvard School of Public Health and Dana-Farber in 2005, including the Master's Core Course, Biostatistics 280, Genomics and Genetics for Health Research. I have also taught numerous courses and workshops on the analysis of genomic data and served as an organizer of the EMBO course on DNA microarray analysis for more than five years.

11. Prior to joining the faculty at Dana-Farber and Harvard, I was a Professor of Chemical Engineering at the University of Maryland from 2003-2005; an Investigator with The Institute for Genomic Research from 2002-2006; a Professor in the Department of Biochemistry at The George Washington University from 2000 – 2005; a Lecturer in The Department of

Biostatistics at The Johns Hopkins University from 1998 – 2005; an Associate Investigator at The Institute for Genomic Research from 1997 – 2001; and an Assistant Investigator at The Institute for Genomic Research in 1997.

12. I received my Ph.D. in Theoretical Particle Physics at the University of California, Los Angeles in 1990. I also hold a Master of Science in Physics from University of California, Los Angeles and a Bachelor of Science in Physics from the California Institute of Technology.

13. I have studied, taught, practiced, and conducted research involving the use of genomic technologies, including DNA sequencing and DNA microarrays, and involving computational analysis of data related to genomic technologies. I have expertise in genomic technologies, computational analysis, and modeling of a plant, animal, and microbial systems with an emphasis on the study of human diseases, such as cancer.

14. I have received numerous awards and honors including being recognized as a White House Open Science Champion of Change, an Australia Fellow, and a Distinguished International Advisor for the International Conference of BioInformatics and BioEngineering sponsored by the Institute of Electrical and Electronics Engineers.

15. I have published more than 320 peer reviewed scientific papers that have been cited more than 87,000 times. I have had continuous grant support for my research from the National Institutes of Health and other organizations for nearly twenty-eight years. In 2018, I received an NCI Outstanding Investigator Career Award, a seven-year research grant recognizing a lifetime record of substantial contributions to the field.

16. Based on my professional experience, I believe I am qualified to testify as an expert on matters related to the Asserted Patents.

III. UNDERSTANDING OF THE LAW

17. I am not a legal expert and therefore I offer no opinions on the law. However, I have been informed and am aware of legal standards that are relevant to my analysis, as summarized below.

18. It has been explained to me that a patent is presumed valid. I understand that a patent (or the claims of a patent) may be invalidated only if the party challenging validity proves that the claims are invalid by clear and convincing evidence.

19. I have been informed and understand that claims are generally given their ordinary and customary meaning as understood by a POSITA at the time of the alleged invention, in light of the patent specification and prosecution history. Such an individual is considered to possess ordinary skills and knowledge in a particular technical field and is not an automaton. Other than the patent specification and prosecution history, I understand that it is also sometimes permissible to refer to “extrinsic” evidence which includes, among other things, relevant scientific principles, the general meaning of technical terms, and the state of the art. However, these extrinsic sources of evidence are inherently less reliable than the intrinsic evidence identified above.

20. I have also been advised that a POSITA is a hypothetical person who is capable of understanding the scientific and engineering principles applicable to the relevant art of the claimed subject matter. I understand that a POSITA is presumed to have known the relevant prior art at the time of the alleged invention.

21. It has been explained to me that the patent statute includes a requirement that claims be definite. I have been informed that, to meet this “definiteness” requirement, the claims must particularly point out and distinctly claim the subject matter that the applicant regards as his or her invention. I understand that indefiniteness is evaluated from the perspective of a POSITA

at the time of a patent's filing. It has been explained to me that a patent claim is indefinite if the claim, when read in light of the specification and the prosecution history, fails to inform, with reasonable certainty, a POSITA of the scope of the invention. It was further explained to me that absolute or mathematical precision in claim language is not required. However, it is not enough that some meaning can be ascribed to a patent's claims. A claim is indefinite if its language might mean several different things and no informed and confident choice is available among the contending definitions.

22. I have been informed that claim construction is a matter of law and that the final claim constructions for this proceeding will be determined by the Court.

IV. BACKGROUND OF THE TECHNOLOGY

23. DNA is a double-stranded molecule within each cell that stores genetic information, a blueprint for living organisms, including cancer-causing tumor cells. DNA contains four building block molecules (nucleotides)—Adenine (A), Thymine (T), Guanine (G) and Cytosine (C). These nucleotides are arranged into long polynucleotide chains. The order of nucleotides is important for normal protein synthesis and healthy cells. Variants (or mutations) in this code, for example one nucleotide replaced with another (C instead of A) or an added or deleted nucleotide (normal sequence reads C-A-T but now reads C-T or C-A-A-T) can lead to cancer.

24. Detection and quantification of these mutations is important for diagnostics, early treatment, and disease management, but detection was difficult using previous DNA sequencing methods due to sequencing errors and low DNA abundance in samples. For example, Next Generation Sequencing ("NGS") allowed for sequencing of millions of DNA fragments at the same time. However, NGS has an error rate of 0.1-1% due to errors introduced during sample preparation and systematic errors (i.e., misreads during the sequencing process itself). These

systematic errors create “background noise,” which makes it difficult to distinguish true mutations, especially rare mutations present at extremely low frequencies.

25. The Guardant Asserted Patents are directed to novel sequencing methods for detecting, for example, cancer-causing mutations using cell-free DNA (“cfDNA”), which is found in very small quantities in blood and other bodily fluids. By analyzing cfDNA, cancerous mutations can be detected using, for example, a simple blood draw instead of a traditional tumor biopsy—which is a painful, costly, and slow process. These non-invasive methods are referred to as “liquid biopsies.”

26. Generally, the claimed methods are directed to: (1) collecting a bodily fluid sample from a patient; (2) extracting and isolating double-stranded DNA, including cfDNA, from the sample; (3) tagging the double-stranded DNA with an adapter/barcode in which the Watson strand tag is distinguishable from the Crick strand tag; (4) amplifying (copying) the tagged DNA; (5) sequencing the amplified DNA to produce a set of sequence reads; and; (6) identifying true mutations in said sequence reads. *See e.g.*, Ex. 7, '221 patent at FIG. 1.

27. The claimed methods can be used to correct errors and reduce background noise present in NGS sequencing methods resulting from the DNA amplification step and/or sequencing step. For example, the claimed methods allow for tagging of both strands of DNA (both the Watson and Crick strands, or “complementary strands”), amplifying both strands, and sequencing of both strands.

28. The claimed methods allow for the comparison of complementary strands of the original target molecule, and since true mutations in a molecule must inherently appear on both strands, this strand comparison allows true mutations to be distinguished from sequencing errors, which occur on only one of the two strands.

29. The claimed methods therefore provide the sensitivity and specificity necessary for accurate cancer detection and monitoring with liquid biopsies, allowing for the identification of a true mutations previously lost in the noise.

30. The TwinStrand Asserted Patents also describe methods to detect genetic variations in DNA sequences. The claimed methods of the TwinStrand Asserted Patents include steps of isolating circulating DNA from a patient sample, tagging both strands of DNA with adapters, amplifying the tagged DNA, sequencing the amplified DNA, and identifying mutations based on the resulting consensus sequence reads. *See* Plaintiffs' Opening Claim Construction Brief ("Op. Br.") at 2-3.

31. Unlike Guardant's technology, three of the TwinStrand Asserted Patents require the use of molecular tags in which some or all the nucleotides have been randomly generated (*i.e.*, degenerate or semi-degenerate tags). I have provided my opinions on the meaning of the terms "degenerate" or "semi-degenerate" as understood by a POSITA below.

I. LEVEL OF ORDINARY SKILL IN THE ART

32. A person of ordinary skill in the art at the time of the earliest effective filing date of the Asserted Patents would typically have an advanced degree, such as a Ph.D., with research experience in genomics, molecular biology, bioinformatics, or a related field, or could have less education but significant professional experience in one or more of these fields.

33. I understand that Dr. Ehrlich has offered an opinion that a person of ordinary skill in the art at the time of the invention of the Asserted Patents would have had knowledge of the scientific literature concerning methods of DNA sequencing and analysis, including DNA sample preparation for sequencing, amplification, methods of DNA sequencing, and bioinformatics methods for raw data analysis, and that as of the priority date (March 20, 2012 for the TwinStrand Asserted Patents, and December 28, 2013 for the Guardant Asserted Patents) this

person also typically would have had a Ph.D. in molecular biology, biochemistry, genetics, bioinformatics, or a related field, and would have had at least two years of experience in the use or development of sequencing technologies, or alternatively, this person would have had a Master's degree in one of the same fields with several more years of the same practical experience beyond what a Ph.D. scientist would have had, and a person of ordinary skill in the art may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but the skill of others on the team, such as a chemist and statistician.

34. My opinion is based on my understanding of a POSITA at the time of the respective priority dates.

II. AGREED-UPON CONSTRUCTIONS

35. I understand the parties have agreed to the construction of certain terms as listed below.

A. Agreed-Upon Constructions of Terms in TwinStrand Asserted Patents

Term	Agreed Upon Construction
uniquely labels '631 patent, claim 1	Plain and ordinary meaning
"quantifying at least two of (i) said paired sequence reads, (ii) said unpaired sequence reads, (iii) read depth of said paired sequence reads, and (iv) read depth of said unpaired sequence reads" '951 patent, claim 1	Plain and ordinary meaning
"partially single-stranded adapters" '127 patent, claim 22	Plain and ordinary meaning with the understanding that the term can include both Y-shaped and U-shaped adaptors
"partially complementary, asymmetrical double-stranded adapter-DNA molecules" '127 patent, claim 1	Plain and ordinary meaning with the understanding that the term can include both Y-shaped and U-shaped adaptors

“other fragment regions” '631 patent, claim 18	Plain and ordinary meaning
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B. Agreed-Upon Constructions of Terms in Guardant Asserted Patents

Term	Agreed Upon Construction
“cell-free deoxyribonucleic acid (cfDNA)” '063 patent, claims 15 and 24; '858 patent, claims 1, 3, and 5; '221 patent, claims 1–5; '306 patent, claims 17, 19, and 20	“DNA that exist(s) outside of a cell while in the body, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, cerebral spinal fluid, or tears.”
“a family of the families” '063 patent, claim 17	“a single family from the plurality of families”

III. OPINIONS REGARDING CLAIM CONSTRUCTION

36. I have read the Asserted Patents and their prosecution histories, and I have reviewed Dr. Ehrlich’s opinion regarding claim construction. I have arrived at my opinions as set forth below based upon my analysis of the materials identified throughout this declaration.

A. Disputed Claims in the TwinStrand Asserted Patents

1. “degenerate ... sequence(s)” and “semi-degenerate ... sequences(s)”

Disputed Term	Patent, Claims	Plaintiffs’ Proposed Construction	Guardant’s Proposed Construction
“degenerate ... sequence(s)”	'631 patent, claims 1, 12, 13, 15; '951 patent, claim 23; '127 patent, claim 13	“a nucleotide sequence that is known or unknown in which every nucleotide position is unrestricted in its nucleotide variability”	“[single molecule identifier (SMI) / oligonucleotide] sequence in which all of the nucleotides have been randomly generated”

“semi-degenerate ... sequence(s)”	’631 patent, claims 1, 12, 13, 15; ’951 patent, claim 23; ’127 patent, claim 13	“a nucleotide sequence that is known or unknown in which at least one nucleotide position is fixed or restricted in its nucleotide variability”	“[single molecule identifier (SMI) / oligonucleotide] sequence in which some of the nucleotides have been randomly generated”
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37. I understand that Plaintiffs and Guardant have proposed competing constructions for these terms. I understand that Plaintiffs contend that the concept of degeneracy, in the context of the TwinStrand Asserted Patents, is best explained in terms of nucleotide variability. Ehrlich Decl. at ¶¶ 58-60. Yet, the patents repeatedly, and expressly define degeneracy in terms of randomness.

38. After reviewing both the intrinsic and extrinsic evidence, in my opinion, the claimed degeneracy is achieved by randomization of nucleotides. This is consistent with Guardant’s constructions, which use the concept of randomness.

39. In my opinion, a POSITA as of the priority date reading the TwinStrand Asserted Patents would readily understand that “degenerate” means random. However, Plaintiffs contend that a “degenerate sequence” or a portion of a “semi-degenerate sequence” may be “known or unknown” and can also be totally “unrestricted” with regard to nucleotide “variability.” Under this construction, seemingly any nucleotide sequence is a “degenerate sequence.”

40. While Plaintiffs construe “degenerate sequence” in terms of “variability,” none of the TwinStrand patents ever refer to “variability” or “variable” to describe degenerate or semi-degenerate sequences. Plaintiffs rely solely on an expert declaration to advance this argument. Op. Br. at 11-12; Ehrlich Decl. at ¶¶ 66-68.

41. Moreover, Plaintiffs' use of the phrase "at least one nucleotide position is fixed" in their construction of "semi-degenerate" would encompass a sequence having fixed nucleotides at every position. Such an entirely fixed sequence is neither a degenerate or "semi" degenerate sequence.

42. The specifications of the TwinStrand Asserted Patents support Guardant's constructions. Importantly, a key aspect of the invention in the TwinStrand Asserted Patents is the use of "unique" SMIs attached to DNA fragments to lower the error rate in DNA sequencing. *See e.g.*, Ex. 1, '631 patent at 28:4-51 ("using the unique SMI tag affixed to each molecule to group PCR products together in order to create a consensus of all PCR products that came from an individual molecule of single-stranded DNA" results in "3-million-fold improvement over the error rate . . . obtained by a standard sequencing approach."). To achieve this reduction in error rate, the patents describe unique SMIs as including "a double-stranded, complementary SMI sequence (or 'tag') of 12 *random* nucleotides (or *a random 'degenerate sequence'*) per strand." *Id.* at 22:22-27 (emphasis added); 22:28-30 (explaining that "random" 12-nucleotide sequence will have a "unique 24 nucleotide SMI sequence.").

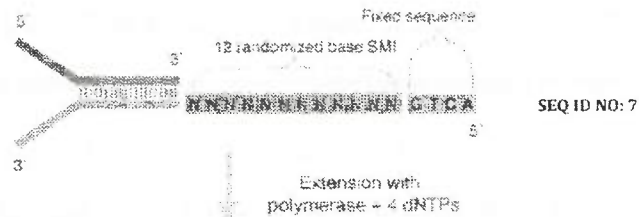
43. The target DNA molecules with "a random SMI sequence n-mer that is 12 nucleotides in length on each end will therefore have a unique 24 nucleotide SMI sequence." *Id.* at 22:28-30. This random, degenerate sequence on each end would therefore result in 4^{24} different unique tags, enabling every molecule to be tagged with a different, unique SMI.

44. The TwinStrand Asserted Patents specifications are replete with other statements where the inventors equate degeneracy and randomness. *See, e.g.*, Ex. 1, '631 patent at 6:48-63 (explaining that SMI sequence may be a "random degenerate sequence"); 6:66-7:2 (describing an SMI sequence that is a "random degenerate nucleotide n-mer sequence"); 7:6-18 (explaining that

SMI sequence may be “random and degenerate, wherein each sequence position may be any nucleotide”); 22:28-30 (explaining that the “random” 12-nucleotide sequence will have a “unique 24 nucleotide SMI sequence”).

45. The figures in the specification are in accord with these descriptions. For example, Figure 2 of the '631 patent (reproduced below) depicts synthesis of an exemplary SMI adaptor molecule. In the figure, the “*degenerate* lower arm sequence” is represented by “Ns,” which may be any nucleotide (A or T or C or G).

Figure 2



Ex. 1, '631 patent at FIG. 2; 3:63-4:3 (emphasis added). This ‘degenerate lower arm sequence’ is labeled “12 *randomized* base SMI.”

46. Moreover, the annotations in FIG. 2 and the specifications distinguish the “randomized” (*i.e.*, degenerate) portion from the adjacent “fixed sequence.” *Id.* at 20:46-48 (“SMI adapters include a 12-nucleotide *random* sequence, followed by a 5-nucleotide *fixed* sequence.”).

47. This is consistent with the other disclosures in the specification. *See, e.g., id.* at 12:58-61 (distinguishing an SMI with a “random oligonucleotide sequence” from one with a “set of fixed sequences”); 3:63-4:3 (“Oligonucleotides are annealed and the complement of the degenerate lower arm sequence (N’s) plus adjacent fixed bases is produced by polymerase extension. . .”); 12:58-61 (“The single-stranded SMI sequence tag can be synthesized as a random oligonucleotide sequence, or can be sequenced as a set of fixed sequences. . .”); 21:4-6

(“Discard reads that do not have the 5nt fixed reference (or “spacer”) sequence (CAGTA; SEQ ID NO: 6) present after 12 random nucleotides.”). These passages further demonstrate that the patents teach that degenerate (i.e., non-fixed) sequences (or degenerate portions of semi-degenerate sequences) are generated by randomization.

48. In my opinion, random and degenerate are not “different concepts” as Plaintiffs contend and the specification runs counter to this argument. Op. Br. at 12, Ehrlich Decl. at ¶ 72. The specification repeatedly uses “random” interchangeably with “degenerate” and explains that SMIs include random sequences. *See* Ex. 1, ’631 patent at 3:44-50 (noting that “every adapter contains a unique, double-stranded, complementary n-mer random tag on each end. . .”); 6:48-63 (explaining that SMI sequence may be a “random degenerate sequence”); 6:66-7:2 (describing an SMI sequence that is a “random degenerate nucleotide n-mer sequence”); 7:6-18 (explaining that SMI sequence may be “random and degenerate, wherein each sequence position may be any nucleotide”); 22:23-36 (describing addition of SMI sequence “of 12 random nucleotides (or a random ‘degenerate sequence’) per strand.”).

49. Neither Plaintiffs nor their expert explain what the purported difference is in the context of the TwinStrand Asserted Patents. Op. Br. at 12; Ehrlich Decl. at ¶ 72. Indeed, the passages cited by Plaintiffs employ the words in expressing a single concept rather than in any way distinguishing between the two. *See, e.g.*, Ex. 1, ’631 patent at 7:6-8 (“the SMI tag nucleotide sequence may be completely random and degenerate, wherein each sequence position may be any nucleotide”).

50. Plaintiffs also argue that the specifications disclose that the SMI sequences may be “designed” and are therefore not random. Op. Br. at 12-13; Ehrlich Decl. at ¶¶ 64-65, 72-73. But the portion of the specification relied upon by Plaintiffs is concerned with the design of

oligonucleotide adaptors that include SMI sequence, not the design of SMI sequences. The passage states that “[t]he *oligonucleotide* may be designed with appropriate regions of self-complementarity” Ex. 1, ’631 patent at 13:15-24 (emphasis added).

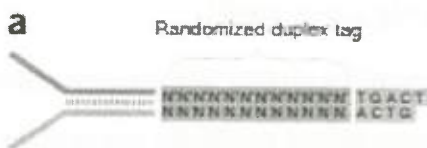
51. The specification consistently uses “design” to refer to the overall adaptor design, and not the SMI sequence specifically. *See, e.g., id.* at 9:16-19 (referring to “design” that “may include use of any sequencing adaptor (such as one lacking an n-mer tag) in conjunction with an n-mer tag that is incorporated into the U-shaped linker molecule.”). Where the SMI sequence in the adaptor (X’s) is “degenerate,” the specification teaches that the complementary bases (Y’s) may be added using a DNA polymerase, which supports the view that the degenerate sequence is itself not designed or known. *Id.* at 9:31-44.

52. In my opinion, the extrinsic evidence also supports Guardant’s constructions. I have reviewed several third-party patents, additional TwinStrand patents, and publications authored by an inventor listed on the TwinStrand Asserted Patents—which all establish that degenerate and random are equated.

53. For example, TwinStrand’s patents and applications directed to Duplex Sequencing (the technology at issue here) define “degenerate” and “semi-degenerate” to mean “random” and “semi-random.” For example, U.S. Patent No. 11,332,784 (the “’784 patent”), titled “Adapters, Methods, and Compositions for Duplex Sequencing” states that SMIs may be “*random/degenerate, semi-random/semi-degenerate*, or pre-defined.” Ex. 23, ’784 patent at Table 1, Col. 18 (emphasis added). *See also* Ex. 24, ’390 application, at [0048], [0076] (defining “*degenerate* SMIs” as “*Random* Unique Molecular Identifiers,” and explaining that during SMI synthesis, “the template strand can include . . . a region of *random* or *semi-random* nucleotide sequence (e.g., a *degenerate* or *semi-degenerate* sequence).”) (emphasis added).

54. Dr. Jesse Salk, TwinStrand’s co-founder and listed inventor on the TwinStrand Asserted Patents, also publicly described TwinStrand’s degenerate SMI sequences as random.

55. For example, the below figure comes from a paper on which Dr. Salk was a co-author (“Detecting ultra-low frequency mutations by Duplex Sequencing,” by Kennedy et. al. (“Kennedy 2014”)) and which is promoted by TwinStrand on its website as describing its technology. Ex. 25, Kennedy 2014; *see also* TwinStrand Website, Available at <https://twinstrandbio.com/resources/publications/> (Accessed August 25, 2022).



56. Like the figures in the patents, this figure labels the 12-nucleotide SMI sequence as a “*Randomized* duplex tag” and describes it elsewhere as a “*random* double-stranded tag.” Ex. 25 at FIG. 1. The adapters are “constructed by annealing two oligonucleotides, one of which contains a 12-nt [nucleotide] single-stranded *randomized* tag sequence. A DNA polymerase is used to copy the *degenerate* tag sequence, thereby converting it to a double-stranded form.” *Id.* at 2590 (emphasis added). The “[t]welve random nucleotides per adapter (24 nt per final ligated molecule) significantly exceed the degeneracy needed to ensure unique labeling of every molecule in the library.” *Id.* at 2591.

57. I have also reviewed a 2019 AACR presentation given by Dr. Jesse Salk. *See* Jesse Salk, *TwinStrand Biosciences discusses Duplex Sequencing AACR 2019* (Aug. 4, 2020) at 2:44-3:17 min (Available at https://www.youtube.com/watch?v=DGSGhjz_GQ.) During his presentation, Dr. Salk uses the same schematic from Figure 1 of Kennedy 2014 and confirms that the degenerate SMI sequence is randomized. He states that “the way duplex sequencing works is

we have a unique label that is affixed to every single molecule, so in this particular case, those 'Ns' represent a random degenerate sequence" and "the top sequence and the bottom sequence (N and N') just means that there is a complimentary randomized sequence, and in this case there are twelve N's which means there are 4^{12} possible combinations and if we ligate one of these adaptors on one end and one of the other end we have 4^{24} possible random combinations and there is just simply no way that two molecules have the same label by random chance." *Id.* at 2:44-3:17min. He goes on to state that after ligation the molecules now have "random and arbitrary sequences on each end." *Id.* at 3:20-3:22min.

58. As Dr. Salk's comments recognize, randomization of bases in the SMI sequence is necessary to uniquely tag target molecules. Indeed, if a portion of the 12-nucleotide sequence were fixed in advance, it would not be possible to achieve 4^{12} (or 4^{24} using adaptors on both ends) possible random sequences described by Dr. Salk.

59. In addition, other patents in the sequencing adaptor art define degenerate and semi-degenerate as random and semi-random, respectively. U.S. Patent No. 11,085,084 assigned to Stanford University states that "[t]he term 'random sequence' is used interchangeably with the term 'degenerate sequence,' i.e., the sequence not having a precise definition." Ex. 21, '084 patent at 8:14-16 (emphasis added); see also Ex. 22, '166 patent application by Menarini Silicon Biosystems at 22:7-10 ("By 'UMI' or 'Unique Molecular Identifier sequence' there is intended degenerate or partially-degenerate (i.e., random or semi-random) oligonucleotide sequences which are virtually unique for each ssDNA or dsDNA molecule.") (emphasis added).

60. In my opinion, a POSITA would understand that a degenerate sequence is random, and a semi-degenerate sequence is semi-random. A degenerate sequence consisting of "Ns" means that each N can be *any* of A or T or G or C (Plaintiffs acknowledge this point), not a

subset (for example, only A or T). This is consistent with the International Union of Pure and Applied Chemistry (“IUPAC”) convention, which provides that “N” in a DNA sequence represents any base (“aNy base”), not a subset of bases or an individual base. Ex. 26, NC-IUB, *Nomenclature for incompletely specified bases in nucleic acid sequences*, Proc. Natl. Acad. Sci. USA 83 (1986) at 5, Table 1; Op. Br. at 10; Ehrlich Decl. at ¶ 61. The patent reflects this understanding—describing its 12-nt SMI sequence of Ns as “degenerate” or “randomized.”

61. In my opinion, the extrinsic evidence cited by Plaintiffs does not support their position and instead, support Guardant’s. For example, the *Molecular Biotechnology* textbook states that a “partially degenerate” sequence contains a “known (fixed) nucleotide at a specific (query) position and *any* nucleotide in the other positions.” Op. Br. at 11 (emphasis added); Ehrlich Decl. at ¶ 68. This is not inconsistent with randomization at the non-fixed positions.

62. Similarly, the passage cited in the *Human Molecular Genetics* textbook, which describes a partially degenerate sequence as one with “the same base at certain nucleotide positions, while differing at other positions,” also is consistent with randomization to create “differing” bases at non-fixed positions. To the extent these passages touch on variability at non-fixed positions, they do not preclude randomization of bases, nor do they support Plaintiffs’ position that degeneracy can be equated with the amorphous and unhelpful concept of “variability.” Op. Br. at 12; Ehrlich Decl. at ¶ 68.

63. For the reasons stated above, it is my opinion that “degenerate” should be construed as “[single molecule identifier (SMI) / oligonucleotide] sequence in which all of the nucleotides have been randomly generated” and “semi-degenerate” should be construed as “[single molecule identifier (SMI) / oligonucleotide] sequence in which some of the nucleotides have been randomly generated.” This is consistent with both the intrinsic and extrinsic evidence.

2. “fragment ends”

Disputed Term	Patent, Claim	Plaintiffs’ Position	Guardant’s Proposed Construction
“fragment ends”	’631 pat., cl. 1	Plain and ordinary meaning	“Each fragment end is the plurality of nucleotides that is made up of fewer nucleotides than the entire fragment at the terminal end of the fragment after shearing and trimming”

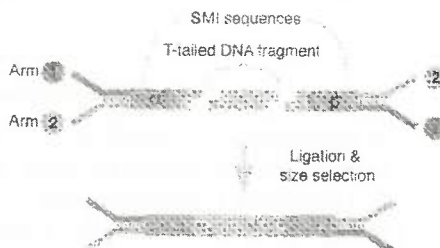
64. I understand that Plaintiffs agree that “fragment ends” includes “the distal or terminal parts of the fragment.” Op. Br. at 14. Thus, my analysis for this term is focused on whether the claimed fragment ends require shearing and trimming as set forth in Guardant’s construction.

65. In my opinion, the methods of the TwinStrand patents depend on the generation of “a sufficiently large number of unique tags to label a set of sheared DNA fragments from a segment of DNA.” Ex. 1, ’631 patent at 6:59-63. This “allows every molecule to be uniquely labeled prior to PCR duplication.” *Id.* at 18:42-47. As the above passages suggest, these DNA fragments are created by shearing of larger DNA molecules. *Id.* at 19:64-20:1 (“DNA . . . was sheared on the Covaris AFA system”); *id.* at 22:48-50 (target DNA is “sheared and end-repaired by standard methods, with size-selection for fragments in the range of ~200-500 [base pairs]. The specification also discloses shearing using a restriction endonuclease. *Id.* at 14:12-18.

66. Adaptors containing SMI sequences are then ligated to the fragment ends. *See, e.g.*, Ex. 1, ’631 patent at 3:44-53 (“Sheared double-stranded DNA that has been end-repaired and T-tailed is combined with A-tailed SMI adaptors”); 15:10-15 (“The sheared target DNA or RNA molecule may be end repaired and a double-stranded target nucleic acid sequence ligation adaptor may be added to each end of the sheared target DNA or RNA molecule.”), 21:2-24.

67. Figure 1 illustrates the ligation of SMI-containing adaptors to the ends of the sheared fragment in the middle:

Figure 1



68. The patents teach that the fragment ends play a role in unique labeling. For example, the fragment ends are used in conjunction with SMI tags to uniquely label the target sequence. *Id.* at cl. 1 (SMI sequence “alone or in combination with the target nucleic acid fragment ends uniquely labels each ligated double-stranded target nucleic acid molecule”); *id.* at 9:11-15 (combination of “sheared ends” and n-mer tag “may also serve as unique molecular identifiers.”).

69. In addition to being used in conjunction with tags, the sheared ends of the fragments may themselves be used “as identifiers to differentiate unique individual molecules.” *Id.* at 9:3-6; see also *id.* at 17:46-50 (“the sequencing method may be performed . . . without the use of SMI adaptor molecules, but instead by using the random shear points of DNA as identifiers.”); 26:24-28 (“the randomly sheared DNA ends were used as SMI’s.”); 18:42-49; 23:39-46.

70. Because the specification does not disclose any method of generating fragments other than shearing, and because shearing is an integral part of creating sufficient variability in the fragment end sequences to permit unique labeling or tagging, a POSITA would understand that fragment ends, as used in claim 1, are the result of shearing.

71. In my opinion, Guardant's construction reflects the meaning of fragment ends in the context of the specification and the understanding of a person of ordinary skill in the art.

3. The “non-unique” and “sufficiently/substantially unique/identifiable” Terms

Claim Term	Patent, Claim	Plaintiffs' Proposed Construction	Guardant's Position
“non-uniquely tagged parent polynucleotide (s)”	'699 pat., cl. 1, 16, 18; '951 pat., cl. 21	“a population of parent polynucleotide molecules affixed to polynucleotide barcodes, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the [population/sample], and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule”	Indefinite
“non-uniquely tagged double stranded adapter- DNA molecules”	'127 pat., cl. 26	“a population of double-stranded DNA fragment molecules affixed to adapters having barcodes, wherein the same barcode nucleotide sequence tags multiple double-stranded DNA fragment molecules in the library, and wherein the barcode nucleotide sequence serves as a molecular identifier only when combined with other information from the double-stranded adapter-DNA molecule”	Indefinite
“non-unique polynucleotide barcode”	'699 pat., cl. 16	“a polynucleotide barcode that is affixed to a parent polynucleotide molecule and having a polynucleotide sequence, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the population, and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule”	Indefinite
“non-unique tag”	'951 pat., cl. 25	“a tag that is affixed to a parent polynucleotide molecule and having a nucleotide sequence, wherein the same tag nucleotide sequence is affixed to multiple parent polynucleotide molecules in the sample, and wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule”	Indefinite

“substantially unique”	’699 cl. 1, 20; ’951 patent, cl. 21	Plain and ordinary meaning	Indefinite
“substantially identifiable”	’127, cl. 26	Plain and ordinary meaning	Indefinite
“sufficiently unique . . . substantially differentiated”	’951 cl. 24	Plain and ordinary meaning	Indefinite

72. In my opinion, the TwinStrand Asserted Patents and file histories provide no meaningful guidance as to what constitutes “non-unique,” “substantially” or “sufficiently” unique, or “substantially identifiable.” Since the patents provide no guidance as to where the line is drawn between unique, substantially/sufficiently unique, and non-unique, it is my understanding that the substantially/sufficiently unique and non-unique terms are indefinite.

73. The claims themselves provide no guidance. ’699 claims 1, 20, ’951 claim 21, and ’127 claim 26 describe non-uniquely tagged DNA fragments that are “substantially unique” or “substantially identifiable.” Independent claim 1 of the ’699 patent is illustrative. It recites, in relevant part:

1.b) converting the population of circulating DNA molecules into a population of non-uniquely tagged parent polynucleotides, wherein **each of the non-uniquely tagged parent polynucleotides comprises** (i) a sequence from a circulating DNA molecule of the population of circulating DNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes, such that **each non-uniquely tagged parent polynucleotide is substantially unique with respect to other non-uniquely tagged parent polynucleotides** in the population;

Claim 24 of the '951 patent is slightly different in that it claims duplex tags that are "sufficiently unique" from each other so that the tagged DNA fragments can be "substantially differentiated."

24. The method of claim 1, wherein the tagging step further comprises attaching duplex tags to ends of each of said double-stranded polynucleotide molecules in said sample, and **wherein said set of duplex tags comprise tag sequences that are sufficiently unique so that individually tagged double-stranded polynucleotide molecules can be substantially differentiated** from other tagged double-stranded polynucleotide molecules.

74. In my opinion, nothing in any of these claims provides any guidance as to how to identify, much less distinguish among, non-unique, substantially unique, sufficiently unique or substantially identifiable tagged DNA fragments and tags. The claims thus plainly fail to provide any objective boundaries of their scope.

75. The specifications similarly fail to provide any discernable boundary of claim scope for a "non-unique," "substantially unique," or "sufficiently unique" tagged DNA fragment or a "substantially unique" tag.

76. For example, the term "non-unique" is not defined, or even mentioned, anywhere in any of the specifications of the '699, '127, or '951 Patents. Instead, the specifications of the '699, '127, or '951 Patents describe instance of **uniquely** tagging fragments but provide no guidance as to the meaning of "non-unique." For example, the '699 Patent specification recites:

"For example techniques whereby DNA fragments to be sequenced are each **uniquely tagged** [34, 35] prior to amplification [36-41] have been reported. Because all amplicons derived from a particular starting molecule will bear its specific tag, any variation in the sequence or copy number of identically tagged sequencing reads can be discounted as technical error."

'699 patent Col 2, lines 16-23 (emphasis added).

"Because every adaptor contains a **unique**, double-stranded, complementary n-mer random tag on each end (n-mer=12 bp according to one embodiment), every DNA fragment becomes labeled with two distinct SMI sequences (arbitrarily designated α and β in the single capture event shown)."

'699 Pat. Col 3, lines 55-61 (emphasis added).

“FIG. 3 illustrates error correction through Duplex Consensus Sequencing (DCS) analysis according to one embodiment. (a-c) shows sequence reads (brown) sharing a *unique* set of SMI tags are grouped into paired families with members having strand identifiers in either the $\alpha\beta$ or $\beta\alpha$ orientation.”

’699 Pat, Col. 4, lines 12-17 (emphasis added). The specifications explain that PCR amplification of the SMI tagged-target nucleic acid molecule results in a set of “uniquely labeled, amplified SMI-target nucleic acid products” and that “the use of SMI tags . . . allows every molecule to be uniquely labeled prior to PCR duplication.” *See, e.g., id.* at 16:10-15, 19:20-23. The specifications further describe the use of “unique” SMI tags, “unique identifiers,” and “uniquely sheared DNA ends.” *See, e.g., id.* at 4:56-57, 4:14-15, 7:2, 22:45, 18:34-35, 23:3, 23:10, 24:22, 27:36, 27:57, 26:52. Significantly, while these specification passages describe “unique” tagging, none of this discussion provides any clarity of the differences, if any, among unique, non-unique, substantially unique and sufficiently unique tagging. Plaintiffs and Dr. Ehrlich admit that the categories of “unique” and “non-unique” can overlap, and that “unique” tags can be identical to each other in “extremely rare circumstances.” *Op. Br.* at 6. Plaintiffs and Dr. Ehrlich further cite to the Miner reference and describe Miner as “tagging a population of polynucleotide molecules with a highly diverse set of tags, such that the probability of two genomic fragments being tagged with the same molecular sequence was exceedingly improbable—a .31% chance in one instance.” *Id.*; Ehrlich Decl., at ¶45. But it is my opinion that 0.31% is not “exceedingly improbable,” but rather a significant and measurable fraction. If 0.31% of polynucleotides among a population of millions have the same tag, it is guaranteed that there will be huge numbers of measurable fragments that are tagged identically. For example, an Illumina NextSeq 550 can generate 400,000,000 sequencing reads in a single run so that a 0.31% rate of identical tags would

result in 1,240,000 sequences having the same tags. *See* Ex. B, Illumina Website, *Illumina Sequencing Platforms* at 2 (Available at [Sequencing Platforms | Compare NGS platform applications & specifications \(illumina.com\)](#)) (Accessed August 26, 2022).

77. The prosecution histories of the TwinStrand Asserted Patents also fail to provide guidance to a POSITA to determine the scope of these claim terms. The term “non-unique” appears in the prosecution history only when it was added to pending claims—without any identification of adequate written description support.

78. The prosecution histories are similarly devoid of any explanation of the phrases “substantially unique,” “sufficiently unique,” and “substantially identifiable” or how they can be measured. The terms were added to the claims during prosecution of the ’699 and ’127 patents without citation to any support in the specifications for the amendments. *See* Ex. 27, ’699 file history, 5/24/19 Prelim. Amend.; Ex. 28, ’127 file history, 4/24/20 Amendment and Response. Similarly, these phrases were included in the original claim set filed in the ’951 prosecution, but without any citation to support in the specification. Ex. 29, ’951 file history, 7/17/19 Application. The intrinsic record thus provides no clarification as to how to measure whether a tagged DNA fragment or SMI tag is “substantially/sufficiently unique” or “substantially identifiable.”

79. It is my opinion that “non-unique,” “substantially” or “sufficiently” unique or “substantially identifiable” have no accepted plain meaning to a POSITA. There is no extrinsic evidence that sufficiently clarifies whether a tagged DNA fragment or a tag itself is “non-unique” or “substantially” or “sufficiently” unique or “substantially identifiable.” The phrases “non-unique,” “substantially” or “sufficiently” unique or “substantially identifiable” fail to inform a POSITA with reasonable certainty as to the scope of the claims.

80. Further, Plaintiffs’ construction for “non-unique” adds the limitation “*wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule.*” (Emphasis added). Plaintiffs point to a single sentence in the specification to support this point: “A hybrid method using a combination of sheared ends and a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases) in the adaptor may also serve as unique molecular identifiers.” *See, e.g.,* Ex. 2, ’699 patent, 9:38-42. This same sentence is present in all the patent specifications, with no further explanation, and is the only sentence that describes Plaintiffs’ so-called “hybrid method” on which their proposed construction is based.

81. In my opinion, the sparse description of the “hybrid method” fails to impart sufficient clarity to the “non-unique” terms. It relies on both the sheared ends of the fragment and a “shorter” exogenous molecular barcode to identify each DNA fragment, but the specifications fail to define the length of the sheared ends. Is it one nucleotide, five nucleotides, one hundred nucleotides? If the fragment is short enough and the sheared ends are long enough, this information alone could identify the fragment. Further, there is no industry standard for the size of the sheared fragment end that can be analyzed. This passage does not offer any guidance as to the extent of the additional information that is required to satisfy the undefined “substantially” and “sufficiently” claim requirements.

82. As there is no way to discern from the intrinsic or extrinsic evidence what precisely is encompassed by these phrases, it is my opinion that they are all indefinite.

B. “high accuracy sequence read” and “high accuracy consensus sequence read”

Disputed Term	Patent, Claims	Plaintiffs’ Proposed Construction	Guardant’s Position
“high accuracy sequence read”	’631 pat., cl. 1, 16	Plain and ordinary meaning	Indefinite

“high accuracy consensus sequence read”	‘631 pat., cl. 1, 4, 7, 16, 23	Plain and ordinary meaning	Indefinite
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83. The ‘631 patent claims describe a method of “generating high accuracy sequence reads” that involves generating a “high accuracy consensus sequence read.” It is my opinion that these terms are indefinite as a POSITA would not be informed with reasonable certainty as to the scope of the invention when reading these terms in light of the specification and the prosecution history.

84. Neither the intrinsic nor extrinsic records provide any guidance as to the scope of either phrase. The claims fail to provide any context for what “high accuracy” encompasses. The accuracy of the sequence read is dependent on multiple factors and reflects, in part, the error rate of the underlying DNA sequencing technology used and the location of the fragment. Certain regions of the genome may have characteristics that make sequencing more error prone, such as regions with highly repetitive sequences. The accuracy of a consensus sequence read is also dependent on a number of factors including fragment length, read depth (the number of reads of a particular fragment), and the computational methods used to compile the data. Indeed, the phrases “high accuracy sequence read” and “high accuracy consensus sequence read” never are used in the specification.

85. The file history is similarly lacking. The only guidance to be gleaned from the file history is that during prosecution applicants disclaimed any equivalency between “high accuracy” sequence read/consensus sequence and “error corrected” sequence read/consensus sequence. In this regard, the originally filed claims of U.S. Patent App. No. 15/660,785 included a claim to “a method of generating an error corrected double-stranded consensus sequence.” Ex. 30, ‘631 patent File History, 7/26/17 Application. That original claim was cancelled, and additional claims were added in a preliminary amendment that similarly recited “a method of

generating an error corrected sequence read.” Ex. 31 at 2/9/18 Second Prelim. Amend. The examiner then rejected all the pending claims as anticipated by Steemers et al. WO2012/061832 because, in part, Steemers teaches “a method of generating an error corrected sequence read of a double-stranded target nucleic acid molecule.” Ex. 32 at 4/10/2018 Non-final Rejection. Applicants then amended their pending claims by, among other changes, replacing the phrase “an error corrected sequence read” with the phrase “high accuracy sequence reads,” and by replacing the phrase “generating an error corrected sequence read” with the phrase “generating a high accuracy consensus sequence read.” Ex. 33 at 7/10/18 Amendment. Applicants argued that Steemers did not teach, among other elements, generating high accuracy sequence reads or a high accuracy consensus sequence read. *Id.* The claims then issued because, according to the examiner, Steemers did not teach generating high accuracy sequence reads. Ex. 34 at 12/27/18 Notice of Allowance.

86. While the file history makes plain that “high accuracy” sequence reads and consensus sequence reads are not the same as “error corrected” sequence reads and consensus sequence reads, it fails to offer any guidance as to what accuracy rates may constitute “high accuracy.” Does an accuracy rate of 80% constitute the threshold of high accuracy? 90%? 99%? 99.9%? 99.999%? The intrinsic record provides no instruction to a POSITA as to how high the accuracy must be to satisfy the claim.

87. It is my opinion that the file history makes clear that a “highly accurate” sequence read/consensus sequence is distinct from an “error corrected” sequence read/consensus sequence. The file history offers no guidance on the acceptable accuracy rate to be considered “high accuracy.”

88. Further, there is no industry standard as to the meaning of “highly accurate.” In this regard, the accuracy of a sequence read is dependent on multiple factors and reflects, in part, the error rate of the underlying DNA sequencing technology used and the location of the fragment. Moreover, certain regions of the genome may have characteristics that make sequencing more error prone, such as regions with highly repetitive sequences. The accuracy of a consensus sequence read also is dependent on factors including fragment length, read depth (the number of reads of a particular fragment), and the computational methods used to compile the data. The number and variety of the factors that impact the accuracy of a sequence read in any given case underscore the lack of any accepted meaning of the phrases “highly accurate sequence read” and “highly accurate consensus sequence read.”

89. It is my opinion that “high accuracy sequence read” and “high accuracy consensus sequence read” have no accepted plain meaning to a POSITA. The accuracy of any sequencing read and any resulting consensus sequence read is dependent on a multitude of factors, including, for example, the origin of the sample itself, the bioinformatics parameters applied to the sequencing results during processing. The required precision and clarity of the claim language is lacking here. The phrases “highly accurate [sequence/consensus sequence] read” fails to inform a POSITA with reasonable certainty as to the scope of the invention and it is therefore my opinion that these terms are indefinite.

C. “fragment features” and “DNA fragment specific information”

Disputed Term	Patent, Claims	Plaintiffs’ Proposed Construction	Guardant’s Position
“fragment features”	’631 pat., cl. 16, 18	Plain and ordinary meaning	Indefinite
“DNA fragment-specific information”	’127 pat., cl. 22, 26	Plain and ordinary meaning	Indefinite

90. I understand that Plaintiffs allege that the term “fragment features” found in claims 16 and 18 of the ’631 patent and “DNA fragment-specific information” found in claims 22 and 26 of the ’127 patent should be afforded their “plain and ordinary meaning.” However, the claim terms “fragment feature” and “fragment-specific information” are indefinite because a POSITA does not know what type of “features” or “information” is encompassed by the claims.

91. It is my opinion that the plain and ordinary meaning cannot be determined with sufficient clarity. For example, do the claimed “features” and “information” encompass any or all of the size, specific nucleotide pattern, overall nucleotide composition, nucleotide modification, or any other property of a DNA fragment? The patents shed no light on the answer to this question.

92. Claims 16 and 18 of the ’631 patent do not provide any guidance as to what is encompassed by the claimed “fragment features.” Claim 16 includes the limitations “wherein each double-stranded target nucleic acid molecule comprises *one or more fragment features* that distinguish the individual double-stranded target nucleic acid molecules from other double-stranded target nucleic acid molecules. . . . grouping the first and second strand sequence reads into a family of sequence reads by identifying the *one or more distinguishing fragment features* shared by each strand . . . ” Ex. 1, ’631 patent, claim 16 (emphasis added). The claim language sheds no light on what “one of more fragment features” fall within the scope of the claim. Claim 18 only compounds the lack of clarity by claiming that the “*one or more fragment features* includes a shear point or other fragment region, or a combination thereof.” *Id.* at claim 18 (emphasis added). “Fragment region” is undefined in the specification and describing a “fragment feature” as a “fragment region” without delimiting the size or location of the region does nothing to meaningfully define the scope of the claimed “fragment features.”

93. “Fragment features” does not appear anywhere in the specification. Moreover, the term “fragment features” was added to pending claims 53 and 55 of U.S. Patent Appl. No. 15/660,785 in a preliminary amendment without any corresponding citation to the specification for support. Ex. 31, '631 patent file history, 2/9/2018 Prelim. Amend.

94. The subsequent prosecution history likewise fails to provide any clarity as to the meaning of the term. The examiner recited the term “fragment features” in her non-final rejection dated 4/10/2018, stating that the prior art Steemers reference teaches “pairing the first and second strand sequence reads based on one or more fragment features shared by each strand of the double-stranded target nucleic acid molecule and confirming the presence of at least one first strand sequence read and at least one second strand sequence read.” Ex. 32 at 4/10/2018 Non-Final Rejection. Steemers uses the term “feature” to describe target nucleic acids in an array format, where they are “typically coupled to a surface in a spatially distinguishable manner. . . . The array can include a single copy of a target nucleic acid at each site (also referred to as a feature) or multiple copies having the same sequence can be present at each site or feature.” Ex. 35, Steemers at p. 54, lines 2-17. However, the prosecution history does not purport to define the term “fragment features” as being coextensive with the use of fragment features in Steemers, and therefore fails to provide the requisite clarity as to the scope of that claim term.

95. The '127 patent claims themselves do not provide sufficient guidance as to the meaning of “DNA fragment specific information”. Independent claim 22 recites “grouping the strand sequence reads into families based on i) the barcode sequence, and ii) *DNA fragment-specific information*.” Dependent claim 26 is similar, reciting the use of “one or more barcode sequences and *DNA fragment-specific information*.” At most, claims 22 and 26 teach that both DNA fragment-specific information and barcode sequences can be used to group DNA

fragments into families—thus implying that DNA fragment-specific information is distinguishable from barcode-specific information. This distinction, however, is insufficient to render the claims definite.

96. The phrase “DNA fragment-specific information” is neither mentioned nor defined in the specification. During prosecution of U.S. Patent Appl. No. 16/503,382, the phrase “fragment-specific feature” was introduced in new claim 60. Ex. 36, ’127 patent file history, 8/8/2019 Prelim. Amend. (emphasis added). The examiner rejected the pending claims as obvious over Otwinowski et al. WO2013/181170, noting that the reference teaches “wherein the at least one sequence read derived from the original first strand and the at least one sequence read derived from the original second strand can be related based on an adapter tag sequence, a fragment-specific feature, or a combination thereof.” Ex. 37 at 1/24/2020 Non-final Rejection. Otwinowski teaches grouping fragments by fragment sequence, length, and randomized barcode sequence. Ex. 38, WO2013/181170 at [12]. In response, applicants added new claims 64 and 68 that included the phrase “DNA fragment-specific information.” Ex. 28, ’127 patent file history, 4/24/2020 Response to Non-Final Office Action (emphasis added). The claims were allowed shortly thereafter. There is no further explanation in the prosecution history as to what is encompassed by the term “DNA fragment-specific information” of claims 22 and 26, or how it is distinct from the “fragment-specific feature” of claim 18.

97. It is therefore my opinion that “fragment features” as used in the ’631 patent and “DNA fragment-specific information” as used in the ’127 patents could encompass any fragment length from one nucleotide to the entire length of the fragment. It could also refer to the nucleotide sequence of either a portion of the fragment or the whole fragment.

98. As there is no way to discern from the intrinsic or extrinsic evidence what precisely is encompassed by these phrases, it is my opinion that they are indefinite.

B. Disputed Claims in the Guardant Asserted Patents

1. “a subject having cancer”

Disputed Term	Patent, Claims	Plaintiffs’ Proposed Construction	Guardant’s Position
“a subject having cancer”	’221 pat., cl. 2	“a subject known to currently have cancer”	Plain and ordinary meaning

99. In my opinion, the ordinary meaning of “a subject having cancer” in claim 2 of the ’221 patent as understood by a POSITA is readily apparent from the claim itself. Ex. 7, ’221 patent at claim 2. A POSITA would not alter their understanding of this term after reading the entire patent, including the specification.

100. It is my understanding that Plaintiffs seek a construction that imports a limitation: adding the phrase “known to currently.”

101. The asserted claims do not include the limitation that a subject be “known to currently” have cancer.

102. Moreover, the claimed invention is a diagnostic method; a POSITA would understand that a subject having cancer need not be limited to those with known and current cancer diagnoses. For example, a POSITA would recognize the claimed methods can be used to determine whether a patient has cancer before it is “known” they have cancer. *Id.* These methods could also be used to monitor a patient in remission, which might not constitute “currently” having cancer.

103. In my opinion, “a subject having cancer” should be construed to have its plain and ordinary meaning.

IV. CONCLUSION

I reserve the right to supplement my opinions in the future to consider any new information that becomes available to me, and to respond to any arguments raised by plaintiffs. I am aware that I may be asked to testify at a hearing to address the matters disclosed in my Declaration. If I am asked to do so, I reserve the right to create additional summaries, charts, tutorials, animations, drawings, or other demonstratives to use during my testimony.

I hereby declare under penalty of perjury that the foregoing is true and correct.

Executed this 26th day of August, 2022, at 4:48pm Eastern.

/s/ John Quackenbush/
John Quackenbush, Ph.D.

EXHIBIT A

CURRICULUM VITAE

Date: August 25, 2022

Name: John Quackenbush, Ph.D.

**Office Address: Department of Biostatistics, 655 Huntington Avenue, Building II,
Room 421, Boston, MA 02115**

Home Address: 86 Walpole Street, Dover, MA 02030, USA

Work e-mail: johnq@hsph.harvard.edu

Work Phone: +1.617.432.9028

Work FAX +1.617.432.5619

Mobile Phone: +1.301.526.1740

Date & Place of Birth: January 4, 1962 Kingston, PA, USA

Education:

1983	Physics	B.S.	California Institute of Technology, Pasadena, CA
1984	Physics	M.S.	University of California, Los Angeles, CA
1990	Theoretical Particle Physics	Ph.D.	University of California, Los Angeles, CA

Postdoctoral Training:

1990-1992	Postdoctoral Fellow, Experimental Particle Physics, University of California, Los Angeles, CA
1992-1994	Staff Scientist, Molecular Genetics and Genomics, The Salk Institute for Biological Studies, La Jolla, CA
1994-1996	Research Associate, Genomics and Bioinformatics, Stanford Human Genome Center, Palo Alto, CA

Academic Appointments:

2018- present	Henry Pickering Walcott Professor of Computational Biology and Bioinformatics; Chair, Department of Biostatistics; Director, Harvard Health Data Science Center, Harvard TH Chan School of Public Health <u>Research Activities:</u> Development of methods in network medicine and systems biology aimed at understanding the multifactorial drivers of human health and disease, identifying disease subtypes and new therapeutic interventions, and exploring differences between the sexes in
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John Quackenbush

disease etiology and response to therapy; development of open-source software tools supporting research and clinical applications.

Activities: Founding Director/Co-Director, SM Program in Computational Biology and Quantitative Genetics (CBQG); Director, BD2K T32 Training Grant; Director T32 Cancer Training Grant; Founding Co-Director and Executive Committee, Joint Biostatistics and Bioinformatics T32 Training Grant; Director, Harvard Quantitative Biomedical Research Center.

- 2005- present Professor of Biostatistics and Computational Biology, Department of Data Science, Division of Computational Biology, Dana-Farber Cancer Institute;
Professor of Cancer Biology, Department of Cancer Biology, Dana-Farber Cancer Institute
Research Activities: Application of genomic technologies and integrative computational analysis to model cellular systems with an emphasis on understanding of human cancers and other diseases; development of open-source software tools supporting research and clinical applications.
- 2005- 2018 Professor of Computational Biology and Bioinformatics, Department of Biostatistics, Harvard TH Chan School of Public Health
Research Activities: Application of genomic technologies and integrative computational analysis to model cellular systems with an emphasis on understanding of human cancers and other diseases; development of open-source software tools supporting research and clinical applications.
Activities: Founding Director, SM Program in Computational Biology and Quantitative Genetics (CBQG); Director, BD2K T32 Training Grant; Founding Co-Director and Executive Committee, Joint Biostatistics and Bioinformatics T32 Training Grant.
- 2008- 2018 Director, Center for Cancer Computational Biology, Dana-Farber Cancer Institute
Research Activities: Integrative approaches to data analysis focused on clinical and translational applications and linking clinical and laboratory data in support of basic research; creation of software tools and systems to support research; overall analytical support for investigative research activities for all Dana-Farber Investigators.
- 2007 – present Adjunct Professor of Bioinformatics, Boston University
Activities: Mentoring PhD student thesis research.
- 2003- 2005 Professor, Chemical Engineering, University of Maryland
Activities: Mentoring PhD student thesis research.
- 2002 - 2006 Investigator, The Institute for Genomic Research
Research Activities: Development and implementation of technology and strategies, including computational methods and software tools,

John Quackenbush

necessary for functional analysis of the human and other genomes. Analysis of human gene expression in colon tumors using microarrays, rodent models of heart, lung, blood and sleep disorders and gene expression in Arabidopsis. Director of the TIGR Gene Index Project, providing freely available databases and software to estimate gene content in more than 100 organisms.

- 2000- 2005 Professor, Department of Biochemistry,
The George Washington University
Activities: Instructor in various courses, curriculum committee for Genomics.
- 1998 – 2005 Lecturer, The Department of Biostatistics,
The Johns Hopkins University
Activities: Instructor in the Masters In Biotechnology Program
- 1997 - 2001 Associate Investigator, The Institute for Genomic Research
Research Activities: Development and implementation of technology and strategies, including computational methods and software tools, necessary for functional analysis of the human and other genomes. Analysis of human gene expression in colon tumors using microarrays, rodent models of heart, lung, blood and sleep disorders and gene expression in Arabidopsis. Director of the TIGR Gene Index Project, providing freely available databases and software to estimate gene content in more than 50 organisms.
- 1997 Assistant Investigator, The Institute for Genomic Research
Research Activities: Development and implementation of technology and strategies, including analytical methods and software tools, necessary for functional analysis of the human and other genomes.
- 1994 - 1997 Research Associate, Stanford Human Genome Center
Stanford University
Research Activities: Project leader for development and implementation of a transposon-mediated strategy for large-scale genomic DNA sequencing including development and implementation of laboratory protocols, analytical methods, computer software, and instrumentation. Mapping, sequencing, and annotating regions of human chromosomes 4 and 21.
- 1992 - 1994 Staff Scientist, The Salk Institute for Biological Studies
Research Activities: Development of improved methods for DNA sequencing, combinatoric strategies and devices for screening large libraries, simulation and optimization of single pass sequencing strategies including genome sequence sampling. Project director for the STS content mapping of chromosome 11. Development of methods and software tools to support genome mapping.

John Quackenbush

- 1990 - 1992 Postdoctoral Fellow, Department of Physics
University of California, Los Angeles
Research Activities: Research in particle physics, field theory and phenomenology. Founding member of the Antiproton Experiment (APEX) collaboration that set the world's best experimental limit on the lifetime of the antiproton.
- 1987 - 1992 Visiting Lecturer, Department of Physics
University of California, Los Angeles
- 1984 - 1996 Physics Instructor, Southern California Science Institute
New College of California
- 1983 - 1990 Teaching Fellow, Department of Physics
University of California, Los Angeles
- 1983 - 1990 Research Fellow, Department of Physics
University of California, Los Angeles
Thesis Supervisor: E.T. Tomboulis
Research Activities: Research in elementary particle physics, mathematical physics, field theory focusing on the development of two-dimensional gauge field theory models and the construction of associated string theory models.

Nonacademic Employment

- 2011-2014 Co-Founder, CEO and Board Chairman, Genospace LLC
Activities: Genospace provides software solutions to operationalize precision medicine through the integration of clinical and genomic data and its presentation to clinical and research users in an intuitive format.
- 2014-2017 Co-Founder and Board Chairman, Genospace LLC
Activities: Genospace provides software solutions to operationalize precision medicine through the integration of clinical and genomic data and its presentation to clinical and research users in an intuitive format. In January 2017, Genospace was sold to the Hospital Corporation of America to support research and to acquire our world-leading solution for clinical trials matching.

Hospital or Affiliated Institution Appointments:

- 2003 - 2005 Adjunct Professor, Department of Biostatistics
Bloomberg School of Public Health, The Johns Hopkins University
- 2005- present Professor, Department of Biostatistics and Computational Biology
Dana-Farber Cancer Institute
- 2014- present Professor, Channing Division of Network Medicine, Brigham and Women's Hospital

John Quackenbush

Hospital and Health Care Organization Service Responsibilities:

- 2005- present Primary research areas are computational and system biology focused on the integration of diverse data types to provide insight into biological processes that drive human disease phenotypes.
Department of Data Science, Division of Computational Biology,
Dana-Farber Cancer Institute
- 2014- present Research at the interface of systems biology and pulmonary disease, exploration of how sex and gender affect disease risk, development of methods to better handle sex differences in systems approaches, and advising faculty in their research and the Director in setting directions for future work.
Channing Division of Network Medicine, Brigham and Women's Hospital

Major Committee Assignments:

- 1994 National Laboratory Genome Project Visit Review Panel, DOE
1995 Caltech/BAC Library Construction Site Visit Review Panel, DOE
1996-1998 Bioinformatics Grant Review Panel, DOE
1997-2001 Grant Review Panel, DOE
1997 Hollander Fellowship Review Panel, DOE
1997 Five-Year Program Advisory Committee, NCRR
1997 Cancer Chromosome Anatomy Project program Steering Committee, NCI
1998 National Laboratory Functional Genomic Review Panel, DOE
1998 Full-Length cDNA Library Construction and Sequencing Advisory, Committee, NCI
1998 Functional Genomics Panel, Wellcome Trust
1998 Genomics Grant Review Panel, NSF SBIR
1998 Special Program in Tropical Disease Research Review, UNDP/World Bank/WHO
1999-2000 Low-Dosage radiation Grant Review Panel, DOE
1999 Bioinformatics Review Panel, NSF
1999 Special Emphasis Review Panel, NHLBI
1999 Microarray Working Group Advisory Panel, NIDCR
1999 Special Emphasis Review Panel, NIMH
1999 Plant Biology Review Panel, NSF
1999-2007 Board of Directors, MGED
2000 Grant Review Panel, NIDA SBIR
2000 Plant Biology Review Panel, USDA
2000 Plant Biology Review Panel, NSF
2000 Exceptional Chromosome Regions Working Group, DOE
2000 Working Group on US Scientific Interactions, NSF
2000-2006 Genome/GCAT study section, NIH
2000-2003 PGA Coordinating Committee, HHLBI
2000-2003 PGA Bioinformatics Committee, NHLBI

John Quackenbush

2000-2003	PGA Microarray Committee, NHLBI
2000	Working Group on Australia Scientific Interactions, NSF
2001	Review Meeting RFP ES-01-01 National Center for Toxicogenomics (NCT) Microarray Resource, HIEHS
2001-2003	Plant Genome Scientific Advisory Board, University of Georgia
2001-2003	Innovative Technology Review Panel, NCI
2001-2002	Genome Study Section, NIH
2002-2006	GCAT Study Section, NIH
2001	Bioinformatics in Neuroscience and Sleep Research Workshop, NIDDK
2001	Plant Genome Site Visit Panel, NSF
2001-2003	BISTI Review Panel, NIH
2001-2005	Grant Review Panel, NCI
2002	Microarray Supplement Review Panel, NHLBI
2002-2006	Panel on Emerging Issues in Toxicogenomics, NRC
2004-2006	Panel on Applications of Toxicogenomics, NRC
2003-2010	Genome British Columbia Scientific Advisory Board
2005-2014	EPA Board of Scientific Counselors
2005-2011	St. Jude's Children's Research Hospital Scientific Advisory Board
2006-2007	Harvard School of Public Health, Lefkopoulou Award Committee Member
2006	Dana Farber Cancer Institute, Computational Biology Search Chair
2005	EU FP6 Grant Review Panel
2006-2007	Harvard School of Public Health, Seminar Committee Member
2006-2019	Harvard School of Public Health, Curriculum Committee Member
2006-2009	Harvard School of Public Health, Computational Biology Search Chair
2007-present	EU FP7 Genomics Grant Review Panel
2008-present	Lovelace Respiratory Research Institute, Scientific Advisory Board
2008-2010	NAS Panel on Collecting, Storing, and Distributing Biodata linked to Social Science Surveys
2009	RC1 Grant Review "Editorial Review" Panel
2009	RC2 Genomic Science Grant Review
2009	Epigenomics Roadmap Grant Review Panel
2009-2014	Epigenomics Roadmap Advisory Board
2010	NCI EUREKA Grant Review Panel
2010	Chair, NCRR S10 Grant Review Panel
2016	NASA ISS Genomic Applications Study Section
2019	NASA Human Research Program Long-Duration Flight Advisory Panel
2016	21 st Century Cures Act Biomarker Advisory Group
2012-2019	Research Oversight Committed, Genome British Columbia
2014-present	Shriner's Hospital standing review panel
2005-present	Various NIH grant review panels, either as an ad hoc member or as an ad hoc reviewer. I typically serve on at least six per year and can provide a more detailed list on request.
2005-present	Various EU and Canadian grant review panels, either as an ad hoc member or as an ad hoc reviewer. I can assemble a detailed list on request.
2017-present	Research Foundation Flanders (FWO) standing review panel.
2018-present	Chair, Department of Biostatistics, Harvard T.H. Chan School of Public Health

John Quackenbush

Nonacademic Board and Advisory Board Positions (active or past five years):

2005-2016	Nabsys Inc., Scientific Advisory Board
2010-2017	Lovelace Respiratory Research Institute, Scientific Advisory Board
2012-2016	SynapDx, Scientific Advisory Board
2012-2017	Genospace LLC, Founder, CEO, Board of Directors; Chairman of the Board
2012-2020	Blueprint Genomics, Scientific Advisory Board
2013-2017	Thomson-Reuters, Genomics Advisory Board
2013-present	Caris Life Sciences, Scientific Advisory Board
2020-present	Caris Life Sciences, Data Science Advisory Board
2014-present	Shriners' Hospitals, Scientific Advisory Board
2014-present	Olema Pharmaceuticals, Scientific Advisory Board
2015-present	Haymakers for Hope, Board of Directors
2015-present	Lacriscience, Scientific Advisory Board
2017-present	Merck KGaA, Precision Medicine Advisory Board
2018-present	Renalytix AI, Advisory Board
2018-present	Dover, MA, Capital Budget Committee
2019-present	StitchBio, Scientific Advisory Board
2020-present	Charles River School Health and Safety Committee (COVID Advisory Board)
2020-present	Boston University Academy Health and Safety Committee (COVID Advisory Board)
2021-present	Dover, MA, Board of Health Special Advisor
2021-present	Congreso Futuro International Advisory Board, Chile

Professional Societies:

1988	American Physical Society	Member
1988	APS Biophysics Division	Member
1988	APS International Physics Group	Member
1988	APS Division of Particles and Fields	Member
1988	World Federation of Scientists	Member
1990	Microarray Gene Expression Data Society (MGED)/ Functional Genomics Data Society (FGED)	Member
	(2011-2014)	Board Member
		President
1995	The Human Genome Organization (HUGO)	Member
1996	Association of Science Professionals (ASP)	Member
1998	American Association for the Advancement of Science (AAAS)	Member
1999	Center for the Study of the Evolution of Life (CSEOL)	Member
2005	American Association for Cancer Research	Member

Community Service Related to Professional Work:

I have presented more than 350 talks, courses, and workshops since joining Dana-Farber and the Harvard T.H. Chan School of Public Health in 2005; detailed lists will be

John Quackenbush

provided upon request. I have also taught numerous courses and workshops on the analysis of genomic data and have served as an organizer of the EMBO course on DNA microarray analysis for more than five years.

In addition, I have served on the Scientific Advisory Board of the St. Jude's Children's Research Hospital, the Scientific Advisory Board for the Lovelace Respiratory Research Institute, Research Oversight Committees for various Genome Canada programs, and the Board of Scientific Counselors of the Environmental Protection Agency. I have also been a member of advisory boards for a number of NIH initiatives, including the Roadmap Epigenome Project, the Extracellular RNA Communication Consortium, the Atopic Dermatitis Research Network (ADRN), and the Trans-Omics for Precision Medicine (TOPMed) program.

Since the onset of the COVID19 pandemic, I have served numerous local school and community groups by advising these on policy and practice. I am particularly proud that the two schools I advised instituted a series of policies addressing air quality, masking, distancing, hygiene, and vaccination that allowed them to remain open without any documented cases of in-school transmission during the 2020-2021 and 2021-2022 academic years. I have also become a special advisor to the Dover, MA Board of Health and provide advice to the Dover-Sherborn Regional School District on COVID and other health-related matters.

(Peer Review for Scientific Journals)

1994-2016	<i>Genomics</i>
1994-2009	<i>BioTechniques</i>
1996-2010	<i>Genome Research</i>
2000-2010	<i>Genome Biology</i>
1997-1998	<i>Analytical Biochemistry</i>
1997-present	<i>Nature</i>
1997-2010	<i>Nucleic Acids Research</i>
1999-2010	<i>Nature Genetics</i>
1999-2009	<i>EMBO Reports</i>
1999-2017	<i>Nature Biotechnology</i>
1999-present	<i>Science</i>
2000-2016	<i>Bioinformatics</i>
2000-2009	<i>Journal of Theoretical Biology</i>
2000-2009	<i>Mammalian Genomics</i>
2000-2006	<i>Gene</i>
2000-2016	<i>BMC Genomics, BMC Bioinformatics</i>
2001-2009	<i>Structural and Functional Genomics</i>
2001-2010	<i>Nature Reviews Genetics</i>
2001-2006	<i>American Journal of Applied Statistics</i>
2009-present	<i>PLoS Computational Biology</i>
2015-present	<i>Proceedings of the National Academy of Sciences</i>
2017-present	<i>Molecular Systems Biology</i>

John Quackenbush

Editorial Boards:

2000-2009	Editorial Board	<i>BioTechniques</i>
2000-2012	Associate Editor	<i>Bioinformatics</i>
2000-present	Editorial Board	<i>BMC Genomics</i>
2000-2006	Editorial Board	<i>Genomics</i>
2006-2017	Editor-in-Chief	<i>Genomics</i>
2018-present	Editorial Board	<i>Cancer Research</i>
2022-present	Editorial Board	<i>GEN Biotechnology</i>

Awards and Honors:

1985 - 1991	Outstanding Teaching Award (7) , UCLA Physics Department
1986	Jun John Sakurai Scholarship , 24 th International School of Subnuclear Physics, Ettore Majorana Centre for Scientific Culture, Erice, Italy
1987	UCLA Distinguished Teaching Assistant Award , UCLA Academic Senate
1987	Prize for Best Student and Prize for Best Scientific Secretary , 25 th International School of Subnuclear Physics, Ettore Majorana Centre for Scientific Culture, Erice, Italy
1988	Graduate Distinguished Scholar Award , UCLA Alumni Association
1992 - 1997	SERCA Fellow , National Human Genome Research Institute
2006	George D. Wilbanks Lectureship in Gynecological Oncology , University of South Florida College of Medicine
2007	President's Distinguished Lectureship , American Society of Reproductive Medicine
2007	Leopold G. Koss Lectureship , Universität Bern, Switzerland
2007	Distinguished International Advisors at IEE BIBE, the original and the oldest IEEE flagship international conference in Bioinformatics and Bioengineering.
2008	Distinguished Lecture in Computer Science , Wayne State University
2010	IPM Distinguished Lecture , Mt. Sinai Medical School, New York
2010	The Ian Lawson Van Toch Memorial Seminar Series in Computational Biology , Ontario Cancer Institute
2010	Harvard-Australia Foundation Fellowship
2010	Bancroft Fellow-in-Residence , Queensland Institute for Medical Research, Queensland, Australia
2010	Jackson Memorial Fellowship , Griffith University, Queensland, Australia
2011	Australia Fellow , National Health and Medical Research Council, Australia
2013	White House Open Science Champion of Change , Office of the President of the United States of America
2016	Mentor of the Year Award , Postdoc and Graduate Student Organization, Dana-Farber Cancer Institute
2018	National Cancer Institute Outstanding Investigator Award (R35)

Part II: Research, Teaching, and Clinical Contributions

A. Narrative report (700 words or less) of Research, Teaching, and Clinical Contributions. Please focus primarily on the areas in which most of your time and effort is spent.

My current research involves development of new analytical methods for the integrated analysis of large-scale biomedical data, including genomic data, to better understand the nature of human diseases, including cancer and pulmonary diseases, with the goal of developing better methods for diagnosis and treatment. Two defining characteristics of my work are a commitment to reproducible research through development of open-source software implementations of analytical methods, and an emphasis on studying sexual dimorphism in health and disease.

A longstanding component of my work is methods development for robust biomarkers. We have applied this to identifying reproducible predictive biomarkers in cancer and have explored reproducibility in large, published data sets, demonstrating that many are inconsistent. In collaboration with Hugo Aerts, I have been working to extend our methods to the analysis of quantitative feature data extracted from radiographic images (an emerging field called “radiomics”), to use these to identify predictive biomarkers, and to link these features to genetic mutations in cancer. I have also come to recognize that while individual “features” such as the expression of genes or specific mutations may not be sufficient on their own to identify drivers of biological states or to predict outcome or response to therapy in disease.

I have also been developing methods for inferring gene regulatory network models using gene expression and other sources of data. We published a method, PANDA, that builds on “message passing” (an idea developed communications theory) to optimize information flow through a gene regulatory network model, allowing us to infer condition-specific networks and to compare these between phenotypes. We have developed many extensions of PANDA that incorporate other data types and have applied these to the study of diseases, including ovarian cancer, colorectal cancer, chronic obstructive pulmonary disease, asthma, and Alzheimer’s disease, as well as to the investigation of sexual dimorphism. Consistent with our commitment to open and reproducible science, we have collected these methods (all named for animals) with standardized source code in R, C, Matlab, and Python, into the “Network Zoo” (<https://netzoo.github.io/>). To support the widespread use of these methods, we developed “netBooks” (<http://netbooks.networkmedicine.org/>), a collection of online tutorials that use Jupyter notebooks to introduce the use of our methods and, increasingly, to allow all of our published analyses to be rerun by those interested in the analyses.

We have also been exploring the connection between genotype and phenotype, using gene expression as a surrogate for phenotype. We have developed a new approach, CONDOR, to the analysis of expression quantitative trait loci that uses a bi-partite graph to represent associations between gene expression levels and both local (*cis-acting*) and distant (*trans-acting*) significant genetic variants. We find that the overall structure of the graph provides insight not only into how genetic variants work together to influence phenotype, but also into evolutionary constraints on the genetic variants themselves. This

John Quackenbush

has given us new insight into how many genetic variants of small effect-size can collectively exert strong influence on phenotype.

More recently, we have been asking whether how one can model regulatory networks in the context of genetic background, recognizing that an individual's genotype will manifest its effects through alterations of patterns of gene expression that ultimately will influence the functional processes active in individuals. That method, EGRET, represents an important step forward in the analysis of the link between genotype and phenotype and is the first method for linking genetic cause and phenotypic effect through the action of individual regulatory processes.

Our group also builds and maintains a variety of software tools to support genomic analysis. the TM4 suite of open-source software tools for the analysis of DNA microarray data. The most widely used of these, MeV, is a powerful data mining software tool, that places sophisticated analytical tools behind an intuitive graphical user interface. Developed to be accessible to laboratory biologists, MeV has more than 260,000 users worldwide. We recently transitioned MeV to a cloud-based platform, WebMeV (<http://mev.tm4.org>) to take advantage of cloud scalability to better handle large sequence-based data. WebMeV now has 3000 registered users and provides more than 100 analysis sessions per day.

I am also very involved in teaching and mentoring. I developed, launched, and direct the Computational Biology and Quantitative Genetics (CBQG) master's degree program, I was co-PI and co-director of the first joint Biostatistics and Bioinformatics training grant in the US and recently stepped down to develop and direct a training grant program as part of the NIH's Big Data to Knowledge (BD2K) program. I also developed and teach an introductory genomics tools and methods course and have co-taught an online course on reproducible research through HarvardX (<https://www.edx.org/course/principles-statistical-computational-harvardx-ph527x>).

I have trained more than 80 postdoctoral fellows and graduate students (including MS and PhD students whom I have mentored for their thesis projects) and have mentored a number of junior faculty members since joining the Harvard TH Chan School of Public Health and Dana-Farber Cancer Institute in 2005. I have emphasized diversity in hiring postdocs; more than half of my trainees have been female and four of the five postdocs from my group who have moved onto faculty positions in the past year have been female. I also maintain an extensive network of former trainees (and their current trainees) which meets weekly as we continue to work collaboratively in the development and application of network methods.

B. Funding Information

I have had more than twenty-five years of continuous grant support from the NIH and other organizations. My current support includes:

Active Research Support

5R01CA205406-03 (Ng, K.)	3/1/2017 – 2/28/2022
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NIH/NCI

Novel Randomized Controlled Trials of Vitamin D Supplementation in Patients with Colorectal Cancer: Impact on Survival and Biology

This project is exploring the biology underlying the effects of vitamin D on survival of colorectal patients.

Role: Co-Investigator

1R35CA220523 (Quackenbush, J.)	9/1/2018 – 8/31/2025
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NIH/NCI

Unraveling the Complexities of Risk and Mechanism in Cancer

This NCI Career Award supports Dr. Quackenbush's ongoing work to model genetic processes in cancer and to elucidate the link between genotype and phenotype so as to better understand the drivers of cancer and to identify potential targets for therapeutic intervention, with a particular emphasis on understanding differences between men and women. Role: Principal Investigator

1R01HG011393 (DeMeo, D / Quackenbush, J.)	9/1/2018 – 06/30/2025
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NIH/NCI

Network Tools to Understand Sex- and Gender-Specific Drivers of Disease

This project will develop robust methods for handling male and female multi-omic data, with an emphasis on applying these to the inference of gene regulatory network models and the use of such models for gaining insight into the regulatory processes that drive clinical differences in human health and disease. Role: co-Principal Investigator

1U24CA231846-01A1 (Quackenbush, J.)	9/1/2019 – 8/31/2024
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NIH/NCI

MeV: A Robust Platform for Intuitive Genomic Data Analysis

As part of the Informatics Technology for Cancer Research (ITCR) program, we will develop and support WebMeV, a robust, scalable data analysis software tool that uses intuitive visual interfaces to provide users with access to advanced data analysis methods for large-scale genomic data in a system that helps ensure their research is reproducible.

Role: Principal Investigator

2P50CA127003-11A1 (Bass, A.)	9/1/2019 – 5/31/2024
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NIH (Subcontract: Dana Farber Cancer Institute)

Dana Farber/ Harvard Cancer Center SPORE in Gastrointestinal Cancer

The GI SPORE supports state-of-the-art investigator-initiated translational research that will contribute to improved prevention, early detection, diagnosis, and treatment of gastrointestinal cancers. Dr. Quackenbush will serve as Co-Director of the Biostatistics and Bioinformatics Core, which will support the quantitative needs of the investigators in the design of experiments and the analysis of the resulting data.

Role: Co-Investigator/Core Co-Director

John Quackenbush

C. Report of Current Research Activities other than those mentioned above (bench research, clinical trials, outcome studies, efficacy studies as applicable)

None to report.

D. Report of Teaching (use only those categories that are applicable)

1983 - 1990	Teaching Fellow, Department of Physics, University of California, Los Angeles
1984 - 1996	Physics Instructor, Southern California Science Institute, New College of California
1987 - 1992	Visiting Lecturer, Department of Physics, University of California, Los Angeles
1998 - 2005	Lecturer, The Johns Hopkins University Instructor in the Masters in Biotechnology Program
2000 - 2005	Professor, Department of Biochemistry, The George Washington University
2003 - 2005	Adjunct Professor, Department of Biostatistics, Bloomberg School of Public Health, The Johns Hopkins University Developed program in genomics and bioinformatics; instructor in various courses.
2005-present	Professor, Department of Biostatistics, Harvard TH Chan School of Public Health
2013-present	Director, MS in Computational Biology and Quantitative Genetics

E. Report of Clinical Activities

1. Description of clinical practice (field, areas of major focus, site(s) of practice [private office, HMO, teaching hospital etc.])

None

2. Patient load (indicate complexity of cases, as appropriate)

None

3. Clinical contributions (e.g., introduction of new methods of clinical diagnosis, prevention, treatment, care delivery)

None

4. Other relevant information about clinical role (receipt of clinical awards, locally or nationally, invitation to participate in clinical activities at other sites, special recognition by peers or professional organizations as a leader in a clinical field)

None

Part III: Bibliography (as of August 25, 2022)

Total citations: 87,437

h-index: 105

i10-index: 305

Original Articles (325)

Complete List of Published Works in MyBibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/john.quackenbush.1/bibliography/public/>

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Educational Material: I have taught numerous courses and workshops and make the materials freely available. I developed and co-taught a HarvardX course on reproducible research (<https://www.edx.org/course/principles-statistical-computational-harvardx-ph527x>).

Thesis: Gauge Field Theory in Two Space-Time Dimensions: Anomalies and Applications to String Models.

Nonprint Materials, i.e., film strips, films, videotapes and computer-based materials relevant to appointee's academic field. *Include description of item, who commissioned, purpose, users, penetration in field.*

None

Patents

John Quackenbush

None

Abstracts (*only those containing data not yet published in complete form.*)

None

EXHIBIT B

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*Data calculations on file, Illumina, Inc. 2017.

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Page 1	Page 3
<p>IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE</p> <p>TWINSTRAND BIOSCIENCES,) INC., & UNIVERSITY OF) WASHINGTON,)</p> <p>)Civil Action No. Plaintiffs,)1:21-cv-01126-VAC-SRF) v.)) GUARDANT HEALTH, INC.,)) Defendant.))</p> <p>VIDEOTAPED DEPOSITION of JOHN QUACKENBUSH, PH.D. Friday, September 9, 2022 9:08 a.m. Eastern Daylight Time DLA Piper LLP 33 Arch Street, 26th Floor Boston, Massachusetts 02110-1447 Michelle Keegan, Court Reporter</p> <p>DIGITAL EVIDENCE GROUP 1730 M Street, NW, Suite 812 Washington, D.C. 20036 (202) 232-0646</p>	<p>INDEX</p> <p>Videotaped Deposition of: Page JOHN QUACKENBUSH, PH.D. By Mr. Pickard 6</p> <p>EXHIBITS</p> <p>No. Page Quackenbush Exhibit 1 Declaration of John 7 Quackenbush Ph.D. in Support of Defendant Guardant Health, Inc.'s Answering Claim Construction Brief, USDC, District of Delaware, 21-1126-VAC-SRF, 98 pages without Bates numbering Quackenbush Exhibit 2 U.S. Patent No. 9 10,287,631 B2, 35 pages without Bates numbering</p>
<p>Page 2</p> <p>1 APPEARANCES: 2 STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C. 3 By: Byron L. Pickard, Esq. 4 By: R. Wilson "Trey" Powers III, Esq. 5 By: Louis P. Panzica, Esq. 6 1100 New York Avenue, N.W., Suite 600 7 Washington, D.C. 20005 8 Phone: (202) 371-2600 9 Email: bpickard@sternekessler.com 10 Email: tpowers@sternekessler.com 11 Email: lpanzica@sternekessler.com 12 Counsel for Plaintiffs Plaintiffs TwinStrand 13 Biosciences, Inc., and University of Washington 14 15 DLA PIPER LLP 16 By: Ellen Scordino, Esq. 17 By: Kristin Beale, Esq. (Via Telephone) 18 33 Arch Street, 26th Floor 19 Boston, Massachusetts 02110-1447 20 Phone: (617) 406-6000 21 Email: ellen.scordino@dlapiper.com 22 Email: kristin.beale@dlapiper.com Counsel for Defendant Guardant Health, Inc. and the witness -and- WILSON SONSINI GOODRICH & ROSATI By: Sonja R. Gerrard, Esq. (Via Telephone) 701 Fifth Avenue, Suite 5100 Seattle, Washington 98104-7036 Phone: (206) 883-2500 Email: sgerrard@wsgr.com Counsel for Defendant Guardant Health, Inc. and the witness Also Present: Shawn Budd, Videographer Kellie S. Bickel, Ph.D., TwinStrand</p>	<p>Page 4</p> <p>EXHIBITS, CONT'</p> <p>No. Page Quackenbush Exhibit 3 U.S. Patent No. 125 10,801,063 B2, 54 pages without Bates numbering Quackenbush Exhibit 4 U.S. Patent No. 125 11,149,306 B2, 55 pages without Bates numbering Quackenbush Exhibit 5 U.S. Patent No. 126 11,118,221 B2, 55 page without Bates numbering Quackenbush Exhibit 6 U.S. Patent No. 126 10,889,858 B2, 54 pages without Bates numbering</p> 

1 (Pages 1 to 4)

Page 5	Page 7
<p>1 PROCEEDINGS</p> <p>2 THE VIDEOGRAPHER: We are on the record.</p> <p>3 This is the videographer speaking, Shawn Budd with</p> <p>4 Digital Evidence Group. Today's date is</p> <p>5 September 9th, 2022, and the time is 9:08 a.m.</p> <p>6 We are here to take the video deposition</p> <p>7 of John Quackenbush -- Dr. John Quackenbush in the</p> <p>8 matter of TwinStrand Biosciences, Inc., et al.,</p> <p>9 versus Guardant Health, Inc.</p> <p>10 Would counsel please introduce themselves</p> <p>11 for the record.</p> <p>12 MR. PICKARD: Sure. For the plaintiffs,</p> <p>13 University of Washington and TwinStrand, Byron</p> <p>14 Pickard, Trey Powers, and Louis Panzica from</p> <p>15 Steme Kessler. And we have Kellie Bickel from</p> <p>16 TwinStrand here as well.</p> <p>17 MS. SCORDINO: Ellen Scordino with DLA</p> <p>18 Piper, here on behalf of Guardant Health,</p> <p>19 defendant and counterclaim plaintiff, and also on</p> <p>20 behalf of the witness.</p> <p>21 Here with me on the phone we have Kristin</p> <p>22 Beale, also of DLA Piper, and Sonja Gerrard from</p>	<p>1 right in.</p> <p>2 MR. PICKARD: Let's mark this as</p> <p>3 Exhibit 1.</p> <p>4 (Quackenbush Exhibit 1, marked for</p> <p>5 identification)</p> <p>6 Q. This is your declaration in this case,</p> <p>7 Doctor.</p> <p>8 MR. PICKARD: I'm sure you've got a copy</p> <p>9 already, but . . .</p> <p>10 Q. Dr. Quackenbush, do you recognize what</p> <p>11 we've handed to you as Exhibit 1?</p> <p>12 A. Yes. It looks like my declaration.</p> <p>13 Q. Okay. Great. And I'm correct you</p> <p>14 recently looked at your declaration in preparation</p> <p>15 for your deposition today?</p> <p>16 A. Yes, I have.</p> <p>17 Q. Did you notice any errors or anything that</p> <p>18 needs to be corrected?</p> <p>19 A. Not immediately, no. But if something</p> <p>20 comes up, I'll inform you.</p> <p>21 Q. So as of this moment, you haven't seen</p> <p>22 anything that requires correction, in your view?</p>
Page 6	Page 8
<p>1 Wilson Sonsini.</p> <p>2 THE VIDEOGRAPHER: Okay. Will the court</p> <p>3 reporter please swear in the witness.</p> <p>4 JOHN QUACKENBUSH, PH.D.,</p> <p>5 having been satisfactorily identified and duly</p> <p>6 sworn by the Notary Public, was examined and</p> <p>7 testified as follows:</p> <p>8 EXAMINATION BY COUNSEL FOR</p> <p>9 PLAINTIFFS TWINSTRAND BIOSCIENCES, INC., and</p> <p>10 UNIVERSITY OF WASHINGTON</p> <p>11 BY MR. PICKARD:</p> <p>12 Q. All right. So good morning,</p> <p>13 Dr. Quackenbush.</p> <p>14 A. Good morning.</p> <p>15 Q. You've had your deposition taken before.</p> <p>16 Right?</p> <p>17 A. Yes.</p> <p>18 Q. In fact, quite a few times you've served</p> <p>19 as a professional expert witness. Is that right?</p> <p>20 A. That's correct.</p> <p>21 Q. So I'm going to eschew with a lot of the</p> <p>22 standard preliminary stuff and we can just dive</p>	<p>1 A. Not that I've seen, no.</p> <p>2 Q. Okay. Let's dive into the topic of</p> <p>3 fragment ends, if we can. And that starts at or</p> <p>4 about Paragraph 64 of your dec.</p> <p>5 Let me know when you're there.</p> <p>6 A. All right. I'm there.</p> <p>7 Q. Okay. And I wanted to see if we can find</p> <p>8 some common ground.</p> <p>9 So the dispute between the parties, as you</p> <p>10 understand, is over the meaning of "fragment</p> <p>11 ends." Right?</p> <p>12 A. It's one of the disputed terms. Yes.</p> <p>13 Q. Focusing on this term for this line of</p> <p>14 questioning.</p> <p>15 You understand that's one of the disputes</p> <p>16 in this case?</p> <p>17 A. Yes.</p> <p>18 Q. Okay. Great. In your view, what do the</p> <p>19 TwinStrand patents or University of Washington</p> <p>20 patents, what does "a fragment" mean in the</p> <p>21 context of those patents?</p> <p>22 A. Since we're referring to a term in the</p>

2 (Pages 5 to 8)

Page 9	Page 11
<p>1 '631 patent, would it be possible for me to get a 2 copy? 3 Q. Absolutely. 4 MR. PICKARD: We'll mark that 5 Quackenbush 2. 6 (Quackenbush Exhibit 2, marked for 7 identification) 8 A. Thank you. 9 Q. So just some preliminary, do you recognize 10 what we've marked as Exhibit 2 is what the parties 11 are calling the "'631 patent" in this case? 12 A. Yes, I do. 13 Q. In your opinion, what does the phrase 14 "fragment" mean in the context of the plaintiffs' 15 patents in this case? 16 A. So the question -- would you repeat the 17 question, please? 18 Q. Sure. In your view, what does the term 19 "fragment" mean in the context of the plaintiffs' 20 patents in this case? 21 A. So the term "fragment" and "fragment ends" 22 appears in Claim 1 of the '631 patent.</p>	<p>1 acid fragment ends uniquely labels," and it goes 2 on. 3 So in interpreting this, looking at the 4 claim language and referring back -- and I'd have 5 to look through the patent's written description 6 itself, but since "fragment" only occurs here and 7 this is what the adapters are ligated to, it's the 8 target nucleic acid molecules. 9 If I remember correctly from the 10 specification for this patent, and in fact for all 11 the patents that TwinStrand is asserting, they 12 describe a process known as DCS, duplex complex 13 sequencing or duplex correcting -- I forget 14 what -- DCS method. 15 And all of the examples given in the 16 patent involve taking cellular DNA, sharing it, 17 ligating on adapters of some sort -- and there are 18 different varieties of adapters they describe -- 19 and then generating sequence from those. 20 So the fragment here would be the target 21 nucleic acid molecules after they've been sheared 22 and ligated.</p>
Page 10	Page 12
<p>1 And to summarize what is claimed in that 2 patent, it begins by -- or the process of 3 generating high-quality sequence data begins by 4 "ligating each of the double-stranded target 5 nucleic acid molecules" with an adapter -- and I 6 won't read all of the text -- "to form a 7 population of adapter-target nucleic acid 8 complexes," and then, "wherein each of the 9 adapted" -- "wherein each of the adapter molecules 10 comprises" . . . "a degenerate or semi-degenerate 11 single molecule identifier (SMI) sequence that 12 alone or in combination" . . . "uniquely labels 13 each ligated double-stranded target nucleic acid 14 molecule such that each ligated double-stranded 15 target nucleic acid molecule is" distinguished -- 16 I'm trying to find "fragment" in here again. 17 So let's see. Here we go. I just skipped 18 over it. I'm sorry. 19 "Wherein each of the adapter molecules 20 comprises" . . . "a degenerate or semi-degenerate 21 single molecule identifier" . . . "sequence that 22 alone or in combination with the target nucleic</p>	<p>1 Q. Okay. That's useful. So just so we, I 2 think, have a common understanding, the "fragment" 3 as used in the claims, it's a nucleic acid 4 molecule. Right? 5 A. It is a -- it's not a full nucleic acid 6 molecule. 7 Q. Right. I'll get to that in a moment. But 8 it is a nucleic acid molecule? 9 A. I'm not sure how you're describing a 10 nucleic acid molecule. It is a fragment of a 11 nucleic acid molecule. 12 Q. A moment ago you said that the fragment is 13 the target nucleic acid molecule. So I'm just 14 trying to unpack that a bit. And if I've 15 misstated your answer, please correct me, of 16 course. 17 So just in real simple terms, the fragment 18 as used in the Claim 1 of the '631 patent, for 19 example, when it talks about a fragment, that's a 20 nucleic acid molecule? 21 A. It's a piece of a nucleic acid molecule. 22 So I'm not sure what the specification</p>

3 (Pages 9 to 12)

Page 13	Page 15
<p>1 refers to, the targets of nucleic molecules.</p> <p>2 You know that in your cell there are two</p> <p>3 copies of the genome. Each copy of the genome is</p> <p>4 3 billion bases long. They're packaged in</p> <p>5 46 chromosomes. Some of those are over a hundred</p> <p>6 million bases long.</p> <p>7 So I could describe the whole chromosome</p> <p>8 as a nucleic acid molecule. This is a fragment.</p> <p>9 It has, you know, ends to it. It's been sonicated</p> <p>10 and sheared.</p> <p>11 So it is a nucleic acid. It's a fragment</p> <p>12 of a nucleic acid molecule.</p> <p>13 Q. Okay. And just so we can contextualize</p> <p>14 that within Claim 1, if you look at that ligating</p> <p>15 step that you read a moment ago, it mentions a</p> <p>16 target nucleic acid or it mentions target nucleic</p> <p>17 acid molecules. Do you see that?</p> <p>18 A. I see where it says that. Yes.</p> <p>19 Q. So is it your view that the fragment or</p> <p>20 fragment ends is a piece of that target -- one of</p> <p>21 those target nucleic acid molecules?</p> <p>22 A. So I don't recall the specification of the</p>	<p>1 A. Along one strand. And there's also a</p> <p>2 complementary strand.</p> <p>3 Q. If there's a complementary strand, you'll</p> <p>4 have two backbones with complementary nucleotides</p> <p>5 running the length of those two strands. Right?</p> <p>6 A. Correct. That's the basic structure of</p> <p>7 DNA.</p> <p>8 Q. And so if we take a given nucleic molecule</p> <p>9 and let's say it has N nucleotides, do you agree</p> <p>10 that if you remove one of the nucleotides, so</p> <p>11 anything of N minus 1, or so on, would be</p> <p>12 considered a fragment of that given nucleotide --</p> <p>13 given nucleic acid molecule?</p> <p>14 A. It would depend on the context in which</p> <p>15 the term is used. Someone could refer to the</p> <p>16 whole molecule as a fragment.</p> <p>17 I think of a fragment as being a subset.</p> <p>18 And in mathematics, a proper subset is the entire</p> <p>19 set.</p> <p>20 So it's going to depend on the context.</p> <p>21 But in the context of what's described in this</p> <p>22 patent, cellular DNA is sheared. And I'm not sure</p>
Page 14	Page 16
<p>1 patent -- I'm sorry.</p> <p>2 Could you repeat the question so I make</p> <p>3 sure --</p> <p>4 Q. Of course. A moment ago I think your</p> <p>5 testimony was that the fragment, in your view, is</p> <p>6 a piece of a target or -- sorry -- a piece of a</p> <p>7 nucleic acid molecule. Do I have that right?</p> <p>8 A. I believe so.</p> <p>9 Q. Okay. I mean, is that your testimony? Do</p> <p>10 you agree with that statement?</p> <p>11 A. The fragment is going to be a piece of a</p> <p>12 nucleic acid molecule. Yes.</p> <p>13 Q. Okay. And so if you start with a nucleic</p> <p>14 acid molecule -- maybe we can get some real basic</p> <p>15 stuff. I'm not a scientist, so let's not take</p> <p>16 anything for granted today.</p> <p>17 A nucleic acid molecule is going to -- in</p> <p>18 general terms, going to have like a sugar</p> <p>19 phosphate backbone. Correct?</p> <p>20 A. Correct.</p> <p>21 Q. And there's going to be a sequence of</p> <p>22 nucleotides along that backbone. Is that right?</p>	<p>1 whether or not -- I don't recall the term "target</p> <p>2 nucleic acid molecule" appearing. I was looking</p> <p>3 for that.</p> <p>4 But you asked me about the fragments in</p> <p>5 the context of the target. So if you look at the</p> <p>6 '631 patent, there's a really nice figure, Figure</p> <p>7 1.</p> <p>8 And in Figure 1, you see the SMI sequences</p> <p>9 at the top with a T-tailed DNA fragment. So this</p> <p>10 is the type of fragment that, at least based on</p> <p>11 the specification, the claim language is referring</p> <p>12 to.</p> <p>13 And while you might call that a DNA</p> <p>14 molecule, one might consider the target of the</p> <p>15 analysis to be a gene like BRAC1, which is</p> <p>16 important in breast cancer.</p> <p>17 So I'm not sure in the context of the</p> <p>18 claim language what "target nucleic acid molecule"</p> <p>19 refers to. But it appears that it's being used</p> <p>20 synonymously in this case with the fragments. All</p> <p>21 right?</p> <p>22 But I'm not sure if that's the actual</p>

<p style="text-align: right;">Page 17</p> <p>1 language used in the specification. So if you 2 could point me to that phrase in the 3 specification, it would be really helpful to 4 interpret it.</p> <p>5 But at least in Claim 1.(a), the nucleic 6 acid fragment ends, that fragment is going to be 7 the T-tailed DNA fragment to which the SMI 8 sequence and adapters are ligated. And that's 9 described more fully in the legend in Figure 1.</p> <p>10 Q. Let me come at this a little differently.</p> <p>11 So a moment ago we talked about a nucleic 12 acid molecule is going to have that sugar 13 phosphate backbone with a length or sequence of 14 nucleotides along its length. Correct? And in 15 the case of DNA, it will be double-stranded. 16 Right?</p> <p>17 A. So a nucleic acid has a sugar phosphate 18 backbone, either deoxyribose for DNA or ribose for 19 RNA, to which are attached the nucleoside bases, 20 so the series of As, Cs, Gs, and Ts.</p> <p>21 RNA in its natural form is single- 22 stranded. DNA can be either single-stranded or</p>	<p style="text-align: right;">Page 19</p> <p>1 Claim 1?</p> <p>2 A. So if we read Claim 1, the easiest 3 interpretation is that they're using it 4 synonymously with "target nucleic acid fragment 5 ends."</p> <p>6 But what's unclear in the way this is 7 written is the term "target nucleic acid 8 molecule." And it is used in one instance, and 9 "target nucleic acid fragment ends" is used in 10 another instance.</p> <p>11 So the "target nucleic acid" is modifying 12 something. And what it's modifying is slightly 13 different.</p> <p>14 The best assumption based on the fact that 15 you're ligating something onto it and what's shown 16 in Figure 1 is that the inventors are simply using 17 "target nucleic acid" to modify "molecules" and 18 "target nucleic acid" to modify "fragments," which 19 would indicate that they're using "molecules" in 20 this instance and "fragment" synonymously.</p> <p>21 Q. Okay. But in any event, can we agree that 22 what the claim spells out as a fragment end is a</p>
<p style="text-align: right;">Page 18</p> <p>1 double-stranded, depending on the context.</p> <p>2 The use of the term "molecule" has to be 3 looked at in context. So again, I'm not sure in 4 the specification where the phrase "target nucleic 5 acid molecule" appears.</p> <p>6 Q. Well, it does appear in Claim 1. Right? 7 Correct?</p> <p>8 A. The phrase "target nucleic acid molecule" 9 appears in Claim 1. And if we read Claim 1 --</p> <p>10 Q. Doctor, I apologize. I'm sure you have a 11 lot to say. My question is a very simple one.</p> <p>12 Just the phrase "target nucleic acid 13 molecule," that appears in Claim 1. Right?</p> <p>14 A. Yes, it does, the term does appear in 15 Claim 1.</p> <p>16 Q. I don't mean to be impolite. But if you 17 can answer the questions I ask, I think we can 18 have a pretty quick day.</p> <p>19 All right. And so a moment ago you 20 said -- I think you said you don't have an 21 understanding of what that means, "target nucleic 22 acid molecule." Is that right, in the context of</p>	<p style="text-align: right;">Page 20</p> <p>1 nucleic acid? Correct?</p> <p>2 MS. SCORDINO: Objection, asked and 3 answered.</p> <p>4 A. So the fragment is a -- again, it's a 5 nucleic acid which is part of a larger nucleic 6 acid.</p> <p>7 Q. Okay. Or was a part?</p> <p>8 A. Well --</p> <p>9 Q. Right?</p> <p>10 A. You know --</p> <p>11 Q. Because in your view, it has to be 12 sheared, right, in order to become a fragment?</p> <p>13 A. That's what the specification teaches. It 14 teaches analyzing cellular DNA, which is sheared 15 and then T-tailed and ligated.</p> <p>16 Q. That actually is helpful. I'm just trying 17 to get to see if I can understand your position. 18 That's all I'm trying to do.</p> <p>19 So in your view of the claims, what makes 20 the claim "fragment ends" a fragment is that it 21 had been sheared from a larger nucleic acid 22 molecule. Correct?</p>

5 (Pages 17 to 20)

Page 21	Page 23
<p>1 A. The fragment, to my understanding, has 2 been sheared from a larger nucleic acid molecule 3 and then T-tailed so that the adapters could be 4 ligated onto it. 5 Q. The T-tailing you referred to, is that 6 required by Claim 1? 7 A. So in interpreting claim language, my 8 understanding is that if we're not given specific 9 details what we should do is refer back to the 10 specification. 11 I believe the only examples they give in 12 the specification involve T-tailing and ligating 13 on these SMI sequences. 14 A big part of the reason why that appears 15 to be true is that even the adapters here are very 16 similar to adapters that Illumina sells as part of 17 its standard ligation and sequencing kits. And as 18 of 2012, I believe most of the adapter kits that 19 Illumina sold were adapter kits that required 20 T-tailing. 21 So absent any other evidence in the 22 specification, I believe that, even though it's</p>	<p>1 just want to make sure we're clear on this point. 2 It is your view that a fragment, as 3 claimed in the '631 and other of the plaintiff's 4 patents, is a piece of a potentially larger DNA 5 molecule which has been T-tailed to the adapters, 6 which can be ligated following the methods 7 described in the patent? That's your view of what 8 a fragment is? 9 MS. SCORDINO: Objection to form. 10 A. So I think you're mischaracterizing what I 11 said. 12 Q. I'm sorry. Because I literally just read 13 from the realtime. So if you didn't say it 14 correctly, I would like to get your precise view 15 on that issue. 16 A. All right. So if you like, we can read 17 through some of the examples that are provided in 18 the specification for how the DNA is prepared. 19 Q. I don't want to go through the examples at 20 this moment. 21 You said a moment ago that, in your view, 22 the fragment is a piece of potentially larger DNA</p>
Page 22	Page 24
<p>1 not stated here, it's actually required that 2 they're T-tailed for the adapters to be ligated. 3 Q. I just want to be real clear. 4 It's your position that the claims require 5 this what you're referring to as T-tailing. Is 6 that right? 7 MS. SCORDINO: Objection to form. 8 A. So I don't see a requirement in the claims 9 for T-tailing. But if they're telling me to 10 ligate on an adapter and to look at the fragment, 11 the only examples I have in the patent to refer 12 back to are those which do involve T-tailing. 13 So I believe "requirement" is a legal 14 term, and I'm not in a position to render an 15 opinion on that. 16 But in the case of -- you're asking me to 17 interpret what a fragment is. A fragment is a 18 piece potentially of a larger DNA molecule which 19 has been T-tailed so the adapters can be ligated 20 on, following the methods described in the patent 21 itself. 22 Q. All right. And you said quite a bit, so I</p>	<p>1 molecule which has been T-tailed to the adapters, 2 which can be ligated following the methods 3 described in the patent. 4 So I just want to know, is that your 5 position or did you misspoke? If you misspoke, I 6 do want to get that clear because it's going to 7 dictate my followup questions. 8 MS. SCORDINO: Objection to form. 9 A. All right. So if we look at Example 1 in 10 Column 19, starting at about line 63, they 11 describe "Sequencing Library Preparation," and 12 I'll just read a few highlighted pieces of this. 13 But higher up, they talk about isolating 14 genomic DNA from normal human colonic mucosa. And 15 I won't read through the preparation protocol. 16 But they're taking mucosa, which is the 17 lining of the -- colonic mucosa, which is the 18 lining of the colon. They talk about the adapter 19 synthesis. So these are the adapters that are 20 going to be used in a minute. 21 And then where I was starting at in 22 line 63, "Sequencing Library Preparation.</p>

6 (Pages 21 to 24)

<p style="text-align: right;">Page 25</p> <p>1 3 micrograms of DNA was diluted into</p> <p>2 130 milliliters [sic] of TE buffer."</p> <p>3 So the 3 micrograms of the DNA that was</p> <p>4 extracted from these colon cells was diluted.</p> <p>5 Now, those DNA molecules in the process of</p> <p>6 DNA extraction are damaged and fragmented. Okay?</p> <p>7 So they're not the full DNA molecules. They're</p> <p>8 fragments.</p> <p>9 But then the DNA was sheared on the</p> <p>10 Covaris AFA system -- and they give the parameters</p> <p>11 for this.</p> <p>12 The Covaris system is a system for</p> <p>13 fragmenting DNA, and it fragments it in a pretty</p> <p>14 reproducible way. It's actually a sonic wand that</p> <p>15 you dip into a tube, and it sets up high frequency</p> <p>16 ultrasonic oscillations in the liquid where the</p> <p>17 wavelength of the sound in water actually controls</p> <p>18 the fragment size.</p> <p>19 So it's reasonably tunable. All right?</p> <p>20 So now this DNA has been fragmented.</p> <p>21 Okay? So the whole molecules in the cell are now</p> <p>22 fragmented into smaller pieces. And then we read</p>	<p style="text-align: right;">Page 27</p> <p>1 ligated based on what's described in the</p> <p>2 specification, have already been prepared in a</p> <p>3 particular way.</p> <p>4 And again, we can look for other examples,</p> <p>5 but I believe the examples all involve this</p> <p>6 T-tailing.</p> <p>7 So the fragment is going to be, just like</p> <p>8 in Figure 1, a piece of the larger DNA molecule,</p> <p>9 and it itself is a DNA molecule. We'd have to</p> <p>10 look for target DNA molecules. It's going to be a</p> <p>11 DNA molecule to which Ts have been added to the 3'</p> <p>12 end of each of the two strands.</p> <p>13 Q. Okay. And just so -- well, let me ask you</p> <p>14 this: Do you recall the question I asked a few</p> <p>15 minutes ago?</p> <p>16 A. You can repeat it. I'm not sure I recall</p> <p>17 the full question.</p> <p>18 Q. Okay. My question -- and I'll simplify it</p> <p>19 a bit -- is whether in your view the claims</p> <p>20 require the fragments to be T-tailed.</p> <p>21 And you pointed me to an example in the</p> <p>22 patent that describes T-tailing. Correct?</p>
<p style="text-align: right;">Page 26</p> <p>1 on, "the beads were washed and" blah, blah, blah.</p> <p>2 So the DNA has been captured.</p> <p>3 And the DNA was T-tailed in a reaction</p> <p>4 containing 5 units of Klenow exo-, and it gives</p> <p>5 you the parameters. "The custom adapters were</p> <p>6 ligated by combining 750 ng of T-tailed DNA with</p> <p>7 250 pmol adapters in a reaction containing" . . .</p> <p>8 "DNA ligase" and other parameters. All right?</p> <p>9 So if we go back to the language of the</p> <p>10 claim, ligating each of the double-stranded target</p> <p>11 nucleic acid molecules.</p> <p>12 The process of ligation requires that</p> <p>13 the -- at least in the way it's described in other</p> <p>14 examples in the patent too, requires this</p> <p>15 T-tailing. Right?</p> <p>16 So if we look at Figure 1, Figure 1 very</p> <p>17 clearly recapitulates what we just talked about</p> <p>18 where we have a fragment that has been T-tailed.</p> <p>19 So the patent says in Claim 1, "ligating</p> <p>20 each of the double-stranded target nucleic acid</p> <p>21 molecules."</p> <p>22 But these molecules here, which are</p>	<p style="text-align: right;">Page 28</p> <p>1 A. I did point you to Example 1, which</p> <p>2 describes, I believe, the only protocol in the</p> <p>3 patent for attaching these -- attaching adapters.</p> <p>4 Q. Okay. And it involves T-tailing?</p> <p>5 A. Yes.</p> <p>6 Q. And so my question is not whether there's</p> <p>7 an example that has T-tailing but whether, in your</p> <p>8 view, in order to meet the -- what's claimed as a</p> <p>9 fragment there must be T-tailing.</p> <p>10 Is that your position, there has to be</p> <p>11 T-tailing for something to be a fragment in the</p> <p>12 claims?</p> <p>13 MS. SCORDINO: Objection to form.</p> <p>14 A. I'm not an attorney, and I know "required"</p> <p>15 is a term which has legal ramifications to the</p> <p>16 meaning. I'm not sure what "required" means.</p> <p>17 One skilled in the art would understand</p> <p>18 and know other ways of attaching adapters.</p> <p>19 But this whole discussion started with the</p> <p>20 term "fragment" and "fragment ends." All right?</p> <p>21 And so we're talking about the fragments here that</p> <p>22 are described in the patent.</p>

7 (Pages 25 to 28)

<p style="text-align: right;">Page 29</p> <p>1 And in the context of the patent, the</p> <p>2 fragments are prepared in a particular way. And</p> <p>3 the term "fragment ends" is used in the context of</p> <p>4 a larger discussion about fragments and how the</p> <p>5 fragments are handled, how the fragments are</p> <p>6 analyzed.</p> <p>7 So preparing these fragments involves</p> <p>8 shearing, involves other steps that are involved</p> <p>9 in cloning. And to identify the fragment ends</p> <p>10 requires that once the DNA is sequenced we</p> <p>11 understand how that DNA is prepared so we can</p> <p>12 actually identify the sequence that comes from</p> <p>13 those fragments.</p> <p>14 So to the best of my understanding of the</p> <p>15 word "requires," there could be other ways to</p> <p>16 attach these adapters. What's really important is</p> <p>17 that once the DNA is sequenced, the adapter</p> <p>18 sequence and any added sequence has to be trimmed</p> <p>19 to identify the fragment itself, the fragment</p> <p>20 itself.</p> <p>21 Q. All right. Let's look at your</p> <p>22 declaration, Exhibit I, Dr. Quackenbush.</p>	<p style="text-align: right;">Page 31</p> <p>1 But the DNA fragments -- the definition</p> <p>2 includes shearing, which is what's described as</p> <p>3 the preparation of the fragments from the original</p> <p>4 nucleic acid molecules. And then trimming is an</p> <p>5 essential element of identifying a fragment end.</p> <p>6 If the fragments were cloned or if the</p> <p>7 adapters were attached using the protocols</p> <p>8 described in Example 1, and I believe the other</p> <p>9 examples in the specification for the patent, they</p> <p>10 would be T-tailed.</p> <p>11 And trimming refers to the part of the</p> <p>12 analysis pipeline that involves identifying the</p> <p>13 exogenous sequence and removing it to identify the</p> <p>14 fragment ends.</p> <p>15 So implicit in trimming is the idea that</p> <p>16 if T-tailing were used -- which is the only method</p> <p>17 I believe that's described in the patent. If</p> <p>18 T-tailing were used, that T should be trimmed to</p> <p>19 identify the end of the fragment as part of the</p> <p>20 process of identifying the end of the fragment.</p> <p>21 Q. All right. So it's your view that</p> <p>22 although T-tailing isn't -- the words "T-tailing"</p>
<p style="text-align: right;">Page 30</p> <p>1 A. Okay.</p> <p>2 Q. Let me know -- and there's that table</p> <p>3 above Paragraph 64. Let me know when you're</p> <p>4 there.</p> <p>5 A. Okay. I'm there.</p> <p>6 Q. You're familiar with the table. Right?</p> <p>7 A. Yes, I am.</p> <p>8 Q. And that sets forth succinctly the</p> <p>9 parties' competing positions on the proper</p> <p>10 construction of "fragment ends." Right?</p> <p>11 A. That sets out each party's position for</p> <p>12 the construction.</p> <p>13 Q. Great. And it's your opinion that what's</p> <p>14 shown in the table under Guardant's proposed</p> <p>15 construction, you believe that is the correct one.</p> <p>16 Is that fair to say?</p> <p>17 A. I would believe that is a correct</p> <p>18 definition of "fragment ends." Yes.</p> <p>19 Q. Okay. Great. And I think we can agree</p> <p>20 that in the proposed Guardant construction there's</p> <p>21 no mention of T-tailing. Is that right?</p> <p>22 A. So T-tailing isn't explicitly mentioned.</p>	<p style="text-align: right;">Page 32</p> <p>1 aren't used in that construction, they are</p> <p>2 implicitly part of it because that is a portion of</p> <p>3 the trimming that's stated in that proposed</p> <p>4 construction. Is that fair?</p> <p>5 MS. SCORDINO: Objection to form.</p> <p>6 A. If the method that is practiced is the one</p> <p>7 described in the patent, which the only one there</p> <p>8 is T-tailing, then that T has to be identified.</p> <p>9 If other methods for ligating on the</p> <p>10 adapter -- for example, blunt-end ligation -- is</p> <p>11 used, then T-tailing wouldn't be part of the</p> <p>12 process.</p> <p>13 So whatever process is used to ligate on</p> <p>14 the adapters is one which is going to be integral</p> <p>15 to the part -- to the process of trimming and</p> <p>16 identifying where the actual DNA from the</p> <p>17 individual who is being analyzed, where that DNA</p> <p>18 actually begins and where the exogenous adapters</p> <p>19 and other cloning artifacts end.</p> <p>20 Q. You talk -- you keep going back to what's</p> <p>21 being described. I want to focus on what's being</p> <p>22 claimed.</p>

8 (Pages 29 to 32)

<p style="text-align: right;">Page 33</p> <p>1 Can you tell me what in your understanding</p> <p>2 of the function of the claims in the patents</p> <p>3 you've analyzed in this case is?</p> <p>4 MS. SCORDINO: Objection, outside the</p> <p>5 scope, form.</p> <p>6 Q. Let me break that down.</p> <p>7 Do you understand the function of a patent</p> <p>8 claim in the context of a patent?</p> <p>9 A. I have an understanding. I don't know if</p> <p>10 I could recite the full legal definition of what a</p> <p>11 claim is.</p> <p>12 A claim is -- to the best of my</p> <p>13 understanding, is a recitation of what the</p> <p>14 inventors of the patent believe they have invented</p> <p>15 or claim to have invented.</p> <p>16 Q. Okay. Do you understand that the claims</p> <p>17 set forth one or more requirements that must be</p> <p>18 present in the accused method or product for there</p> <p>19 to be infringement?</p> <p>20 MS. SCORDINO: Objection to form, calls</p> <p>21 for a legal conclusion.</p> <p>22 A. So I'm not a licensed patent examiner or</p>	<p style="text-align: right;">Page 35</p> <p>1 adapters ligated to it and the data is generated.</p> <p>2 Otherwise, one would interpret the adapter</p> <p>3 sequence as being part of the fragment.</p> <p>4 And clearly that's not what the inventors</p> <p>5 intended, based on the specification of the patent</p> <p>6 itself.</p> <p>7 In the specification, they talk about</p> <p>8 using the two strands that are complementary and</p> <p>9 the true mutations found in the same position in</p> <p>10 both strands.</p> <p>11 We're talking about mutations, errors in</p> <p>12 the DNA of the individual from which these</p> <p>13 fragments are sequenced.</p> <p>14 And a natural consequence of generating</p> <p>15 sequence data is we generate the additional</p> <p>16 sequence that has to be trimmed.</p> <p>17 So one could use a method other than</p> <p>18 T-tailing to ligate on the adapters. But the only</p> <p>19 method that I believe is described in the</p> <p>20 specification of the patent is one that involves</p> <p>21 T-tailing.</p> <p>22 Q. Okay. And given that the patent only</p>
<p style="text-align: right;">Page 34</p> <p>1 patent agent or attorney. So I'm not prepared to</p> <p>2 render an opinion on the full scope of what a</p> <p>3 claim requires or grants to its inventors.</p> <p>4 Q. Okay. But it's your view that what the</p> <p>5 claim does is set forth what the inventors think</p> <p>6 they have invented. Right?</p> <p>7 MS. SCORDINO: Objection to form.</p> <p>8 A. My understanding is that a claim describes</p> <p>9 the invention that the patent owners are hoping to</p> <p>10 protect.</p> <p>11 My understanding is that if language in a</p> <p>12 claim is not clear that the first place one should</p> <p>13 turn is to the specification of the patent to try</p> <p>14 to interpret it.</p> <p>15 You're correct when you ask me whether or</p> <p>16 not the claim actually specifies the T-tailing.</p> <p>17 And it does not.</p> <p>18 What's important, though, in my answer,</p> <p>19 since we're ultimately talking about fragments, is</p> <p>20 that to identify the end of the fragment and the</p> <p>21 sequence of the fragment itself, one must</p> <p>22 understand the process by which that fragment had</p>	<p style="text-align: right;">Page 36</p> <p>1 describes methods that use T-tailing, is it</p> <p>2 therefore your view that the claims require</p> <p>3 fragment ends to be T-tailed in order to meet the</p> <p>4 claim limitation?</p> <p>5 A. So I know "required" has a specific legal</p> <p>6 meaning --</p> <p>7 Q. Let me stop you right there because you</p> <p>8 used "require" in your declaration. Right?</p> <p>9 A. Can you point me --</p> <p>10 Q. In Paragraph 64, in your discussion of</p> <p>11 fragment ends, you use "require." So I'm a little</p> <p>12 confused by your pushback on the use of that word.</p> <p>13 MS. SCORDINO: Objection, argumentative.</p> <p>14 Q. Do you see that second sentence? You</p> <p>15 wrote, "Thus, my analysis for this term is focused</p> <p>16 on whether the claimed fragment ends require</p> <p>17 shearing and trimming as set forth in Guardant's</p> <p>18 construction."</p> <p>19 That's an accurate statement of your view.</p> <p>20 Correct?</p> <p>21 A. So --</p> <p>22 Q. That's just a simple question. Is that an</p>

Page 37	Page 39
<p>1 accurate statement?</p> <p>2 MS. SCORDINO: Counsel, stop interrupting</p> <p>3 the witness. Let him answer.</p> <p>4 A. So the term "fragment" here, if we read</p> <p>5 the sentence, "Thus, my analysis for this term is</p> <p>6 focused on whether the claimed fragment ends</p> <p>7 require shearing and trimming as set forth in</p> <p>8 Guardant's construction."</p> <p>9 So here, I'm not trying to -- I'm not</p> <p>10 trying to argue for the legal requirements of</p> <p>11 what's laid out in the patent.</p> <p>12 The requirement here is the simpler</p> <p>13 nonlegal definition of "require." If I'm going to</p> <p>14 find the fragment ends, how do I actually get</p> <p>15 those fragments. Right?</p> <p>16 If I took your Chromosome 1 and tried to</p> <p>17 ligate it on adapters and sequence it, it simply</p> <p>18 wouldn't work. The duplex consensus sequencing</p> <p>19 method described in the specification would not</p> <p>20 work because I couldn't read end to end with a</p> <p>21 next-generation sequencer across all of</p> <p>22 Chromosome 1. Okay?</p>	<p>1 molecular biology. I have to interpret them in</p> <p>2 the context of what is here.</p> <p>3 So if I'm going to identify those fragment</p> <p>4 ends with duplex consensus sequencing, I need to</p> <p>5 shear the DNA; I need to ligate things on.</p> <p>6 I grant there are other ways of ligating</p> <p>7 things on, aside from T-tailing. The protocols in</p> <p>8 this patent are all built around variations on</p> <p>9 Illumina's standard kits. Okay?</p> <p>10 So could you ligate on the adapters in</p> <p>11 other ways? Yes. But the only way to do duplex</p> <p>12 consensus sequencing as laid out in the examples</p> <p>13 in the patent would require shearing, ligating,</p> <p>14 sequencing, and then trimming that sequence.</p> <p>15 Okay?</p> <p>16 So the identification of the fragment</p> <p>17 ends, which is what we're going to analyze,</p> <p>18 necessitates shearing and trimming.</p> <p>19 Q. Can you tell me what question you just</p> <p>20 answered?</p> <p>21 A. You were asking me about the use of the</p> <p>22 word "require" in Paragraph 64 in the second</p>
Page 38	Page 40
<p>1 So the specification describes the method</p> <p>2 that they refer to as "duplex consensus sequence"</p> <p>3 that requires smaller DNA fragments that can be</p> <p>4 read across from both sides so the consensus</p> <p>5 sequences can be built on both strands.</p> <p>6 So the specification is laying out the</p> <p>7 general -- my understanding is it's laying out the</p> <p>8 general framework of what the inventors have done.</p> <p>9 And then specific aspects of the invention are</p> <p>10 laid out in the claim, which is why we had the</p> <p>11 same specification in four separate patents but</p> <p>12 different sets of claims.</p> <p>13 So how do we do duplex consensus</p> <p>14 sequencing? Everything in the specification. We</p> <p>15 need fragments that are small enough to sequence</p> <p>16 across. Right?</p> <p>17 And the only way we're going to get that</p> <p>18 from whole genomes is to shear it. Okay? So I</p> <p>19 have to interpret these claims in the context of</p> <p>20 the specification.</p> <p>21 I can't interpret them in the context of</p> <p>22 some protocol laid out in Maniatis's bible for</p>	<p>1 sentence.</p> <p>2 Q. Yeah. And I think that might be part of</p> <p>3 the problem. That's actually not what I asked.</p> <p>4 I asked you whether that second sentence</p> <p>5 in Paragraph 24, whether that is a correct</p> <p>6 statement of your opinions, whether that's a</p> <p>7 correct statement.</p> <p>8 A. Could you repeat the question, please?</p> <p>9 Q. "Do you see that second sentence? You</p> <p>10 wrote," and I said it to you, "That's an accurate</p> <p>11 statement of your view. Correct?"</p> <p>12 And then you spoke at length.</p> <p>13 What you wrote there in the second</p> <p>14 sentence of Paragraph 64, is that an accurate</p> <p>15 statement, in your view?</p> <p>16 A. I already answered that question. If you</p> <p>17 like, I can recapitulate it for you.</p> <p>18 Q. It's Paragraph 64. I might have said 24.</p> <p>19 Paragraph 64 in your dec, the second</p> <p>20 sentence. You've read that to yourself?</p> <p>21 A. Yes.</p> <p>22 Q. Is that an accurate statement of at least</p>

10 (Pages 37 to 40)

<p style="text-align: right;">Page 41</p> <p>1 one of your views you've formed in this case?</p> <p>2 A. You didn't ask me that question by itself.</p> <p>3 Q. I don't want to argue with you. We can</p> <p>4 just answer the question and we can move on,</p> <p>5 because it ought not be a long day.</p> <p>6 A. Okay.</p> <p>7 Q. And I think we can get there quickly.</p> <p>8 So my question -- and I apologize. I</p> <p>9 probably did ask a compound question, and it's my</p> <p>10 fault. So I'm going to do better this time.</p> <p>11 My question is very simple. The second</p> <p>12 sentence of Paragraph 64, does that accurately</p> <p>13 state your view?</p> <p>14 A. The second sentence -- and I already</p> <p>15 answered this question for you.</p> <p>16 The second sentence in Paragraph 64 says,</p> <p>17 "Thus, my analysis for this term is focused on</p> <p>18 whether the claimed fragment ends require shearing</p> <p>19 and trimming as set forth in Guardant's</p> <p>20 construction."</p> <p>21 This is an accurate representation of my</p> <p>22 view, but it's not intended to set a legal</p>	<p style="text-align: right;">Page 43</p> <p>1 documents, the patents themselves, my declaration,</p> <p>2 shouldn't be taken out of context and just set up</p> <p>3 on its own.</p> <p>4 The term "fragment ends" is used in a</p> <p>5 specific way. And so if we're going to define</p> <p>6 "fragment ends," we're not just going to say</p> <p>7 "fragment ends." We're going to say "fragment</p> <p>8 ends" in the context of what's claimed in the</p> <p>9 patent.</p> <p>10 In Claim 1 of the '631 patent, the term</p> <p>11 "fragment ends" -- and this begins about line 36,</p> <p>12 in Column 37 -- "with the target nucleic acid</p> <p>13 fragment ends uniquely labels each ligated</p> <p>14 double-stranded target nucleic acid molecule."</p> <p>15 So the fragment ends uniquely label along</p> <p>16 with -- uniquely label each ligated double-</p> <p>17 stranded targeted nucleic acid molecule.</p> <p>18 So they label them. The only way you can</p> <p>19 find the label is through the process of</p> <p>20 sequencing. If I give you a tube of ligated DNA</p> <p>21 fragments, however they're ligated, T-tailed or</p> <p>22 prepared another way, I give you two ligated DNA</p>
<p style="text-align: right;">Page 42</p> <p>1 definition in the bounds of the term "require,"</p> <p>2 which is what you're asking me about.</p> <p>3 What it does -- and I could use -- if you</p> <p>4 prefer, we can modify this to say "necessitate."</p> <p>5 And I'll use "necessitate" today. Does</p> <p>6 identifying the fragment ends necessitate shearing</p> <p>7 and trimming?</p> <p>8 And the answer is absolutely yes, that in</p> <p>9 order to find the ends of the fragments, one has</p> <p>10 to perform some steps in order to generate the</p> <p>11 fragment sequence itself and identify its ends.</p> <p>12 There are additional steps.</p> <p>13 So those are necessary to find the</p> <p>14 fragment ends.</p> <p>15 Q. Okay. If we look closely at this</p> <p>16 sentence, when you use the word "require" -- which</p> <p>17 I know you will substitute "necessitate," fair</p> <p>18 enough -- you're talking about what the claimed</p> <p>19 fragment ends necessitate. Right? That's what</p> <p>20 you wrote.</p> <p>21 MS. SCORDINO: Objection to form.</p> <p>22 A. So again, any statement in any of these</p>	<p style="text-align: right;">Page 44</p> <p>1 fragments, there's nothing you can do with that.</p> <p>2 So the interpretation of "fragment ends"</p> <p>3 requires some additional steps, and one of the</p> <p>4 steps is sequencing. To sequence, one has to</p> <p>5 shear and ligate on adapters and generate sequence</p> <p>6 and then analyze the sequence.</p> <p>7 So in Paragraph 64, "Thus, my analysis for</p> <p>8 this term" -- the analysis of what the term</p> <p>9 "fragment end" means really does require for a</p> <p>10 fragment end to be a fragment end, that shearing</p> <p>11 occur, sequencing occur, and trimming of that</p> <p>12 sequence must happen as set forth in Guardant's</p> <p>13 construction.</p> <p>14 So in the broader context of how one uses</p> <p>15 the "fragment end" as described in Claim 1 of the</p> <p>16 '631 patent, yes, those shearing and trimming are</p> <p>17 necessary for identifying using the fragment ends</p> <p>18 as laid out.</p> <p>19 Q. Okay. Great. And you actually added</p> <p>20 something there in your last answer and that was</p> <p>21 "sequencing."</p> <p>22 Is shearing, sequencing, and trimming</p>

11 (Pages 41 to 44)

Page 45	Page 47
<p>1 required, in your view, or just sequencing and</p> <p>2 trimming?</p> <p>3 A. I believe you're incorrect. I used</p> <p>4 "sequencing" before. I talked about the process</p> <p>5 of Illumina sequencing, adding on Illumina</p> <p>6 sequence adapters, and trimming the resulting</p> <p>7 sequence to identify the fragment ends.</p> <p>8 Q. Sequencing is not required for there to be</p> <p>9 a fragment end?</p> <p>10 MS. SCORDINO: Objection to form.</p> <p>11 Q. Necessitate. Would that be better for</p> <p>12 you?</p> <p>13 MS. SCORDINO: Same objection.</p> <p>14 Q. I really need to know your answer because</p> <p>15 I'm going to ask you this at trial in front of the</p> <p>16 judge and jury.</p> <p>17 A. Okay. Good.</p> <p>18 Q. In your view, does the term "fragment</p> <p>19 ends" necessitate any sequencing?</p> <p>20 A. So if we read Claim 1 -- I won't run</p> <p>21 through the whole thing.</p> <p>22 But if we start, the invention they claim</p>	<p>1 only way to use that fragment end is to trim it so</p> <p>2 that we know where the fragment end is.</p> <p>3 So could I define "fragment end" in the</p> <p>4 abstract to mean other things? Certainly. But if</p> <p>5 we want to look at what these inventors are</p> <p>6 claiming, what we should understand is they're not</p> <p>7 going to use the fragment ends in random ways.</p> <p>8 They're going to use the fragment ends or the</p> <p>9 sequence of those fragment ends.</p> <p>10 And so fragment ends don't exist in a</p> <p>11 vacuum. The fragment ends that are used to</p> <p>12 identify the molecules are the sequences of those</p> <p>13 fragment ends. Or the sequence of those fragment</p> <p>14 ends are what are used to identify the molecule.</p> <p>15 The identification -- they refer to</p> <p>16 identifying using the fragment ends, but the only</p> <p>17 way to do that in the context of the invention is</p> <p>18 through sequencing.</p> <p>19 So yes, the fragments have to be -- the</p> <p>20 DNA molecules have to be sheared, have to be</p> <p>21 ligated, have to be sequenced, and the sequence</p> <p>22 has to be trimmed.</p>
Page 46	Page 48
<p>1 comprises "ligating each of the double-stranded</p> <p>2 target nucleic acid molecules to at least one</p> <p>3 adapter molecule, to form a population of</p> <p>4 adapter-target nucleic acid complexes, wherein</p> <p>5 each of the adapter molecules comprises--</p> <p>6 "(a) a degenerate or semi-degenerate</p> <p>7 single molecule identifier (SMI) sequence that</p> <p>8 alone or in combination with the target nucleic</p> <p>9 acid fragment ends uniquely labels each ligated</p> <p>10 double-stranded target nucleic acid molecule such</p> <p>11 that each ligated double-stranded target nucleic</p> <p>12 acid molecule is distinguishable from the other</p> <p>13 ligated double-stranded target nucleic acid</p> <p>14 molecules in the population, and</p> <p>15 "(b) a strand-distinguishing nucleotide</p> <p>16 sequence that, following the ligation step,</p> <p>17 provides a region of non-complementarity between</p> <p>18 the first strand of each" . . . "target nucleic</p> <p>19 acid complex and a second strand," and so on.</p> <p>20 If we look at "fragment end" in the</p> <p>21 context of the claim, the only way to use that</p> <p>22 fragment end is to perform sequencing. And the</p>	<p>1 Q. All right. Thank you.</p> <p>2 So the short answer is, yes, all three of</p> <p>3 those things need to be present: The molecules</p> <p>4 have to be sheared, have to be ligated and have to</p> <p>5 be sequenced, and the sequence has to be trimmed.</p> <p>6 Correct?</p> <p>7 MS. SCORDINO: Objection to form.</p> <p>8 A. In the context of the Claim 1 of the '631</p> <p>9 patent, "fragment ends" are used in a specific</p> <p>10 way.</p> <p>11 So we can define the term "fragment ends"</p> <p>12 in the abstract in a variety of different ways.</p> <p>13 In the context of the patent, the "fragment ends"</p> <p>14 are really referring to the sequence of the ends</p> <p>15 of the fragments, not the whole fragment but some</p> <p>16 subregion of the entire fragment.</p> <p>17 And to generate those fragment ends, one</p> <p>18 must shear the DNA, ligate on adapters in some</p> <p>19 way, sequence it, and then trim the sequence.</p> <p>20 Q. Okay.</p> <p>21 MR. PICKARD: Why don't we do a short,</p> <p>22 five-minute break.</p>

12 (Pages 45 to 48)

<p style="text-align: right;">Page 49</p> <p>1 THE VIDEOGRAPHER: The time is 10:02. 2 We're off the record. 3 (Recess from 10:02 a.m. to 10:17 a.m.) 4 THE VIDEOGRAPHER: We are back on the 5 record. The time is 10:17. 6 BY MR. PICKARD: 7 Q. All right. Welcome back, Dr. Quackenbush. 8 I apologize in advance if I get my terminology 9 wrong. I'm sure you'll correct me. 10 We talked a little bit or you talked a 11 little bit about ligating adapters earlier. And I 12 think in Example 1, the patent, as you testified, 13 talks about a step involving T-tailing as part of 14 ligation. Is that right? 15 A. T-tailing is a part of the ligation 16 process used in Example 1. There are other 17 methods for ligating that don't involve T-tailing. 18 Q. Great. And these other ways of ligating 19 adapters, among them is blunt-end ligation one of 20 them? 21 A. Blunt-end ligation is a method for 22 ligating adapters.</p>	<p style="text-align: right;">Page 51</p> <p>1 MR. PICKARD: Understood. 2 A. There are a few places I've highlighted 3 just so I can find things easily. 4 MR. PICKARD: I'm going to guess we're 5 going to have like 20 copies of the '631 patent in 6 this case. 7 MS. SCORDINO: This will be the dirty one. 8 MR. PICKARD: The paralegals are going to 9 hate us at some point. Such is life. 10 Q. Are you there, Doctor? 11 A. Yes, I am. 12 Q. Good. You're familiar with this portion 13 of the patent specification, I trust? 14 A. I've read the specification a number of 15 times. 16 Q. And in general terms, what's being 17 described here are suitable ways for ligating 18 adapters. Is that right? 19 A. Yeah. They describe a number of ways of 20 ligating adapters. There are, of course, 21 additional ways one can do it too. 22 Q. Fair enough. And one of the ways that the</p>
<p style="text-align: right;">Page 50</p> <p>1 Q. And in a blunt-end ligation, there isn't 2 any T to trim, if I'm saying that correctly. 3 Correct? 4 A. There is no T to trim in the process of 5 sequence analysis because it's not added on to 6 ligate on the adapters. 7 The TA cloning, as it's often referred to, 8 uses T-tailing on one DNA piece and A-tailing on 9 another DNA piece to provide complementary places 10 where the nucleic acids can bind together. 11 And it's pretty commonly used. 12 Q. You've got the '631 patent in front of you 13 as Exhibit 2? 14 A. Yes, I do. 15 Q. All right. If you could take a look at 16 Column 7, and I'll draw your attention to line 60. 17 Let me know when you're there. 18 MS. SCORDINO: Just so the record is 19 clear, with respect to Exhibit 2, I noted 20 Dr. Quackenbush has made some markings with a pen 21 on it, so it won't be a completely clean copy of 22 the patent for future use.</p>	<p style="text-align: right;">Page 52</p> <p>1 patent specifically sets forth there in line 64 is 2 a blunt end. Correct? 3 A. They include GC overhangs and blunt-end 4 ligation as viable alternatives for SMI 5 ligation -- adapter ligation. 6 Q. So given that disclosure, do you agree 7 that the claimed fragment end can be met without 8 the step or use of T-tailing? 9 A. So identifying the fragment end is going 10 to require cloning -- sorry -- shearing, some 11 method for ligating on those adapters, sequencing, 12 and then trimming the sequence to remove the 13 adapter. And I believe earlier I said "cloning 14 artifacts." 15 So you are correct, it could be done 16 without T-tailing, in which case if it was done 17 with blunt-end ligation you'd simply trim off the 18 adapter sequence. You wouldn't have to trim off 19 that additional T or A. 20 Q. Okay. I think I understand your position 21 that in the context of the patents, the TwinStrand 22 or UW patents, what is claimed necessitates a</p>

13 (Pages 49 to 52)

Page 53	Page 55
<p>1 shearing step. Correct? In order to get a 2 fragment end. Is that right?</p> <p>3 A. The '631 patent describes this process 4 called duplex consensus sequencing. And that 5 requires that the DNA sequence on both strands is 6 obtained and that eventually consensus sequences 7 for those strands are overlapped.</p> <p>8 So the only way for that to happen is to 9 be able to sequence through. So the fragment size 10 has to be smaller than the read length. In fact, 11 you need to be able to pick up the SMIs and other 12 adapter sequences.</p> <p>13 So one has to have fragments that are 14 smaller than a whole chromosome, which requires 15 some kind of fragmentation. And again, shearing 16 is the most common.</p> <p>17 Q. Okay. And that's what I'm trying to get 18 at. So you've got to have some kind of 19 fragmentation. And that's to get your nucleic 20 acid so it's appropriately sized so you can do the 21 sequencing. Correct? Among other things?</p> <p>22 MS. SCORDINO: Objection to form.</p>	<p>1 fragmentation is used of that, and that 2 fragmentation as described in the patent is 3 shearing. Correct? So we've got shearing.</p> <p>4 And you said then, there is "a variety of 5 reasons why shearing is a good approach. One 6 could use restriction enzymes to cut the DNA," 7 which you use "different adapter ligation 8 strategy.</p> <p>9 "But restriction enzymes are nonrandom." 10 Do you remember that testimony?</p> <p>11 A. I think I said which would require the use 12 of different ligation strategies.</p> <p>13 Q. What I want to know is, as you're 14 proposing or as Guardant is proposing to construe 15 "fragment ends" as requiring the shearing, the use 16 of restriction enzymes you just testified to, 17 would that be a type of shearing or is that 18 distinct from shearing?</p> <p>19 MS. SCORDINO: Objection to form.</p> <p>20 A. Would you please repeat the question?</p> <p>21 Q. I will.</p> <p>22 A. Thank you.</p>
Page 54	Page 56
<p>1 A. So we're talking about fragment ends. And 2 one has to generate fragments that are ultimately 3 sequenced. And so some kind -- some type of 4 fragmentation is used, and that fragmentation, as 5 described in the patent, is shearing.</p> <p>6 Q. Okay.</p> <p>7 A. And there are a variety of reasons why 8 shearing is a good approach. One could use 9 restriction enzymes to cut the DNA, which require 10 the use of different adapter ligation strategy.</p> <p>11 But restriction enzymes are nonrandom.</p> <p>12 Q. I see. Okay. I think that's 13 illuminating.</p> <p>14 So the shearing, as it's used in the 15 Guardant proposed construction, does not encompass 16 the use of restriction enzyme. Is that right?</p> <p>17 MS. SCORDINO: Objection to form.</p> <p>18 A. I'm sorry. Could you repeat the question, 19 please?</p> <p>20 Q. Yeah. You said a moment ago that one has 21 to generate fragments that are ultimately 22 sequenced and so some kind -- some type of</p>	<p>1 Q. Just for a bit of context, do you recall a 2 moment ago you were talking about shearing? And 3 you provided the example of restriction enzymes. 4 Do you remember that?</p> <p>5 A. Yes, I do.</p> <p>6 Q. So what I'd like to know is, if we look at 7 the Guardant proposed construction for "fragment 8 ends" where it has "shearing" there, does shearing 9 encompass the use of restriction enzymes in that 10 proposed construction?</p> <p>11 A. So shearing, if we look at the examples in 12 the specification, shearing is the method which is 13 described for fragmentation of larger DNA 14 molecules to prepare them for the ligation step, 15 ultimately sequencing analysis and trimming to 16 identify those fragment ends.</p> <p>17 And so the use of "shearing" here is meant 18 to encompass what's described in the various 19 examples.</p> <p>20 The patent itself does envision other 21 methods for attaching adapters. So if we look at 22 the Paragraph 13 -- sorry -- Column 13 and 14,</p>

14 (Pages 53 to 56)

Page 57	Page 59
<p>1 starting at about line 54, "DCS" -- duplex</p> <p>2 consensus sequence -- "SMI adaptor molecules</p> <p>3 contain ligatable ends to allow attachment to a</p> <p>4 target DNA molecule. In some embodiments, the</p> <p>5 ligatable end may be complementary to a DNA</p> <p>6 overhang of the target DNA, for example, one</p> <p>7 generated by digestion of target DNA with</p> <p>8 restriction endonuclease. Selective ligation of</p> <p>9 the adaptor to the targeted DNA containing the</p> <p>10 matching Single-stranded overhang DNA sequence</p> <p>11 will then allow for partial purification of the</p> <p>12 targeted DNA. A non-limiting example of this</p> <p>13 embodiment is shown in paragraphs [0048]-[0053].</p> <p>14 In some embodiments, the DCS" sequence "adaptor"</p> <p>15 or a hairpin-like "SMI adaptor molecule, may</p> <p>16 additionally contain modifications such as biotin</p> <p>17 to facilitate" . . . "purification of target</p> <p>18 DNA . . .</p> <p>19 "In another embodiments, specific PCR</p> <p>20 primers can selectively amplify" selected "regions</p> <p>21 of" the "genome where the adaptor" is</p> <p>22 ligated" . . . "Alternatively, this method may be</p>	<p>1 let me break this down in small bites. I think</p> <p>2 this is a defensible position.</p> <p>3 The use of the "shearing" term in the</p> <p>4 proposed Guardant construction is intended to</p> <p>5 encompass at least the examples that are described</p> <p>6 in the patents. Correct?</p> <p>7 A. Would you please repeat the question?</p> <p>8 Q. Yeah. Sure.</p> <p>9 A. You were asking me about shearing.</p> <p>10 Q. I am. Just be patient with me for a</p> <p>11 moment.</p> <p>12 A. Just trying to help jog the question.</p> <p>13 Q. I appreciate that.</p> <p>14 A few responses ago, you made a comment</p> <p>15 and I want to explore that a bit.</p> <p>16 In you comment in your answer was, "So</p> <p>17 here in Guardant's proposed construction" --</p> <p>18 sorry.</p> <p>19 "So 'shearing' here, in Guardant's</p> <p>20 proposed construction, was referring to the</p> <p>21 process described in the examples."</p> <p>22 Do you remember that?</p>
Page 58	Page 60
<p>1 used with or without the need for this cleavable</p> <p>2 sequence."</p> <p>3 "Another embodiment," going further in</p> <p>4 Column 14, "involves fragmentation of DNA at</p> <p>5 defined regions, for example by treatment of DNA</p> <p>6 with a site-specific restriction endonuclease or a</p> <p>7 mixture of such endonucleases," and it goes on.</p> <p>8 So "shearing" here, in Guardant's proposed</p> <p>9 construction, was referring to the process</p> <p>10 described in the examples. One skilled in the art</p> <p>11 would understand that there are other methods.</p> <p>12 "Fragmentation" might be a better term.</p> <p>13 But even our discussion here really underscores</p> <p>14 the fact that there's no plain and ordinary</p> <p>15 meaning to "fragment ends." Right? Even the</p> <p>16 patent itself lists out a number of ways in which</p> <p>17 those fragments can be prepared.</p> <p>18 And one must fragment the DNA, ligate on</p> <p>19 the adapters, sequence, and then trim the</p> <p>20 exogenous sequence in order to be able to identify</p> <p>21 and use those fragment ends.</p> <p>22 Q. Okay. I'm not quite sure I follow. So</p>	<p>1 A. I believe that's what I said. Yes.</p> <p>2 Q. And so when you said that, I understand</p> <p>3 that you mean that the proposed construction is</p> <p>4 intended to encompass those examples. Right?</p> <p>5 MS. SCORDINO: Objection to form.</p> <p>6 A. I'm not exactly sure what you mean. I</p> <p>7 don't have the benefit of seeing --</p> <p>8 Q. Okay. Earlier you said that the</p> <p>9 "shearing" term in Guardant's proposed</p> <p>10 construction is referring to the processes</p> <p>11 described in the examples. Correct?</p> <p>12 A. I'll take your word for that's what I</p> <p>13 said.</p> <p>14 Q. The examples you were referring to were</p> <p>15 those in the University of Washington patents.</p> <p>16 Right?</p> <p>17 A. The '631 patent and the other patents in</p> <p>18 the same family. Yes.</p> <p>19 Q. Very good. And you have made mention of</p> <p>20 restriction enzymes as a way to generate a</p> <p>21 fragment. Correct?</p> <p>22 A. Restriction enzymes and other methods are</p>

15 (Pages 57 to 60)

Page 61	Page 63
<p>1 actually listed in Columns 13 and 14 as other ways 2 of generating fragments to which the SMI adapters 3 are attached.</p> <p>4 Q. Okay. Great. And what I want to 5 understand is, in your view, in that proposed 6 Guardant construction for shearing, does it 7 include within it the use of restriction enzymes?</p> <p>8 MS. SCORDINO: Objection to form.</p> <p>9 A. So I think that was your previous 10 question. And as I told you earlier, in looking 11 at this and this construction, the fragment 12 ends . . .</p> <p>13 Fragment ends are the ends of the sequence 14 at the ends of DNA fragments that are generated 15 using a variety or described in a variety of 16 different examples.</p> <p>17 So earlier we talked about Example 1, 18 which has genomic DNA isolated from normal human 19 colonic mucosa. And it's subsequently sheared on 20 the Covaris A system, which we described earlier 21 as being a system that uses sonication to fragment 22 DNA to particular sizes.</p>	<p>1 the M13 DNA was isolated and then digested.</p> <p>2 So I was incorrect earlier when I said 3 that the only examples that were described, the 4 only DNA fragment methods that were described in 5 the patent itself used shearing.</p> <p>6 But the only human example described in 7 the patent both used genomic DNA or genomic DNA 8 and mitochondrial DNA that was sheared using the 9 Covaris system.</p> <p>10 So "shearing" here really does refer to 11 that process of fragmentation. As I said, it's 12 the one which is most commonly used. The patent 13 does allow other methods to be used for 14 fragmentation.</p> <p>15 But fragmentation, whether it's shearing 16 or any other approach, in fact is necessary to 17 create these fragment ends.</p> <p>18 And if one looks at all the examples of 19 SMI adapters attached to DNA -- to human DNA, 20 those involve this TA ligation which revolves -- 21 involves shearing and T-tailing. And that's 22 actually what's shown in Figure 1.</p>
Page 62	Page 64
<p>1 Example 2 talks about "Duplex Sequencing 2 of Human Mitochondrial DNA."</p> <p>3 And in Column 24, line 35, "Mitochondrial 4 DNA was isolated as previously described." And 5 then it goes on to talk about data processing.</p> <p>6 So I'm assuming it was isolated and 7 sequenced as previously described because we're 8 not given any other definition.</p> <p>9 This would indicate that the Covaris 10 method was used to shear the mitochondrial DNA.</p> <p>11 In "Example 3: Demonstration of 12 Error-Correction" -- and this is in Column 25 -- 13 "of Error-Correction by DCS Using Randomly Sheared 14 DNA Ends as Single Molecule Identifiers."</p> <p>15 And again, they tell us genomic DNA was 16 isolated in this case from yeast and then sheared 17 by the Covaris AFA system.</p> <p>18 Example 4 is even sort of a more -- an 19 example not using the duplex consensus sequencing 20 but single-stranded consensus sequencing.</p> <p>21 And here, it's an analysis of a virus that 22 infects E. coli, called M13. And in this case,</p>	<p>1 Q. Thank you. A moment ago you talked about 2 Example 4. You said the M13 DNA was digested. Do 3 you remember that?</p> <p>4 A. Okay.</p> <p>5 Q. There was mention of complete digestion at 6 about line 47. Do you see that?</p> <p>7 A. Yes, I do.</p> <p>8 Q. What do you understand that to refer to?</p> <p>9 A. So as I mentioned earlier, M13 is a virus 10 that infects E. coli. So E. coli is bacteria. 11 The way a virus works is it attaches to the outer 12 surface of the cell and injects its genetic 13 material into the cell.</p> <p>14 M13's genome, if I recall, is about 1,100 15 bases long as opposed to the human genome, which 16 is 3 billion bases long.</p> <p>17 So the human genome is about 30 million 18 times the size of the M13 genome. In this case, 19 this is an example that demonstrates something 20 called single-stranded consensus sequencing.</p> <p>21 And what they tell us is, "To allow for 22 greater sequencing depth in a defined region of</p>

16 (Pages 61 to 64)

Page 65	Page 67
<p>1 the M13Mp2 genome, an 840-bp fragment was enriched</p> <p>2 by complete digestion with the restriction enzymes</p> <p>3 Bsu361 and NaeI" from "(New England Biolabs)."</p> <p>4 So what restriction enzymes do -- and</p> <p>5 there are a variety of different types of</p> <p>6 restriction enzymes, but the easiest way to</p> <p>7 describe what they do is, they recognize a</p> <p>8 particular DNA sequence and they cut that DNA.</p> <p>9 So it's sort of interesting, these</p> <p>10 restriction enzymes, in many ways they're isolated</p> <p>11 from bacteria and they're kind of a viral immune</p> <p>12 defense against -- bacterial immune defense</p> <p>13 against viral infection.</p> <p>14 So these two enzymes, Bsu361 and NaeI, cut</p> <p>15 DNA in a particular, specific sequence-based</p> <p>16 location.</p> <p>17 So Bsu is from Bacillus subtilis, not</p> <p>18 E. coli. NaeI, I'm not sure where it's from. I</p> <p>19 don't know what restriction sites they recognize,</p> <p>20 but we could look those up in the NEB catalog.</p> <p>21 But what they're going to do is they're</p> <p>22 going to cut the DNA. It's going to create an</p>	<p>1 Q. Why don't we stay with Example 4. Do you</p> <p>2 agree it describes enzymatic digestion?</p> <p>3 A. It describes the use of duplex -- it says</p> <p>4 "Demonstrations of Duplex Consensus Sequencing,"</p> <p>5 so it describes duplex consensus sequencing as an</p> <p>6 intermediate step to enrich a fragment they wanted</p> <p>7 to study.</p> <p>8 It uses enzymatic digestion, but to</p> <p>9 perform the DCS and ligate on the adaptors, it</p> <p>10 actually uses shearing, as we discussed earlier.</p> <p>11 Q. Now, is shearing, as you've just used it a</p> <p>12 moment ago, is that distinct from or inclusive of</p> <p>13 the use of an enzyme to cleave a nucleic acid?</p> <p>14 A. So the DNA was first digested -- and</p> <p>15 again, I can't tell you exactly what happened</p> <p>16 without knowing fully what these enzymes, what</p> <p>17 their restriction sites are. They're not</p> <p>18 specified in the patent.</p> <p>19 There are thousands of restriction</p> <p>20 enzymes, and I don't know them all. We can look</p> <p>21 them up in the NEB catalog, if you'd like.</p> <p>22 But the DNA was digested, as they tell us,</p>
Page 66	Page 68
<p>1 840-base-pair fragment. I don't know what else</p> <p>2 it's going to create. But -- ah. Okay. Here we</p> <p>3 go.</p> <p>4 This substrate, it's the M13mp2 DNA --</p> <p>5 (Interruption)</p> <p>6 A. I missed "sheared" earlier. It was</p> <p>7 actually first digested completely. But then if</p> <p>8 we go down to line 55, 56, 57, 58, the "DNA was</p> <p>9 sheared and ligated" onto "adaptors."</p> <p>10 So the DNA was first digested completely.</p> <p>11 And then I misspoke earlier, it was actually</p> <p>12 sheared as well. So all four examples that they</p> <p>13 use to do the ligation involved shearing.</p> <p>14 So if we look to the examples, shearing is</p> <p>15 actually the way in which the DNA fragments for</p> <p>16 DCS are prepared.</p> <p>17 Q. So what does "enzymatic digestion" mean in</p> <p>18 the context of the '631 patent?</p> <p>19 MS. SCORDINO: Objection. Outside the</p> <p>20 scope.</p> <p>21 A. Could you point me to a specific example</p> <p>22 and we can talk about that example?</p>	<p>1 to enrich for a particular 840-base-pair fragment.</p> <p>2 But before DCS was used and the adaptors were</p> <p>3 ligated, the DNA was sheared.</p> <p>4 So in this case, the enzymatic digestion</p> <p>5 is a pre-DCS purification step.</p> <p>6 Q. All right. Let's turn back to that table</p> <p>7 just before Paragraph 64 in your declaration.</p> <p>8 A. Sure. I'm here. It's been open.</p> <p>9 Q. Okay. And so I want to focus on that</p> <p>10 phrase "after shearing and trimming."</p> <p>11 It's your view that both shearing and</p> <p>12 trimming must occur before a fragment end can be</p> <p>13 generated, within the meaning of the claim term.</p> <p>14 Correct?</p> <p>15 MS. SCORDINO: Objection to form.</p> <p>16 A. So the question, if I can put this in a</p> <p>17 way that's really easy to understand, if I were to</p> <p>18 tell you that you were reading "To Kill a Mocking</p> <p>19 Bird." Right? And I said we're going to look at</p> <p>20 the end of Chapter 3. Okay?</p> <p>21 To look at the end of Chapter 3 and use</p> <p>22 that in some way, Harper Lee would first have to</p>

17 (Pages 65 to 68)

<p style="text-align: right;">Page 69</p> <p>1 write it and then you would have to read it.</p> <p>2 Because without Harper Lee writing the book and</p> <p>3 without you reading the book, although the end of</p> <p>4 Chapter 3 exists, it has no practical use to you.</p> <p>5 Right?</p> <p>6 So DNA fragments exist, but for those DNA</p> <p>7 fragment ends to be identified and used, they</p> <p>8 first have to be prepared, just like Harper Lee</p> <p>9 had to write "To Kill a Mocking Bird," and you</p> <p>10 have to read them and identify the end of the</p> <p>11 chapter. It's not going to be the whole chapter.</p> <p>12 It's going to be a piece of that chapter.</p> <p>13 And so if we're talking about the fragment</p> <p>14 ends in the context of how Claim 1 described their</p> <p>15 use, they first have to be prepared, which</p> <p>16 involves shearing, ligation, and sequencing, and</p> <p>17 then trimming that sequence to identify.</p> <p>18 Not all of Chapter 3, not part of</p> <p>19 Chapter 3 and Chapter 4. The end of Chapter 3.</p> <p>20 Right?</p> <p>21 So in context, fragment ends require,</p> <p>22 necessitate the shearing and trimming, as set</p>	<p style="text-align: right;">Page 71</p> <p>1 to read the chapter.</p> <p>2 So shearing is, you know, part of the</p> <p>3 process of preparing those fragments and getting</p> <p>4 them so you can read the ends. And trimming is</p> <p>5 the process of narrowing down what you're going to</p> <p>6 use and really identifying those ends.</p> <p>7 Q. Okay. And I do want to get to, like, what</p> <p>8 each of those things mean.</p> <p>9 But as a threshold question, I just want</p> <p>10 to know, in your mind they mean different things,</p> <p>11 "shearing" versus "trimming." Correct?</p> <p>12 A. Shearing is part of the process of</p> <p>13 preparing the libraries for sequencing or the DNA</p> <p>14 fragments for sequencing. And trimming is part of</p> <p>15 the process of analyzing the resulting data.</p> <p>16 Q. Great. Now I want to dive into each of</p> <p>17 those terms. I do want to be transparent so you</p> <p>18 don't have to tell me everything in one fell</p> <p>19 swoop, if you will.</p> <p>20 A moment ago you said that shearing is the</p> <p>21 physical fragmenting of the nucleic acid. Right?</p> <p>22 A. I'll take your word for it.</p>
<p style="text-align: right;">Page 70</p> <p>1 forth in Guardant's construction.</p> <p>2 Q. Great. And thank you for that colorful</p> <p>3 example. All right.</p> <p>4 So with that in mind, can you tell me what</p> <p>5 is different between the trimming and the shearing</p> <p>6 as proposed here in this table?</p> <p>7 A. So shearing is the process, as we talked</p> <p>8 about earlier, of physically fragmenting the DNA.</p> <p>9 And all four examples in the '631 patent and all</p> <p>10 the other patents from the University of</p> <p>11 Washington involve the shearing step.</p> <p>12 Adapters are ligated. These adapters are</p> <p>13 designed specifically for use with the Illumina</p> <p>14 sequencer. They contain these SMI tags, single</p> <p>15 molecule identifier tags. And sequence is</p> <p>16 generated.</p> <p>17 And before the fragment end can be</p> <p>18 identified and used, one has to trim off the</p> <p>19 adapter sequence and trim the end, as many</p> <p>20 nucleotides at the end as one is going to use.</p> <p>21 In the same way, to use the end of</p> <p>22 Chapter 3 in "To Kill a Mocking Bird," you've got</p>	<p style="text-align: right;">Page 72</p> <p>1 Q. That's a fair summary of what shearing is?</p> <p>2 A. Shearing is a process for fragmenting DNA.</p> <p>3 I can tell you we've used other physical</p> <p>4 processes, like pushing DNA in solution through</p> <p>5 fine-gauge needles. But shearing is one process</p> <p>6 that you can use for fragmenting DNA.</p> <p>7 Q. What I want to understand is the various</p> <p>8 ways one can shear DNA. And so you can do it</p> <p>9 enzymatically. Is that right?</p> <p>10 A. I wouldn't describe enzymatic DNA --</p> <p>11 enzymatic -- I don't think one skilled in the art</p> <p>12 would necessarily describe enzymatic digestion as</p> <p>13 shearing.</p> <p>14 But the four examples given in the patent</p> <p>15 all involve shearing with the Covaris instrument.</p> <p>16 Q. You kind of tailed off there on the</p> <p>17 answer. Shearing with what?</p> <p>18 A. I believe they all involve shearing with</p> <p>19 the Covaris instrument.</p> <p>20 Q. And the Covaris instrument is that</p> <p>21 sonication device that pulsates the sample with</p> <p>22 ultrasound to break up the DNA?</p>

<p style="text-align: right;">Page 73</p> <p>1 A. Essentially that's how the Covaris device</p> <p>2 works.</p> <p>3 Q. Okay.</p> <p>4 A. I think it's still manufactured. I'm</p> <p>5 pretty sure it is.</p> <p>6 Q. All right. So I think given that, you</p> <p>7 agree that as proposed here in Guardant's</p> <p>8 construction of fragment ends, the use of the</p> <p>9 Covaris device or other ultrasound approaches</p> <p>10 would be a type of shearing. Correct?</p> <p>11 A. The use of the Covaris device would be a</p> <p>12 type of shearing of DNA to prepare it for adapter</p> <p>13 ligation sequencing.</p> <p>14 Q. Okay. Great. I'd like to understand if</p> <p>15 one fragmented DNA using an enzyme, restriction</p> <p>16 enzyme or otherwise, would that qualify as</p> <p>17 shearing, within the Guardant proposed</p> <p>18 construction?</p> <p>19 MS. SCORDINO: Objection to form.</p> <p>20 A. So the only examples that I can give or</p> <p>21 the only examples that University of Washington</p> <p>22 gives do involve shearing using the Covaris</p>	<p style="text-align: right;">Page 75</p> <p>1 past each other a little bit.</p> <p>2 What I'm trying to get at is, let's assume</p> <p>3 the court agrees with your opinion that shearing</p> <p>4 and trimming are necessary steps in order to</p> <p>5 generate the claimed fragmented ends.</p> <p>6 What I want to understand is, what does</p> <p>7 "shearing" mean? And I think we've established</p> <p>8 that it includes this sonication device --</p> <p>9 A. Covaris.</p> <p>10 Q. Okay. And so I have a simple question;</p> <p>11 and that is, does it also encompass the use of</p> <p>12 enzymes that would cleave or fragment a nucleic</p> <p>13 acid?</p> <p>14 A. So that's a very complex question which I</p> <p>15 believe would require a legal conclusion.</p> <p>16 From -- as you've mentioned, I've worked</p> <p>17 as an expert before and I understand there's</p> <p>18 something called the doctrine of equivalents, that</p> <p>19 one would have to look at prior literature, look</p> <p>20 at how "shearing" is used ultimately in the</p> <p>21 context of preparing these libraries, look at</p> <p>22 whether or not those other methods could be</p>
<p style="text-align: right;">Page 74</p> <p>1 instrument.</p> <p>2 The thing that I think is really important</p> <p>3 here is that -- and this is really underscored by</p> <p>4 your question -- that even if -- you said, well,</p> <p>5 this shouldn't be limited to shearing, we should</p> <p>6 include other methods -- that the TwinStrand</p> <p>7 position that "fragments ends" has a plain and</p> <p>8 ordinary meaning is absolutely absurd.</p> <p>9 Because if we have to prepare the DNA and</p> <p>10 we have to ligate on adapters and we don't use the</p> <p>11 methods which TwinStrand describes in the</p> <p>12 specification but choose some other method, then</p> <p>13 there are many possible ways of preparing these</p> <p>14 fragments, which means there's no plain and</p> <p>15 ordinary meaning.</p> <p>16 So while you may find fault with</p> <p>17 Guardant's proposed construction and you may say,</p> <p>18 well, there are other ways of fragmenting DNA,</p> <p>19 there's not a plain and ordinary meaning.</p> <p>20 And the only guidance we have in the</p> <p>21 specification is using the Covaris instrument.</p> <p>22 Q. Thank you for that. I think we're talking</p>	<p style="text-align: right;">Page 76</p> <p>1 considered equivalent.</p> <p>2 In fact, it would seem that, based on the</p> <p>3 disclosure of other possible methods for ligating</p> <p>4 on adapters, that one could consider those</p> <p>5 equivalent to shearing, based on University of</p> <p>6 Washington and TwinStrand's own patent language.</p> <p>7 So I couldn't tell you the breadth of what</p> <p>8 "shearing" would ultimately encompass if the court</p> <p>9 adopts this.</p> <p>10 But again, the fact that we're discussing</p> <p>11 this in such great depth really points at the</p> <p>12 absurdity of saying that there's a plain and</p> <p>13 ordinary meaning for this.</p> <p>14 Q. Let's set aside for the moment the</p> <p>15 doctrine of equivalents and let's just talk about</p> <p>16 what you think the literal meaning of "shearing"</p> <p>17 is. Can we do that for the purposes of the next</p> <p>18 question?</p> <p>19 A. I'll do my best. But again, we have to</p> <p>20 understand that all these terms are used in</p> <p>21 context. And they're in the context of the patent</p> <p>22 and its written description.</p>

<p style="text-align: right;">Page 77</p> <p>1 Q. Fair enough. And I want you to understand</p> <p>2 what I'm getting on about here.</p> <p>3 I happen to think it's very important that</p> <p>4 the court understand precisely what the dispute is</p> <p>5 between Guardant and my clients so that it can</p> <p>6 make a good decision. Maybe we win, maybe we</p> <p>7 lose.</p> <p>8 And I think in order to do that the court</p> <p>9 has to be fairly told what you mean or you</p> <p>10 understand by "shearing."</p> <p>11 And so the question that I'm going to put</p> <p>12 in front of the judge, and I'd like to know your</p> <p>13 answer, is, in your view as proposed by Guardant,</p> <p>14 does shearing include the use of enzymes to</p> <p>15 fragment nucleic acids?</p> <p>16 MS. SCORDINO: I object to the form.</p> <p>17 A. So again, I think you're asking me to</p> <p>18 arrive at a legal conclusion, which is beyond the</p> <p>19 scope of what I'm prepared to do today.</p> <p>20 In choosing the word "shearing" here</p> <p>21 specifically, my understanding is that Guardant</p> <p>22 was likely looking at the four examples laid out</p>	<p style="text-align: right;">Page 79</p> <p>1 MS. SCORDINO: Counsel, I find your</p> <p>2 pointing to be incredibly obstructive.</p> <p>3 MR. PICKARD: I disagree. The witness has</p> <p>4 not answered many of my questions.</p> <p>5 Q. Let me try this again.</p> <p>6 So earlier you mentioned what Guardant</p> <p>7 might intend. What I'm trying to get at is what</p> <p>8 you understand "shearing" to mean, as you've</p> <p>9 opined in your declaration.</p> <p>10 So this is the last time I'll ask it. In</p> <p>11 your opinion, does "shearing," as you've said,</p> <p>12 properly limits "fragment end," does it encompass</p> <p>13 the use of enzymes?</p> <p>14 A. So I believe I've answered that question</p> <p>15 multiple times. I'm happy to answer it again.</p> <p>16 TwinStrand has proposed that "fragment</p> <p>17 ends" has a plain and ordinary meaning.</p> <p>18 The fragment ends are -- and this is laid</p> <p>19 out in Claim 1 and in the four examples in the</p> <p>20 patent -- are not just random occurrences.</p> <p>21 They're actually the result of a fairly complex</p> <p>22 laboratory protocol that involves manipulation of</p>
<p style="text-align: right;">Page 78</p> <p>1 in the patent, and the only four examples laid out</p> <p>2 in the patent for attaching these adapters.</p> <p>3 And so in each one of those four, shearing</p> <p>4 is described using this Covaris instrument.</p> <p>5 As I mentioned earlier, there may be other</p> <p>6 ways of generating these DNA fragments. But</p> <p>7 fragmentation of the DNA is absolutely required.</p> <p>8 So what the breadth and scope of methods</p> <p>9 use to generate those fragments might ultimately</p> <p>10 be, I don't know.</p> <p>11 Q. Okay.</p> <p>12 A. But again, the fact that Guardant's</p> <p>13 proposed construction includes shearing and the</p> <p>14 fact that you're asking me about all the different</p> <p>15 ways of even preparing and attaching the adapters</p> <p>16 means that there is no simple plain and ordinary</p> <p>17 meaning to "fragment ends."</p> <p>18 Q. I understand that. Actually, I've only</p> <p>19 asked you about one way, and that's enzymatic, I</p> <p>20 think. We'll get to others. For right now, I</p> <p>21 think we can stipulate I've only asked you about</p> <p>22 enzymatic.</p>	<p style="text-align: right;">Page 80</p> <p>1 DNA and ultimately generation of sequence.</p> <p>2 The choice of the word "shearing" here, I</p> <p>3 believe, really reflects the fact that the four</p> <p>4 examples in the patent use shearing as a method of</p> <p>5 DNA fragmentation.</p> <p>6 And if we look at the wealth of examples,</p> <p>7 even Figure 1 shown in the patent, which is the</p> <p>8 only one which really involves the attachment of</p> <p>9 the SMI sequences -- I believe it's that one -- of</p> <p>10 the SMI sequences to the DNA fragments, this</p> <p>11 refers to DNA that has been sheared and T-tailed.</p> <p>12 I don't know ultimately if the use of the</p> <p>13 word "shearing" would exclude other methods that</p> <p>14 may be equivalent. But shearing is the only</p> <p>15 method which the University of Washington and</p> <p>16 TwinStrand actually teach in the examples in the</p> <p>17 '631 patent.</p> <p>18 Q. Let's talk about trimming. What does</p> <p>19 "trimming" mean, as you understand it, in the --</p> <p>20 what you say is the correct construction of</p> <p>21 "fragment ends"?</p> <p>22 A. Sure. Conceptually, I think the example I</p>

<p style="text-align: right;">Page 81</p> <p>1 gave earlier of the end of Chapter 3 in "To Kill a</p> <p>2 Mocking Bird" is a really good analogy to this.</p> <p>3 If I were to read from the -- from</p> <p>4 somewhere near the end of Chapter 3 into the -- I</p> <p>5 think the end of Chapter 3. If I were to begin</p> <p>6 reading somewhere in Chapter 3 through the end and</p> <p>7 into Chapter 4 and then ask you to identify the</p> <p>8 end of Chapter 3, what you would have to do in</p> <p>9 identifying that end is exclude or trim off the</p> <p>10 part of the book that includes Chapter 4.</p> <p>11 So I'd start where Chapter 3 ends. I'd</p> <p>12 see Chapter 4. I'd stop.</p> <p>13 Q. And so let's say -- sorry.</p> <p>14 A. Okay. So you asked me about trimming in</p> <p>15 this context. If I were to read DNA sequence and</p> <p>16 I want to use the fragment ends, I have to know in</p> <p>17 my DNA sequence which comes off of the instrument</p> <p>18 where chapter -- the end of Chapter 3 is or where</p> <p>19 the end of the fragment is.</p> <p>20 So I need to know ahead of time that</p> <p>21 there's some demarcation which is the adapter</p> <p>22 sequence. So I'm going to look at the sequence.</p>	<p style="text-align: right;">Page 83</p> <p>1 fragment ends is essential.</p> <p>2 Q. I understand it's essential. I understand</p> <p>3 it's part of the process.</p> <p>4 What I want to know is, in order to trim,</p> <p>5 do you have to physically alter a nucleic acid?</p> <p>6 A. In order to trim, you have to sequence.</p> <p>7 In order to sequence, you need in this case --</p> <p>8 there are other ways to sequence it, but we need</p> <p>9 to ligate on adapters. In order to ligate on</p> <p>10 adapters, we need to fragment, to shear.</p> <p>11 So, you know, could I read "To Kill a</p> <p>12 Mocking Bird" if Harper Lee hadn't written it?</p> <p>13 No. Is reading intrinsically -- does reading</p> <p>14 intrinsically involve the fact that Harper Lee</p> <p>15 wrote "To Kill a Mocking Bird"? No.</p> <p>16 I could read another book. But all of</p> <p>17 these things are used together in context.</p> <p>18 So in this case, in order to use the</p> <p>19 fragment ends, they had to at one point have been</p> <p>20 sheared from larger pieces of DNA.</p> <p>21 Q. Okay. So that mentions shearing. My</p> <p>22 questions are about trimming. So if we stay with</p>
<p style="text-align: right;">Page 82</p> <p>1 I'm going to identify the adapter sequence.</p> <p>2 And to find the end of the fragment, just</p> <p>3 like when I find Chapter 4, I stop. When I find</p> <p>4 the last nucleotide in the adapter in any cloning</p> <p>5 artifacts in my cloning strategy, I stop.</p> <p>6 And that's how I begin the process of</p> <p>7 identifying the fragment end. So trimming off the</p> <p>8 exogenous, the external sequence as part of my</p> <p>9 laboratory protocol, that's what trimming</p> <p>10 encompasses.</p> <p>11 Q. Okay. So when we talk about shearing,</p> <p>12 that's a physical alteration of the nucleic acid</p> <p>13 itself. Right?</p> <p>14 A. Shearing physically alters the original</p> <p>15 nucleic acid molecules.</p> <p>16 Q. As you used "trimming" in your</p> <p>17 declaration, does trimming involve any physical</p> <p>18 alteration of the -- of a nucleic acid?</p> <p>19 A. Trimming is part of the sequence analysis</p> <p>20 process. But remember, use of these fragment ends</p> <p>21 is really use of the sequence of these fragment</p> <p>22 ends. So trimming the sequence to identify the</p>	<p style="text-align: right;">Page 84</p> <p>1 your Harper Lee example -- we're focused again on</p> <p>2 Chapter 3.</p> <p>3 A. Chapter 3.</p> <p>4 Q. This trimming analogy you're trying to</p> <p>5 use, does one literally excise the physical book</p> <p>6 contents after Chapter 3 and just before the end</p> <p>7 of Chapter 3 and they're left with the end of</p> <p>8 Chapter 3 physically, or is it simply the mental</p> <p>9 act of just, like, I'm going to focus on the end</p> <p>10 of this chapter, it being 3?</p> <p>11 A. It would depend on how you wanted to use</p> <p>12 that. And so context matters. Right? You could</p> <p>13 identify the end of Chapter 3 by taking a pair of</p> <p>14 scissors and cutting out the last few sentences or</p> <p>15 the last few words.</p> <p>16 In this case, trimming requires that you</p> <p>17 have sequence. Sequencing requires that -- in the</p> <p>18 examples here, using the Illumina or other</p> <p>19 equivalent sequencing instruments, all of those</p> <p>20 instruments require specific adapters to be</p> <p>21 ligated on at some point or specific adapters to</p> <p>22 be attached. And there are other ways of</p>

<p style="text-align: right;">Page 85</p> <p>1 attaching those adapters.</p> <p>2 So the trimming as part of exercising that</p> <p>3 act requires -- is predicated on all the other</p> <p>4 steps that go before.</p> <p>5 So once I have the sequence on the</p> <p>6 computer, do I physically have to reach in and</p> <p>7 alter the electrons? No. But in order to get</p> <p>8 that sequence on the computer, I did have to</p> <p>9 shear; I did have to do other things in the lab.</p> <p>10 So the actual act of trimming is done</p> <p>11 computationally. When I first started doing DNA</p> <p>12 sequencing in the early 1990s, people would</p> <p>13 actually print out the sequence and physically</p> <p>14 circle them. And you'd find the equivalent of the</p> <p>15 adapter sequence and X it out in your DNA</p> <p>16 sequence.</p> <p>17 Now we do it computationally. One</p> <p>18 physical, the other not. It's not a physical</p> <p>19 alteration of the molecule, but it is a necessary</p> <p>20 step for using the data derived from that</p> <p>21 molecule.</p> <p>22 And ultimately it's the data derived from</p>	<p style="text-align: right;">Page 87</p> <p>1 processing to identify the fragment ends, but it's</p> <p>2 predicated on all the steps that occur previously.</p> <p>3 If I had chosen, I can't do trimming in a</p> <p>4 vacuum. If I don't know what my adapter sequences</p> <p>5 are, then I don't know where to trim. Right?</p> <p>6 So it doesn't -- I mean, the actual</p> <p>7 trimming step is computational, but trimming</p> <p>8 doesn't happen in a vacuum.</p> <p>9 Q. Okay.</p> <p>10 MR. PICKARD: Why don't we take another</p> <p>11 break for a few minutes.</p> <p>12 THE VIDEOGRAPHER: The time is 11:12.</p> <p>13 We're off the record.</p> <p>14 (Reccss from 11:12 a.m. to 11:28 a.m.)</p> <p>15 THE VIDEOGRAPHER: We are back on the</p> <p>16 record. The time is 11:28.</p> <p>17 BY MR. PICKARD:</p> <p>18 Q. All right. So, Dr. Quackenbush, just to</p> <p>19 get level set, I think earlier we talked about at</p> <p>20 a high level the structure of a nucleic acid</p> <p>21 fragment. And I think we agree that it has a</p> <p>22 sugar phosphate backbone and a sequence of</p>
<p style="text-align: right;">Page 86</p> <p>1 those molecules which is used in everything else.</p> <p>2 Q. I think you did get to an answer. So</p> <p>3 trimming is not physical alteration of the</p> <p>4 molecule. Right?</p> <p>5 A. Trimming itself does not physically alter</p> <p>6 the molecule, but the molecule had to be</p> <p>7 physically altered in order for us to get to the</p> <p>8 stage where we trimmed.</p> <p>9 Q. Right. And that physical alteration is</p> <p>10 referred to as "shearing," as you've defined the</p> <p>11 "fragment end" term. Right?</p> <p>12 A. In Guardant's claim construction, the</p> <p>13 proposed claim construction, the physical</p> <p>14 preparation involves shearing, other steps. And</p> <p>15 then once the sequence is generated, an analysis,</p> <p>16 which we refer to as trimming.</p> <p>17 Q. Great. So there's some biochemistry, some</p> <p>18 alteration to the nucleic acid, there's</p> <p>19 sequencing. And then trimming is a part of the</p> <p>20 analytical portion of these protocols. Right?</p> <p>21 MS. SCORDINO: Objection to form.</p> <p>22 A. So the trimming is part of the analytical</p>	<p style="text-align: right;">Page 88</p> <p>1 nucleotides and in some cases it may be</p> <p>2 double-stranded. Right?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. So if you have a fragment, then, I</p> <p>5 want to understand the different characteristics</p> <p>6 that you have.</p> <p>7 The given fragment is going to have some</p> <p>8 length, which is typically specified by the number</p> <p>9 of nucleotides that it contains. Right? Like</p> <p>10 base pairs?</p> <p>11 A. One could count the number of nucleotides</p> <p>12 in a DNA fragment. Yes.</p> <p>13 Q. And those nucleotides may have a</p> <p>14 particular sequence. Right?</p> <p>15 A. Yes. And that's typically the goal of</p> <p>16 this kind of analysis is to trim the sequence of</p> <p>17 those nucleotides.</p> <p>18 Q. What other physical characteristics would</p> <p>19 a fragment have, a given fragment? You've got</p> <p>20 length, sequence of the nucleotides. Can you</p> <p>21 think of anything else?</p> <p>22 MS. SCORDINO: Objection to form.</p>

22 (Pages 85 to 88)

<p style="text-align: right;">Page 89</p> <p>1 A. So in the abstract, a DNA molecule could</p> <p>2 have all sorts of different characteristics. One</p> <p>3 could measure the molecular weight. One could</p> <p>4 measure the three-dimensional structure. One</p> <p>5 could look to see whether or not the nucleic acid</p> <p>6 itself included modifications such as methylation.</p> <p>7 One could, with a synthetic nucleic acid,</p> <p>8 include nonnatural bases like inosine. One could</p> <p>9 talk about the coding potential of the nucleic</p> <p>10 acid. One could talk about the length in microns</p> <p>11 or nanometers or whatever the appropriate length</p> <p>12 scale might be.</p> <p>13 One could compare molecular weight to</p> <p>14 other nucleic acids with the same sequence to</p> <p>15 determine if a particular isotope had been</p> <p>16 incorporated in, which might indicate the age of</p> <p>17 the nucleic acid for ancient DNA samples.</p> <p>18 There are all sorts of things in the</p> <p>19 abstract that one could, in fact, use or measure</p> <p>20 on a particular nucleic acid.</p> <p>21 Q. All right. Well, let's talk a little bit,</p> <p>22 you said its length in microns versus length in</p>	<p style="text-align: right;">Page 91</p> <p>1 Q. Okay. But the choice of microns or</p> <p>2 nanometers or kilobase pairs, those are just</p> <p>3 different units of measurement. Right? All</p> <p>4 relating to length?</p> <p>5 A. Well, not quite. How one determines</p> <p>6 length is going to be -- is going to depend on the</p> <p>7 pH of the solution in which the DNA molecule</p> <p>8 exists, whether it's in its natural conformation,</p> <p>9 whether or not it's single-stranded and it's</p> <p>10 folded back and hybridized on itself.</p> <p>11 In the case of the example I gave you,</p> <p>12 with David Schwartz doing optical mapping, when</p> <p>13 the DNA was on the surface, it had a particular</p> <p>14 length. When it was cut with restriction enzymes,</p> <p>15 pieces actually recoiled and shrunk so they could</p> <p>16 identify where those restriction enzymes are.</p> <p>17 So we could characterize the length of the</p> <p>18 DNA fragment in part based on its length, based on</p> <p>19 the number of bases and nucleotides, or in base</p> <p>20 pairs if it's double-stranded, or under the</p> <p>21 appropriate laboratory conditions in distance --</p> <p>22 physical distance units, like microns or</p>
<p style="text-align: right;">Page 90</p> <p>1 nanometers, that that's a possible feature?</p> <p>2 A. You could measure lots of things in a DNA</p> <p>3 molecule.</p> <p>4 Q. Those are two that you mentioned? That's</p> <p>5 my question.</p> <p>6 A. So a friend of mine, David Schwartz, when</p> <p>7 he was at the University of Wisconsin -- was it</p> <p>8 University of Wisconsin? -- he developed a method</p> <p>9 to basically lay nucleic acids down on a glass</p> <p>10 substrate and would actually measure their</p> <p>11 physical length under a microscope.</p> <p>12 And then he would add restriction enzymes</p> <p>13 which would cut it, and he used it for a technique</p> <p>14 called "optical mapping."</p> <p>15 So you could measure lots of things</p> <p>16 without a piece of DNA.</p> <p>17 Q. My question was, two of the things you</p> <p>18 mentioned in your previous answer was length in</p> <p>19 microns and length in nanometers. Right?</p> <p>20 A. I believe that was among the many things I</p> <p>21 mentioned as physical characteristics which could</p> <p>22 be measured in the abstract for a piece of DNA.</p>	<p style="text-align: right;">Page 92</p> <p>1 nanometers.</p> <p>2 Q. And you also mentioned, I think, atomic or</p> <p>3 molecular weight of a given fragment. Right?</p> <p>4 A. You could measure the molecular weight.</p> <p>5 There are many things you could do in the</p> <p>6 abstract.</p> <p>7 Q. And that would be a direct function of the</p> <p>8 overall length of a given fragment. Right?</p> <p>9 A. Not necessarily. You could imagine a</p> <p>10 situation in which particular isotopes were</p> <p>11 present at the time in which the nucleoside bases</p> <p>12 were formed and it might change the weight of that</p> <p>13 nucleic acid.</p> <p>14 Q. All right. In Paragraph 91 of your</p> <p>15 declaration -- let me know when you're there.</p> <p>16 A. Yes. I'm here.</p> <p>17 Q. And you mentioned "specific nucleotide</p> <p>18 pattern." Do you see that?</p> <p>19 A. I'm sorry. In Paragraph 91?</p> <p>20 Q. Yes. The second sentence.</p> <p>21 A. Yes, I do.</p> <p>22 Q. Okay. Is that in any way different from</p>

23 (Pages 89 to 92)

<p style="text-align: right;">Page 93</p> <p>1 the nucleotide sequence, that phrase?</p> <p>2 A. I think here I'm using it to refer to the</p> <p>3 nucleotide sequence. Yes.</p> <p>4 Q. All right. And then you also wrote</p> <p>5 "overall nucleotide composition." What did you</p> <p>6 refer to when you wrote that?</p> <p>7 A. So one of the things that we often use to</p> <p>8 characterize DNA is its overall composition. And</p> <p>9 we tend to refer to it -- we tend to talk about</p> <p>10 double-stranded DNA. And we tend -- and since</p> <p>11 this is duplex consensus sequencing, that's</p> <p>12 probably the most sensible way to refer to the DNA</p> <p>13 in this instance.</p> <p>14 If we're looking to characterize DNA, we</p> <p>15 talk about the AT or GC content. Typically it's</p> <p>16 referred to as GC as a percentage because any base</p> <p>17 which is not a G or a C is going to be an A or a</p> <p>18 T. And the reason we group GC together is because</p> <p>19 G and C are complementary bases.</p> <p>20 So in characterizing different genomes, we</p> <p>21 often talk about the AT or the GC content, and</p> <p>22 that's actually important.</p>	<p style="text-align: right;">Page 95</p> <p>1 modification" in the next portion there. And then</p> <p>2 in your earlier answer, you gave an example of</p> <p>3 methylation. Is that right?</p> <p>4 A. Yes.</p> <p>5 Q. And methylation is what you would call a</p> <p>6 type of nucleotide modification?</p> <p>7 A. It's really not a nucleotide modification.</p> <p>8 Q. Let's set that aside.</p> <p>9 What's a nucleotide modification?</p> <p>10 A. So nucleotides can actually be changed</p> <p>11 through a variety of laboratory processes. They</p> <p>12 can sometimes mimic mutation.</p> <p>13 So we refer to purines and pyrimidines</p> <p>14 when talking about nucleic acids, and As and Gs</p> <p>15 are purines and Cs and Gs are pyrimidines.</p> <p>16 The purines and pyrimidines are</p> <p>17 distinguished by the number of rings in their</p> <p>18 specific structure, the number of aromatic</p> <p>19 hydrocarbon rings.</p> <p>20 And there are changes called -- there's</p> <p>21 transversions in which -- I forget. I have to</p> <p>22 look it up. But there are changes that occur that</p>
<p style="text-align: right;">Page 94</p> <p>1 It's important for molecular biology for</p> <p>2 DNA sequence analysis. So as an example,</p> <p>3 Plasmodium falciparum, which is the organism which</p> <p>4 causes malaria, or one of the organisms which</p> <p>5 causes malaria, has a very AT-rich genome. And</p> <p>6 that presents a whole bunch of laboratory problems</p> <p>7 when sequencing its genome. It also influences</p> <p>8 its -- a number of biological processes in its</p> <p>9 interaction with the human immune system.</p> <p>10 So GC content or overall nucleotide</p> <p>11 composition is something we can refer to.</p> <p>12 Q. Okay. So staying with the example of the</p> <p>13 GC content, if one knew the nucleotide sequence of</p> <p>14 a given fragment, then it's easy to determine the</p> <p>15 GC content from that information. Right?</p> <p>16 MS. SCORDINO: Objection to form.</p> <p>17 A. One could potentially -- well, I guess if</p> <p>18 one knew the entire nucleic acid sequence and if</p> <p>19 one knew the -- if one knew whether a single or</p> <p>20 double -- single- or double-stranded, yes, one can</p> <p>21 calculate the GC content.</p> <p>22 Q. All right. You mentioned "nucleotide</p>	<p style="text-align: right;">Page 96</p> <p>1 can turn an A to a G or back and forth, which</p> <p>2 would be a particular nucleotide modification.</p> <p>3 But the nucleotides themselves can be</p> <p>4 potentially modified in a variety of different</p> <p>5 ways. And there are nonsequenced changing</p> <p>6 modifications that can occur to DNA too, such as</p> <p>7 DNA methylation.</p> <p>8 Q. Let's stay with this example that you just</p> <p>9 mentioned, where you turn an A to a G. When that</p> <p>10 happens, the sequence of a given fragment has</p> <p>11 changed. Right?</p> <p>12 A. The sequence of that fragment has changed.</p> <p>13 But when you're referring to transversions or --</p> <p>14 transversions or transitions, they occur in</p> <p>15 context.</p> <p>16 And it may occur in the laboratory. It</p> <p>17 may not occur at a particular -- it may not occur</p> <p>18 at a particular -- it may not occur in the cell</p> <p>19 itself. It may occur in the laboratory. And</p> <p>20 understanding whether or not those transversions</p> <p>21 have occurred is important.</p> <p>22 And then again, we have other types of</p>

<p style="text-align: right;">Page 97</p> <p>1 changes, like DNA methylation, which don't change</p> <p>2 the base sequence but actually really represent</p> <p>3 important changes, biologically important changes</p> <p>4 that can characterize the stretch of DNA.</p> <p>5 Q. So let's stay on the transversion. We'll</p> <p>6 come to methylation in a moment.</p> <p>7 When a transversion has occurred, whatever</p> <p>8 the cause, there is a change in the sequence of</p> <p>9 the fragment. Right?</p> <p>10 A. If it's occurred in the germline, there</p> <p>11 may or may not be a change in the -- not in the</p> <p>12 germline.</p> <p>13 If it's occurred in the cell, there are</p> <p>14 error-correcting mechanisms in the cell which may</p> <p>15 change the nucleic acid on the other strand.</p> <p>16 If it's occurred in the laboratory, the</p> <p>17 sequence itself would only -- the change would</p> <p>18 only be reflected on one strand or only</p> <p>19 potentially on some molecules in that strand.</p> <p>20 Q. I guess I'm trying to understand, there is</p> <p>21 a scenario in which this transversion happens but</p> <p>22 the cell corrects it. Right? That's what you</p>	<p style="text-align: right;">Page 99</p> <p>1 for DNA fragments. And that would be a property</p> <p>2 of DNA fragments.</p> <p>3 If one chose a particular laboratory</p> <p>4 protocol, one could mask that. If one chose an</p> <p>5 appropriate protocol, one could detect that. And</p> <p>6 that would be an important property of the DNA</p> <p>7 molecule.</p> <p>8 In fact, methylation is a critical</p> <p>9 property to understand in many instances.</p> <p>10 For example, I do a lot of work on cancer.</p> <p>11 And understanding the methylation state of DNA</p> <p>12 molecules is of fundamental importance in</p> <p>13 understanding cancer because changes in</p> <p>14 methylation often occur in tumors.</p> <p>15 In the same way, if we look at inherited</p> <p>16 diseases, the methylation state of a particular</p> <p>17 DNA fragment can be fundamental for understanding</p> <p>18 whether or not a particular trait may show up in</p> <p>19 an individual or not.</p> <p>20 Q. All right. That doesn't answer my</p> <p>21 question, so I'm going to ask again.</p> <p>22 If you have a methylated fragment and you</p>
<p style="text-align: right;">Page 98</p> <p>1 just mentioned?</p> <p>2 A. It could happen. Yes.</p> <p>3 Q. In that example, that correction just</p> <p>4 comes through these sequencing methods as sequence</p> <p>5 output. Right?</p> <p>6 A. Eventually you would see a cell -- if we</p> <p>7 follow a particular laboratory process, you could</p> <p>8 see that change occurring in -- you'd see that</p> <p>9 change occurring in the DNA sequence. I guess you</p> <p>10 would see it in both strands, if it occurred and</p> <p>11 was corrected, even if it was miscorrected.</p> <p>12 Q. And if it persists, it would show up in</p> <p>13 the sequence read of these methods. Right?</p> <p>14 A. In the abstract, yes, it could show up in</p> <p>15 the sequence reads.</p> <p>16 Q. Let's talk about methylation. If</p> <p>17 methylation has occurred and you take that</p> <p>18 fragment -- to a given fragment and you amplify it</p> <p>19 with PCR, the amplicons, they don't carry through</p> <p>20 with that same methylation. Right?</p> <p>21 MS. SCORDINO: Objection to form.</p> <p>22 A. So there are ways of detecting methylation</p>	<p style="text-align: right;">Page 100</p> <p>1 amplify it through PCR, do the resulting amplicons</p> <p>2 have the same methylation present as the parent</p> <p>3 acid?</p> <p>4 A. You can do lots of different things in the</p> <p>5 abstract. You're asking me about features in DNA.</p> <p>6 Q. I'm asking you what happens if you take a</p> <p>7 methylated fragment and you PCR it. That's my</p> <p>8 question. Not an abstract molecule. A tangible</p> <p>9 one. What happens in the laboratory? Does that</p> <p>10 make sense?</p> <p>11 A. So you're asking me in the abstract. But</p> <p>12 remember that what we're talking about are</p> <p>13 fragment features. And these fragment features</p> <p>14 are -- this is one of the claim construction</p> <p>15 terms. It appears in the '631 patent in Claims 16</p> <p>16 and 18.</p> <p>17 Let me just find "fragment features" in</p> <p>18 here.</p> <p>19 Actually, can you point me to exactly</p> <p>20 where it occurs?</p> <p>21 Q. No, because it has nothing to do with my</p> <p>22 question.</p>

Page 101	Page 103
<p>1 My question -- I'll ask it again. It's</p> <p>2 not about fragment features, Dr. Quackenbush.</p> <p>3 My question is, if you have a given</p> <p>4 fragment and it's methylated and you amplify it</p> <p>5 through PCR, do the resulting amplicons have</p> <p>6 present the same methylation as the parent</p> <p>7 shearing?</p> <p>8 A. I'm sorry to contradict you, but you are</p> <p>9 talking about -- we started this line of</p> <p>10 questioning by you pointing me to Paragraph 91 of</p> <p>11 my declaration.</p> <p>12 And Paragraph 91 in my declaration is in a</p> <p>13 section on fragment features. So if we're going</p> <p>14 to talk about things, I'd prefer not to talk in</p> <p>15 the abstract about things that you could or</p> <p>16 couldn't do. We're really talking about fragment</p> <p>17 features here.</p> <p>18 And in Paragraph 91 I wrote, "It is my</p> <p>19 opinion the plain and ordinary meaning cannot be</p> <p>20 determined with sufficient clarity" of the term</p> <p>21 "fragment features."</p> <p>22 "For example" -- and this is the sentence</p>	<p>1 population of double-stranded target nucleic acid</p> <p>2 molecules, wherein each individual double-stranded</p> <p>3 target nucleic acid molecule comprises one or more</p> <p>4 fragment features that distinguish the individual</p> <p>5 double-stranded target nucleic acid molecules from</p> <p>6 other double-stranded target nucleic acid</p> <p>7 molecules in the population."</p> <p>8 So we're talking about different features</p> <p>9 that distinguish one molecule from another. And</p> <p>10 DNA methylation is an important feature that can</p> <p>11 distinguish molecules.</p> <p>12 So yes, there are ways to wipe out that</p> <p>13 methylation, wipe out that information. But if I</p> <p>14 were to take the molecule and do bisulfite</p> <p>15 treatment, which is how typically we do</p> <p>16 methylation sequencing, the bisulfite treatment</p> <p>17 actually changes the base sequence of DNA. And</p> <p>18 that can be preserved after PCR.</p> <p>19 So while the raw methylation may be lost,</p> <p>20 the methylation can still be determined and</p> <p>21 determined based on the sequence and the</p> <p>22 difference between the sequence of the fragment</p>
Page 102	Page 104
<p>1 you called out -- "do the claimed 'features' and</p> <p>2 'information' encompass any or all of the size,</p> <p>3 specific nucleotide pattern, overall nucleotide</p> <p>4 composition, nucleotide modification or any other</p> <p>5 property of" the "DNA" fragments?</p> <p>6 And while you may be able to infer some of</p> <p>7 these from others, there are other properties of</p> <p>8 the DNA fragment, including methylation, which are</p> <p>9 important.</p> <p>10 And in the abstract, you can hide that</p> <p>11 methylation. But in real applications in the</p> <p>12 laboratory and in applications to human health,</p> <p>13 hiding that information or losing that information</p> <p>14 can deprive a physician of critical information</p> <p>15 that's important for treating his or her patient.</p> <p>16 So we're not talking about this in the</p> <p>17 abstract. In fact, "fragment features" are a</p> <p>18 claim term. And it appears in Claims 16 and 18 in</p> <p>19 the '631 patent.</p> <p>20 And it reads in Claim 16 -- and this is</p> <p>21 Column 39, starting at line 41. "A method of</p> <p>22 generating high accuracy sequence reads of a</p>	<p>1 following bisulfite conversion and the -- and</p> <p>2 following bisulfite conversion cloning PCR,</p> <p>3 et cetera.</p> <p>4 So bisulfite conversion is actually one of</p> <p>5 those G to A transitions we talked about earlier.</p> <p>6 Q. All right. Why don't you take a look at</p> <p>7 Claim 16, Dr. Quackenbush.</p> <p>8 A. Sure.</p> <p>9 Q. You've studied and you're familiar with</p> <p>10 this claim, I'm sure?</p> <p>11 A. I've looked at it. I don't know if I've</p> <p>12 studied it.</p> <p>13 Q. Okay. You don't think that's -- you</p> <p>14 wouldn't characterize what you've done as study</p> <p>15 it?</p> <p>16 A. I don't know what you would characterize</p> <p>17 as study it. I've spent some time considering it</p> <p>18 and the language used in the claim.</p> <p>19 Q. All right.</p> <p>20 A. Could I recite it from memory? No.</p> <p>21 Q. I don't expect you to do that.</p> <p>22 If we look at the method of Claim 16, look</p>

<p style="text-align: right;">Page 105</p> <p>1 at the steps at the top of Column 40, there's a</p> <p>2 sequencing step, right, "sequencing the</p> <p>3 adapter-target nucleic acid complex amplicons."</p> <p>4 Do you see that?</p> <p>5 A. Yes. There is a step in here following a</p> <p>6 number of other steps that involve sequencing.</p> <p>7 Yes.</p> <p>8 Q. You see that step. Right?</p> <p>9 A. Yes.</p> <p>10 Q. And so again, out of consideration for</p> <p>11 your point and not making this abstract, I want to</p> <p>12 ground this in the claim.</p> <p>13 So what's recited there is the amplicons</p> <p>14 are being sequenced. Right?</p> <p>15 A. It says "sequencing the adapter-target</p> <p>16 nucleic acid complex amplicons to produce a</p> <p>17 plurality of first" and second strand reads.</p> <p>18 Q. You agree with me that it's the amplicons</p> <p>19 that are being sequenced in that step?</p> <p>20 A. It says, "sequencing the adapter-target</p> <p>21 nucleic acid complex amplicons." So amplicons, it</p> <p>22 says, are being sequenced.</p>	<p style="text-align: right;">Page 107</p> <p>1 Q. Okay. But we're talking about this step</p> <p>2 in the claim method. Amplicon there is a nucleic</p> <p>3 acid that has been generated by amplifying a</p> <p>4 parent strand. Right?</p> <p>5 A. Well, to clarify this for you, if you just</p> <p>6 read the claim paragraph or claim subsection</p> <p>7 immediately above, starting at line 4, "amplifying</p> <p>8 each strand at the adapter-target nucleic acid</p> <p>9 complex to produce a plurality of first strand</p> <p>10 adapter-target nucleic acid and a plurality of</p> <p>11 second strand adapter-target nucleic acid complex</p> <p>12 amplicons."</p> <p>13 Q. Right.</p> <p>14 A. So the amplicons come from the amplifying</p> <p>15 step.</p> <p>16 Q. I think we agree, then, that the amplicons</p> <p>17 come from an amplification? That's all I've</p> <p>18 asked.</p> <p>19 A. They come from an amplifying --</p> <p>20 Q. Because that's what it says.</p> <p>21 A. Of Column 40.</p> <p>22 Q. And then the next step has the grouping.</p>
<p style="text-align: right;">Page 106</p> <p>1 Q. And because it's talking about amplicons,</p> <p>2 those are things that are generated in the</p> <p>3 pyridine case by a PCR reaction. Right?</p> <p>4 MS. SCORDINO: Objection to form.</p> <p>5 A. I don't believe the claim language</p> <p>6 mentions PCR.</p> <p>7 Q. Do you agree that the amplicons in that</p> <p>8 step are the nucleic acids that have been</p> <p>9 generated through some kind of amplification</p> <p>10 reaction of a parent strand?</p> <p>11 A. So the use of the term "amplicons" refers</p> <p>12 to the product of some type of amplification</p> <p>13 process, which occurs at some stage in the</p> <p>14 preparation of the molecules for sequencing.</p> <p>15 For example, Illumina in its sequencing,</p> <p>16 which is I believe the method referred to in the</p> <p>17 specification in the different examples, uses a</p> <p>18 protocol called "bridge amplification," which is</p> <p>19 distinct from PCR.</p> <p>20 But one could also perform amplification</p> <p>21 at other stages during the process using PCR,</p> <p>22 using other techniques.</p>	<p style="text-align: right;">Page 108</p> <p>1 Have you seen that? Do you see that?</p> <p>2 A. So the next step after sequencing involves</p> <p>3 something -- the paragraph begins "grouping."</p> <p>4 Yes.</p> <p>5 Q. And what's being grouped are the sequence</p> <p>6 reads. Correct?</p> <p>7 A. So it says, "grouping the first and second</p> <p>8 strand sequence reads into a family of" sequences</p> <p>9 "by identifying the one or more distinguishing</p> <p>10 fragment features shared by each strand of the</p> <p>11 double-stranded target nucleic acid molecule."</p> <p>12 Q. So you agree with me?</p> <p>13 MS. SCORDINO: Objection to form.</p> <p>14 Q. That what's being grouped in that step are</p> <p>15 the reads?</p> <p>16 A. It's talking about grouping first and</p> <p>17 second strand sequence reads. So yes, sequence</p> <p>18 reads are grouped.</p> <p>19 Q. Thank you. And the sequence reads in</p> <p>20 basic terms are the sequence of the nucleotides</p> <p>21 for the nucleic acid that has been sequenced in</p> <p>22 that earlier step. Right?</p>

<p style="text-align: right;">Page 109</p> <p>1 A. The grouping is based on sequence reads --</p> <p>2 Q. I'm not asking about grouping there. I'm</p> <p>3 asking the reads.</p> <p>4 That's just the sequence of the</p> <p>5 nucleotides that have just been sequenced in that</p> <p>6 earlier step. Right? That's the ACGT, whatever</p> <p>7 particular order it comes off the sequencer.</p> <p>8 A. The sequence reads are a series of ACs,</p> <p>9 Gs, and Ts.</p> <p>10 Q. Great. And what's being claimed in that</p> <p>11 step is simply grouping those sequences?</p> <p>12 MS. SCORDINO: Objection to form.</p> <p>13 Q. I just want to make sure we're on the same</p> <p>14 page.</p> <p>15 A. Well, it's not just grouping. Right? If</p> <p>16 you actually read this, it says "grouping the</p> <p>17 first and second strand sequence reads into a</p> <p>18 family of sequence reads." Right? By</p> <p>19 identifying.</p> <p>20 So it can't just all throw them into a</p> <p>21 bucket. We have to do something to group them.</p> <p>22 Right?</p>	<p style="text-align: right;">Page 111</p> <p>1 where any methylation has occurred in the strand.</p> <p>2 Right?</p> <p>3 A. It depends on how the library is prepared.</p> <p>4 If you're asking any question, even grouping is</p> <p>5 going to require some computational analysis of</p> <p>6 what comes out of the sequencer.</p> <p>7 Q. I just want to be clear. So it's your</p> <p>8 testimony that the sequence read itself will</p> <p>9 contain information as to the presence or location</p> <p>10 where methylation has occurred in a given strand?</p> <p>11 A. So if we do bisulfite treatment of the</p> <p>12 DNA, bisulfite treatment converts Gs to As.</p> <p>13 Right?</p> <p>14 So there's going to be an aberration in</p> <p>15 the sequence itself compared to a reference</p> <p>16 sequence. Right?</p> <p>17 So again, this term is really sort of</p> <p>18 indefinite in how the grouping is described</p> <p>19 because we're grouping by fragment features.</p> <p>20 So if you imagine the scenario you're</p> <p>21 talking about, right, and if I did bisulfite</p> <p>22 treatment and if that bisulfite treatment changes</p>
<p style="text-align: right;">Page 110</p> <p>1 So "by identifying the one or more</p> <p>2 distinguishing fragment features shared by each</p> <p>3 of" -- "each strand of the double-stranded target</p> <p>4 nucleic acid molecule."</p> <p>5 So this says "one or more." And the</p> <p>6 problem, the difficulty here in reading fragment</p> <p>7 features and specifically the fact that they're</p> <p>8 referring to one or more features means that, yes,</p> <p>9 one could use sequence, the actual base sequence.</p> <p>10 One could use all of that sequence, a part</p> <p>11 of that sequence, some subset of that sequence.</p> <p>12 One could use -- take this information and process</p> <p>13 it into the potential restriction enzyme cutting</p> <p>14 sites.</p> <p>15 There are a variety of different ways in</p> <p>16 which these can be grouped together. And I think</p> <p>17 the problem we're having here is that the fragment</p> <p>18 features aren't really specified, particularly the</p> <p>19 fact they're telling us we can use one or more.</p> <p>20 Q. Okay. Fair enough. If I have the</p> <p>21 sequence read that's talked about in that step,</p> <p>22 the sequence read itself won't tell me whether or</p>	<p style="text-align: right;">Page 112</p> <p>1 Gs to As, it's going to change them in one strand,</p> <p>2 not the other strand, which would mean if I was</p> <p>3 grouping based on a sequence that comprised that G</p> <p>4 to A change, then I may or may not be able to</p> <p>5 group the sequences together, which could very</p> <p>6 well be why they talk about using one or more</p> <p>7 fragment features, but they don't tell me which</p> <p>8 fragment features to use.</p> <p>9 So in some circumstances, I could use DNA</p> <p>10 sequence. In other fragments -- in other</p> <p>11 circumstances, I may not be able to use just DNA</p> <p>12 sequence.</p> <p>13 Q. If one has the sequence reads that are</p> <p>14 claimed in this Claim 16, the sequence read itself</p> <p>15 doesn't tell you the length in nanometers, for</p> <p>16 example, of a given fragment. Right?</p> <p>17 A. So you seem to be making a number of</p> <p>18 assumptions, one of which is that you're reading</p> <p>19 through the entire fragment.</p> <p>20 And given the fact that is duplex -- that</p> <p>21 the specification describes duplex consensus</p> <p>22 sequencing, the DCS method, you'd have to read</p>

<p style="text-align: right;">Page 113</p> <p>1 through and you'd have to trim off the adapter 2 sequence.</p> <p>3 So assuming we did that and we have the 4 length of that adapter sequence, I might be able 5 in certain circumstances to -- since we know 6 approximately the size of DNA in a helix, how long 7 it is, I think we also know the length of 8 denatured DNA based on base pairs or at least an 9 approximate length. So one could calculate the 10 length in nanometers.</p> <p>11 Q. Okay. So just with the sequence read 12 itself, you can figure out the length in 13 nanometers?</p> <p>14 A. Potentially one could.</p> <p>15 Q. Thank you.</p> <p>16 A. Again, in the abstract. But the challenge 17 here is that the fragment features -- identifying 18 the one or more distinguishing fragment features.</p> <p>19 And so whether or not you could determine 20 one, we're not told which to use. So should we 21 use nucleic acid sequence? Should we use the 22 length in base pairs? Should we use the length in</p>	<p style="text-align: right;">Page 115</p> <p>1 DNA can do a lot of interesting different 2 things as fragments. The structure of that DNA 3 fragment is going to depend on the solution it's 4 in, its pH, salt concentrations, the concentration 5 of nucleic acids.</p> <p>6 So again, just talking about the 3D shape 7 without greater specification doesn't give me a 8 lot of guidance as to how to group things 9 together.</p> <p>10 Q. Let's go back to that case you mentioned 11 earlier, bisulfite treatment. If I understand 12 this correctly, that would change the -- some 13 nucleotides I think from As to Cs. Is that what 14 you said?</p> <p>15 A. So bisulfite treatment changes methylated 16 Gs to As.</p> <p>17 Q. Okay. Thank you. And were that to occur, 18 the impact that such a change would have on a 19 sequence read would simply be to have a different 20 sequence. Right? Instead of a G, you end up with 21 an A. Right?</p> <p>22 A. You would have -- if a G were methylated,</p>
<p style="text-align: right;">Page 114</p> <p>1 nanometers? Should we use the methylation status? 2 Should we use something else? What if we don't 3 read all the way through?</p> <p>4 The fragments and the fragment features 5 are really going to depend on -- it's going to 6 influence how we group things together.</p> <p>7 Q. If again you have the sequence read, do we 8 agree that you can't determine the 3D shape of a 9 given fragment based strictly on its sequence 10 read?</p> <p>11 MS. SCORDINO: Objection to form.</p> <p>12 A. So are we talking about the single- 13 stranded or double-stranded sequence?</p> <p>14 Q. Let's start with single-stranded.</p> <p>15 A. I'm actually not that familiar with the 16 literature on single-stranded conformation. What 17 I can tell you is that single-stranded DNA by 18 itself can take on a variety of different 19 structures.</p> <p>20 One of the things we worry about is cell 21 hybridization of DNA fragments creating hairpins, 22 which in some situations can be important.</p>	<p style="text-align: right;">Page 116</p> <p>1 it would change a G to an A in that strand. If we 2 have the complementary sequence, it would remain 3 an A.</p> <p>4 So if I were to take those two sequences 5 and align them, I would have an AA. I would have 6 a mismatch.</p> <p>7 We're told here that we should group the 8 first and second strand sequences into families by 9 identifying one or more distinguishing fragment 10 features.</p> <p>11 So if I do this bisulfite treatment and 12 sequencing in which a methylated G is changed to 13 an A, do I use that or not to group it? Do I 14 ignore the As? Do I use my prior knowledge of 15 what bisulfite sequencing does?</p> <p>16 Again, the challenge here is we're told to 17 use one or more distinguishing fragment features 18 but we're not told what those fragment features 19 are.</p> <p>20 Q. But in the case where you've got a 21 mismatch, as you call it, you would group those 22 strands in different families. Right?</p>

<p style="text-align: right;">Page 117</p> <p>1 MS. SCORDINO: Objection to form.</p> <p>2 A. So this is -- you're actually touching on</p> <p>3 a really interesting problem in the whole field of</p> <p>4 DNA sequence analysis, really going back to</p> <p>5 assembling genome sequences, particularly with the</p> <p>6 advent of short-read sequencing, what we often</p> <p>7 refer to as next-generation sequencing.</p> <p>8 So one of the challenges in</p> <p>9 next-generation sequencing is that, as in all</p> <p>10 sequencing or all laboratory assays, there's the</p> <p>11 potential for making an error.</p> <p>12 And so if you have a mismatch, the</p> <p>13 question of whether or not to group things</p> <p>14 together even in aligning sequences to do an</p> <p>15 assembly de novo, deciding whether or not to group</p> <p>16 things together is really important. Because if I</p> <p>17 have error-prone sequencing -- in the very early</p> <p>18 days, errors occurred more frequently until the</p> <p>19 chemistry was optimized.</p> <p>20 Whether or not to group things together</p> <p>21 and align them together required decisions. It</p> <p>22 was a subject of intense study.</p>	<p style="text-align: right;">Page 119</p> <p>1 as part of your work in this case. Right?</p> <p>2 A. Yes, I have.</p> <p>3 Q. In fact, it's your opinion that the</p> <p>4 Guardant patents are novel. Right?</p> <p>5 MS. SCORDINO: Objection, outside the</p> <p>6 scope.</p> <p>7 A. Can you point me to where I refer to this</p> <p>8 in my declaration?</p> <p>9 Q. Well, is that your opinion?</p> <p>10 MS. SCORDINO: Same objection, outside the</p> <p>11 scope.</p> <p>12 A. I'm not prepared to offer an opinion on</p> <p>13 that today.</p> <p>14 Q. Would you take a look at Paragraph 25 of</p> <p>15 your declaration. You wrote, "The Guardant</p> <p>16 Asserted Patents are directed to novel sequencing</p> <p>17 methods for detecting, for example, cancer-causing</p> <p>18 mutations using cell-free DNA ('cfDNA'), which is</p> <p>19 found in very small quantities," and you continue</p> <p>20 on.</p> <p>21 A. I'm sorry. Which paragraph?</p> <p>22 Q. Paragraph 25.</p>
<p style="text-align: right;">Page 118</p> <p>1 So the decisions you make are going to</p> <p>2 depend on the application; and which features you</p> <p>3 use to group things together, the degree of</p> <p>4 similarity that you use, is really important.</p> <p>5 And this is particularly important because</p> <p>6 a large part of the human genome is made up of</p> <p>7 repetitive sequences. And so if we're putting</p> <p>8 these together, we do have to know something about</p> <p>9 the families.</p> <p>10 If it's a series of alu repeats or a</p> <p>11 fragment of an alu repeat, we have to make</p> <p>12 decisions about what features of that alu to use</p> <p>13 to group things together.</p> <p>14 We could look at positions in the alu</p> <p>15 which are commonly mutated, or whether or not</p> <p>16 they're families of alu sequences. We could use a</p> <p>17 statistical method to determine how likely these</p> <p>18 sequences should be grouped together.</p> <p>19 Q. All right. Let's shift gears. We have</p> <p>20 talked thus far only about the plaintiff's</p> <p>21 patents.</p> <p>22 You've also analyzed the Guardant patents</p>	<p style="text-align: right;">Page 120</p> <p>1 A. Sorry.</p> <p>2 Q. Do you see that?</p> <p>3 A. I'll find it. Give me a second.</p> <p>4 Okay. I see that.</p> <p>5 Q. Is that a correct statement of your</p> <p>6 opinion, what's stated there in the first sentence</p> <p>7 of Paragraph 25?</p> <p>8 A. In the context of the paragraph, yes. As</p> <p>9 I wrote, "The Guardant Asserted Patents are</p> <p>10 directed to novel sequencing methods for</p> <p>11 detecting, for example, cancer-causing mutations</p> <p>12 using cell-free DNA" -- which we described as</p> <p>13 "cfDNA" -- "which is found in very small</p> <p>14 quantities in blood and other bodily fluids. By</p> <p>15 analyzing cfDNA, cancerous mutations can be</p> <p>16 detected using, for example, a simple blood draw</p> <p>17 instead of a traditional tumor biopsy -- which is</p> <p>18 a painful, costly, and slow process. These</p> <p>19 non-invasive methods are referred to as 'liquid</p> <p>20 biopsies.'"</p> <p>21 That's my opinion, and I believe it is</p> <p>22 correct.</p>

Page 121	Page 123
<p>1 Q. And so you said that in the context of</p> <p>2 this paragraph, it's your opinion.</p> <p>3 Is there some context in which you don't</p> <p>4 hold this opinion?</p> <p>5 A. You're asking me about things in the</p> <p>6 context of my report, and this is my opinion laid</p> <p>7 out in my report.</p> <p>8 Q. Okay. What study did you do, if any, to</p> <p>9 determine that the Guardant asserted patents are</p> <p>10 directed to novel sequencing methods?</p> <p>11 A. Can I have copies of the patents, please?</p> <p>12 Q. Sure. While we get those, let me ask you</p> <p>13 this: Did you study any prior art in forming that</p> <p>14 opinion about the novelty of the Guardant patent</p> <p>15 sequencing methods?</p> <p>16 MS. SCORDINO: Objection to form.</p> <p>17 Q. Doctor?</p> <p>18 A. I asked for copies of the patents.</p> <p>19 Q. I understand. Do you need to look at the</p> <p>20 patents in order to tell me whether you looked at</p> <p>21 prior art in arriving at that opinion?</p> <p>22 A. You asked me a question. I asked for the</p>	<p>1 MS. SCORDINO: Counsel, argumentative. If</p> <p>2 you need to take a break to get yourself --</p> <p>3 MR. PICKARD: The witness is being</p> <p>4 noncompliant with me --</p> <p>5 MS. SCORDINO: Not really.</p> <p>6 MR. PICKARD: -- and I have asked him a</p> <p>7 question.</p> <p>8 Q. And the question is, did you study any</p> <p>9 prior art in arriving at your opinion that the</p> <p>10 Guardant asserted patents are directed to novel</p> <p>11 sequencing methods?</p> <p>12 A. I would like to look at the patents to</p> <p>13 refresh my memory. If you're not willing to</p> <p>14 provide me with the patents, then I'm going to</p> <p>15 defer answering until you honor what was a simple</p> <p>16 and polite request.</p> <p>17 Q. I will hand you the patents. I have one</p> <p>18 question before I do that.</p> <p>19 Can you answer the question without</p> <p>20 looking at the patents?</p> <p>21 MS. SCORDINO: Objection to form.</p> <p>22 A. I prefer to look at the patents before I</p>
Page 122	Page 124
<p>1 patents.</p> <p>2 Q. I understand. I've withdrawn that</p> <p>3 question. I've asked a different question.</p> <p>4 And the question is, did you look at any</p> <p>5 prior art when you formed your opinion that the</p> <p>6 Guardant asserted patents are directed to novel</p> <p>7 sequencing?</p> <p>8 A. May I please have the patents before I</p> <p>9 answer?</p> <p>10 Q. Well, I'm going to give you the patents.</p> <p>11 But can you answer the question without looking at</p> <p>12 the patents?</p> <p>13 A. May I please have the patents --</p> <p>14 Q. You need to answer the question. If you</p> <p>15 can't answer the question without looking at the</p> <p>16 patents, I may give them to you.</p> <p>17 A. May I please have the patents?</p> <p>18 Q. You need to answer my question.</p> <p>19 A. You asked me a previous question. I asked</p> <p>20 for the patents.</p> <p>21 Q. Right. And I have withdrawn that</p> <p>22 question. Do you agree with me?</p>	<p>1 answer the question.</p> <p>2 Q. I understand --</p> <p>3 A. So I've made a simple and polite request.</p> <p>4 And I again politely request -- politely ask that</p> <p>5 you honor my request.</p> <p>6 Q. I thank you for your politeness and I</p> <p>7 appreciate you sharing your preference. But your</p> <p>8 preferences do not matter here. I have a question</p> <p>9 and I'm entitled to an answer.</p> <p>10 Can you answer the question without</p> <p>11 looking at the patents?</p> <p>12 A. I would prefer to look at the patents</p> <p>13 before answering the question.</p> <p>14 Q. I understand that. I'm going to ask you</p> <p>15 one more time and then we're going to mark the</p> <p>16 transcript for your nonresponsive answer.</p> <p>17 Can you answer the question without</p> <p>18 looking at the patents?</p> <p>19 A. In response, so you understand I'm being</p> <p>20 responsive, I asked to please see the patents.</p> <p>21 The purpose of our discussion today is to</p> <p>22 look at claim construction and the terms which are</p>

<p style="text-align: right;">Page 125</p> <p>1 proposed for construction in the current court 2 proceeding. I'm not prepared to offer an opinion 3 on prior art that may or may not be relevant to 4 the Guardant patents. 5 My read of the Guardant patents, when I 6 read them as a person of ordinary skill in the 7 art, was that these represent novel methods for 8 sequencing. 9 Whether or not you're going to allow me to 10 look at the patents is your choice. But it seems 11 like a simple request and one that would help 12 refresh my memory so I actually remember what 13 exactly is claimed in those patents and so that I 14 have information about priority dates associated 15 with those patents. 16 (Quackenbush Exhibit 3, marked for 17 identification.) 18 Q. We've marked Quackenbush 3 patent. Do you 19 recognize this as the '063 patent? 20 A. Yes, this is the '063 patent. 21 (Quackenbush Exhibit 4, marked for 22 identification.)</p>	<p style="text-align: right;">Page 127</p> <p>1 in his declaration. So I think I'm entitled to an 2 answer. 3 A. Thank you for providing me with the 4 patents. Would you please repeat your question? 5 Q. Sure. Did you review any prior art in 6 forming your opinion that the Guardant asserted 7 patents are directed to novel sequencing methods? 8 MS. SCORDINO: Objection to form. 9 A. So as I've told you already today, my goal 10 in providing this deposition is not to provide a 11 full analysis of the Guardant patents. Really my 12 goal today and purpose today is to offer an 13 opinion on the construction of various claim terms 14 that appear in these patents. 15 However, you've asked me about the 16 analysis of four patents held by Guardant. And I 17 believe the priority date is 2013. 18 These patents are actually directed toward 19 the sequencing of cell-free DNA. As you may or 20 may not know, determining the sequence of 21 cell-free DNA is extraordinarily difficult. Why? 22 Because -- and accurately determining the sequence</p>
<p style="text-align: right;">Page 126</p> <p>1 Q. And here is the '306 patent, which is 2 Exhibit 4. 3 (Quackenbush Exhibit 5, marked for 4 identification.) 5 MR. PICKARD: Exhibit 5 is the '221 6 patent. 7 (Quackenbush Exhibit 6, marked for 8 identification.) 9 Q. And the '858 patent as Exhibit 6. 10 Do you recall the question that's pending? 11 Did you look at any prior art when you 12 formed your opinion that the Guardant asserted 13 patents are directed to novel sequencing methods? 14 MS. SCORDINO: Objection to form. 15 Counsel, as the witness has stated, he's 16 not here to give an opinion as to prior art. This 17 is a claim construction deposition. 18 If you'd like to forgo your deposition as 19 to prior art, that will happen in the future if he 20 provides such an opinion, then continue. 21 MR. PICKARD: With respect, he literally 22 testified today that that's his opinion, and it's</p>	<p style="text-align: right;">Page 128</p> <p>1 of cell-free DNA is extraordinarily difficult. 2 Cell-free DNA, in common parlance -- and I 3 understand that there's some agreement about 4 circulating DNA and how that term is construed, 5 and there's agreement between the parties. 6 Cell-free DNA is DNA which exists outside 7 of cells, so not within the individual cells but 8 outside the cells. 9 In the reference to the liquid biopsy in 10 Paragraph 25, which you referred to, we're looking 11 at cell-free DNA that's in very small quantities 12 in blood or other bodily fluids. 13 And one of the bodily fluids which is 14 typically profiled in diseases like bladder cancer 15 is urine. But most commonly when we talk about 16 liquid biopsies, we're talking about blood. 17 Cell-free DNA is DNA which is liberated 18 from cells, often when they die. We see cell-free 19 DNA naturally in our bloodstreams. 20 Accurately determining the sequence of 21 that cell-free DNA is difficult -- not difficult, 22 but is important because in many of the</p>

<p style="text-align: right;">Page 129</p> <p>1 applications in Guardant's inventions and</p> <p>2 products, what they're interested in doing is</p> <p>3 detecting the presence or absence of a tumor and</p> <p>4 monitoring disease progression in individuals who</p> <p>5 have cancer.</p> <p>6 So cell-free DNA is also used in products</p> <p>7 from other companies to look at prenatal</p> <p>8 diagnostics.</p> <p>9 Detecting that cell-free DNA and doing it</p> <p>10 well is a challenge. The DNA is fragmented.</p> <p>11 Typical size is about 160 bases. The DNA -- and</p> <p>12 the tumor DNA that you really want to detect often</p> <p>13 exists in only a few percent of the total quantity</p> <p>14 of cell-free DNA that exists in a cell.</p> <p>15 So I have not done a full prior art</p> <p>16 analysis, and I haven't reviewed all the things I</p> <p>17 may have read at some point in looking at these</p> <p>18 patents. And I'm not prepared to provide a prior</p> <p>19 art analysis today.</p> <p>20 But as counsel mentioned, if I do offer</p> <p>21 opinions on that, I'd be happy to answer questions</p> <p>22 at that point.</p>	<p style="text-align: right;">Page 131</p> <p>1 on one skilled in the art, without doing a full</p> <p>2 analysis but just relying on what I know and what</p> <p>3 I remember as of 2013, was that detecting</p> <p>4 cell-free DNA and detecting mutations was</p> <p>5 incredibly difficult and that Guardant was the</p> <p>6 first, to my knowledge sitting here today, to</p> <p>7 bring a workable product to the market.</p> <p>8 And as far as I understand this workable</p> <p>9 product -- and I don't know what patents Guardant</p> <p>10 is relying on for their individual technologies</p> <p>11 because I haven't had access to that information.</p> <p>12 So I can tell you that Guardant did bring</p> <p>13 one of the first useful products to market. And</p> <p>14 in their patent portfolio, there are patents which</p> <p>15 describe methods that have really allowed them to</p> <p>16 become a leader in the field.</p> <p>17 Q. All right. Now, if we look at</p> <p>18 Paragraph 26 -- first of all, you're familiar with</p> <p>19 that paragraph. Right? You've read it recently?</p> <p>20 A. I'll read it again.</p> <p>21 Can you please repeat the question?</p> <p>22 Q. Right. You're familiar with Paragraph 26?</p>
<p style="text-align: right;">Page 130</p> <p>1 However, if we read these patents and read</p> <p>2 the claims, all four patents discuss a series of</p> <p>3 laboratory and analytical approaches for</p> <p>4 identifying cell-free DNA that resulted in</p> <p>5 products that are widely recognized as leaders --</p> <p>6 in leading products in the market and are actually</p> <p>7 important for treatment of patients.</p> <p>8 So I can tell you that as of 2013, to the</p> <p>9 best of my knowledge sitting here today, these do</p> <p>10 actually represent novel approaches to detecting</p> <p>11 and analyzing cancer-causing mutations in</p> <p>12 cell-free DNA.</p> <p>13 But as of today I cannot tell you -- I</p> <p>14 have not done a full and comprehensive prior art</p> <p>15 analysis.</p> <p>16 Q. Have you done any, any prior art analysis</p> <p>17 when you formed that opinion?</p> <p>18 MS. SCORDINO: Objection to form.</p> <p>19 A. So part of what one relies on as an expert</p> <p>20 is what one of ordinary skill in the art at the</p> <p>21 time of the patents being filed represents.</p> <p>22 And I can tell you that as of 2013, based</p>	<p style="text-align: right;">Page 132</p> <p>1 A. Yes. I refreshed my memory.</p> <p>2 Q. And Paragraph 26, when you talk about the</p> <p>3 claimed methods, you're talking about the claimed</p> <p>4 methods in the Guardant asserted patents. Right?</p> <p>5 A. Yes. I'm referring back to the previous</p> <p>6 methods, the previous paragraph.</p> <p>7 Q. These novel methods?</p> <p>8 A. Yes. And in fact, I call out the '221</p> <p>9 patent, Figure 1.</p> <p>10 Q. Okay. And you list here six things which</p> <p>11 you believe the methods are generally directed to.</p> <p>12 Correct?</p> <p>13 A. So this is a summary. And again, the goal</p> <p>14 in my declaration which you're reading from and</p> <p>15 the purpose of my deposition today is to offer</p> <p>16 opinions about the contested claim terms.</p> <p>17 So what these six steps here summarize --</p> <p>18 and that's why I referred to Figure 1 -- is</p> <p>19 actually a fairly complicated process which is</p> <p>20 described in the claims in these four patents.</p> <p>21 And so it's sort of a high-level summary</p> <p>22 of even Figure 1 and a high-level summary of</p>

<p style="text-align: right;">Page 133</p> <p>1 what's represented in the individual claims.</p> <p>2 Q. And that's why you used the word</p> <p>3 "generally" in your paragraph and that's why I</p> <p>4 used the word "generally" in my question. It's</p> <p>5 just a summary of what the claims are directed to?</p> <p>6 A. Well, I just want to be very clear when I</p> <p>7 answer your questions.</p> <p>8 Q. All right. So let's take collecting a</p> <p>9 bodily fluid sample from a patient. You agree</p> <p>10 that was known before the priority date for the</p> <p>11 Guardant asserted patents. Right?</p> <p>12 MS. SCORDINO: Objection. This is outside</p> <p>13 the scope.</p> <p>14 This is a claim construction deposition.</p> <p>15 Counsel, if you want to have a meet and</p> <p>16 confer, that's fine. That isn't to continue this,</p> <p>17 if you're going to go down a path where you're</p> <p>18 asking him validity opinions when this is a claim</p> <p>19 deposition.</p> <p>20 MR. PICKARD: Are you instructing the</p> <p>21 witness not to answer?</p> <p>22 MS. SCORDINO: I'm going to see how long</p>	<p style="text-align: right;">Page 135</p> <p>1 Q. Before the Guardant patents.</p> <p>2 A. Many ancient cultures --</p> <p>3 Q. You moved the goal posts from the priority</p> <p>4 date of the Guardant patents to the beginning of</p> <p>5 time. I'm just trying to understand how we got</p> <p>6 there.</p> <p>7 A. Sorry. Not the beginning of time. Since</p> <p>8 early humanity. Because you asked me before the</p> <p>9 Guardant patents, you're asking me an abstract</p> <p>10 question. You're taking something out of context.</p> <p>11 You're asking me -- you asked me --</p> <p>12 Would you please repeat the question?</p> <p>13 Q. I guess --</p> <p>14 A. Would you please read back the question?</p> <p>15 Q. I will happily do that. Just so we're</p> <p>16 clear, the context of the question is the Guardant</p> <p>17 asserted patents and your statement in</p> <p>18 Paragraph 26.</p> <p>19 A. All right. Would you please read the</p> <p>20 question?</p> <p>21 Q. So the question is, collecting a bodily</p> <p>22 fluid sample from a patient, do you agree that was</p>
<p style="text-align: right;">Page 134</p> <p>1 you continue on a novelty deposition when this is</p> <p>2 for claim construction.</p> <p>3 Q. Can you answer the question?</p> <p>4 A. So my understanding of patent law is that</p> <p>5 it isn't appropriate to take individual steps out</p> <p>6 of context and analyze those steps out of context.</p> <p>7 As I told you earlier, I'm not prepared to</p> <p>8 do a prior art analysis of the Guardant asserted</p> <p>9 patents.</p> <p>10 You are correct that collecting bodily</p> <p>11 fluids probably has been done since prehistoric</p> <p>12 times. But collecting fluids in the context of</p> <p>13 collecting them such that cell-free DNA can be</p> <p>14 appropriately analyzed has not been done since the</p> <p>15 beginning of time.</p> <p>16 When our ancestors killed each other and</p> <p>17 collected blood to paint their faces, it wasn't in</p> <p>18 the context of analyzing cell-free DNA.</p> <p>19 Q. I'm sorry. Why are we talking about the</p> <p>20 beginning of time?</p> <p>21 A. You asked me if this had been done</p> <p>22 previously.</p>	<p style="text-align: right;">Page 136</p> <p>1 known before the priority date of the Guardant</p> <p>2 asserted patents?</p> <p>3 MS. SCORDINO: Objection to form, outside</p> <p>4 the scope.</p> <p>5 A. So I'm not prepared, as I told you</p> <p>6 earlier, to render an opinion on prior art in the</p> <p>7 context of this entire patent.</p> <p>8 I've also explained to you that my</p> <p>9 understanding is that in looking at patents and</p> <p>10 what they're claiming, one has to look at the</p> <p>11 entire context.</p> <p>12 You've also asked me about a specific</p> <p>13 date. And I answered that prior to -- and I don't</p> <p>14 know if this is the actual priority date or not.</p> <p>15 But prior to 2013, which is my interpretation of</p> <p>16 the potential priority date for these patents,</p> <p>17 there were many examples of collecting of blood.</p> <p>18 I was born in the 1960s and had blood</p> <p>19 drawn then. And collecting blood samples then was</p> <p>20 commonly carried out. So I won't go back to our</p> <p>21 prehistoric ancestors. We'll start with my</p> <p>22 lifetime.</p>

<p style="text-align: right;">Page 137</p> <p>1 In the 1960s, I had blood drawn. But that</p> <p>2 blood wasn't drawn and held appropriately for the</p> <p>3 analysis of cell-free DNA.</p> <p>4 So we can take this one general step out</p> <p>5 of context and recognize that drawing blood is</p> <p>6 something which was known prior to 2013.</p> <p>7 MR. PICKARD: It's 12:30. I propose a</p> <p>8 lunch break. Does that work for you, Doctor?</p> <p>9 THE WITNESS: Sure. That works.</p> <p>10 THE VIDEOGRAPHER: The time is 12:32.</p> <p>11 We're off the record.</p> <p>12 (Lunch recess, 12:32 p.m. to 1:37 p.m.)</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22 AFTERNOON SESSION</p>	<p style="text-align: right;">Page 139</p> <p>1 Q. And just broadly speaking, this is kind of</p> <p>2 a summary of what the Guardant asserted patents</p> <p>3 are directed to. Right? That's what you intend</p> <p>4 here?</p> <p>5 A. So I don't know directed to specifically.</p> <p>6 But it describes or this paragraph describes some</p> <p>7 of the areas of utility for the methods claimed in</p> <p>8 the four Guardant patents.</p> <p>9 Q. All right. And you kind of pushed back on</p> <p>10 the phrase "directed to." Is that because you</p> <p>11 don't know what it means or you don't think it</p> <p>12 applies when talking about that sentence?</p> <p>13 A. So I don't know how you're using "directed</p> <p>14 to" in trying to limit the scope of what these</p> <p>15 sentences refer to.</p> <p>16 Q. You see above in Paragraph 25 you wrote,</p> <p>17 "The Guardant" . . . "Patents are directed to,"</p> <p>18 and you continue on?</p> <p>19 A. Yes, I do.</p> <p>20 Q. And in 26 you wrote, "Generally, the</p> <p>21 claimed methods are directed to"? Do you see</p> <p>22 that? Paragraph 26. "Generally, the claimed</p>
<p style="text-align: right;">Page 138</p> <p>1 THE VIDEOGRAPHER: We are back on the</p> <p>2 record. The time is 1:36.</p> <p>3 BY MR. PICKARD:</p> <p>4 Q. Okay. Dr. Quackenbush, if you could turn</p> <p>5 back to your declaration, please, Exhibit 1.</p> <p>6 A. All right.</p> <p>7 Q. So I want to jump ahead to Paragraph 27 of</p> <p>8 your dec.</p> <p>9 A. All right.</p> <p>10 Q. There you wrote in the first sentence of</p> <p>11 Paragraph 27 that "claimed methods can be used to</p> <p>12 correct errors and reduce background noise present</p> <p>13 in NGS sequencing methods resulting from the DNA</p> <p>14 amplification step and/or sequencing step."</p> <p>15 Did I read that correctly?</p> <p>16 A. Yes, you did.</p> <p>17 Q. And you continued, "For example, the</p> <p>18 claimed methods allow for tagging of both strands</p> <p>19 of DNA (both the Watson and Crick strands, or</p> <p>20 'complementary strands'), amplifying both strands,</p> <p>21 and sequencing of both strands." Right?</p> <p>22 A. You read that correctly. Yes.</p>	<p style="text-align: right;">Page 140</p> <p>1 methods are directed to," and then you wrote some</p> <p>2 stuff. Do you see that?</p> <p>3 A. Yes. Did you refer to another paragraph?</p> <p>4 Q. Paragraph 25. Do you see that?</p> <p>5 A. Yes.</p> <p>6 Q. And Paragraph 26. I just wanted to</p> <p>7 refresh your memory.</p> <p>8 With that meaning in mind, do you agree</p> <p>9 that the -- what you wrote there in Paragraph 27</p> <p>10 is discussing, in a summary fashion, what the</p> <p>11 claimed methods are directed to from the Guardant</p> <p>12 asserted patents?</p> <p>13 A. So I'd have to read the claims again.</p> <p>14 Really reading this now, "The claimed methods can</p> <p>15 be used to correct errors and reduce background</p> <p>16 noise."</p> <p>17 So it's describing the scope of utility.</p> <p>18 I'm not exactly sure what the limitations are. It</p> <p>19 might be encompassed and directed to, if it's</p> <p>20 further trying to limit -- if you're further</p> <p>21 trying to limit the scope of these inventions.</p> <p>22 But this is one of the potential</p>

<p style="text-align: right;">Page 141</p> <p>1 applications of the inventions. And as I stated</p> <p>2 in Paragraph 26, sort of at a very high level, the</p> <p>3 claimed methods are directed to a series of steps.</p> <p>4 That series of steps allows for correction of</p> <p>5 errors and reducing of background noise.</p> <p>6 But to fully answer that, I'd have to</p> <p>7 really read the claims of the patents. And again,</p> <p>8 this is sort of outside the scope of what I was</p> <p>9 prepared to discuss today.</p> <p>10 Q. The reason I ask is because you put it in</p> <p>11 your declaration.</p> <p>12 A. I didn't put "directed to" in this</p> <p>13 paragraph.</p> <p>14 Q. The only issue is my use of the phrase</p> <p>15 "directed to"?</p> <p>16 A. I'm not sure what you're trying to imply</p> <p>17 with the phrase "directed to," if you're trying to</p> <p>18 further limit the scope of the invention.</p> <p>19 Q. I'm not implying anything. I'm just</p> <p>20 asking questions.</p> <p>21 The scope, I'm literally asking you to</p> <p>22 talk about your declaration. Do you agree with me</p>	<p style="text-align: right;">Page 143</p> <p>1 that the claimed methods of the Guardant asserted</p> <p>2 patents can be used for the purposes you describe</p> <p>3 here, which is tagging both strands, amplifying</p> <p>4 both strands, and sequencing both strands. Right?</p> <p>5 A. So my understanding of patents, the</p> <p>6 patents have a series of dependent claims and</p> <p>7 independent claims.</p> <p>8 In preparation for my deposition today, I</p> <p>9 spent time analyzing the terms that are being</p> <p>10 contested in various patents as to the meaning of</p> <p>11 certain phrases and terms as part of the claim</p> <p>12 construction process.</p> <p>13 I have not done an in-depth analysis of</p> <p>14 the claims of the Guardant patents in terms of</p> <p>15 prior art or trying to understand the breadth and</p> <p>16 the scope of the inventions claimed in those</p> <p>17 patents.</p> <p>18 However, my understanding of patents is</p> <p>19 that they are a series of dependent and</p> <p>20 independent claims. Typically the first claim is</p> <p>21 the major independent claim.</p> <p>22 And looking across these four patents,</p>
<p style="text-align: right;">Page 142</p> <p>1 there?</p> <p>2 MS. SCORDINO: Objection to form.</p> <p>3 A. You're asking me questions actually about</p> <p>4 a prior art analysis.</p> <p>5 Q. I'm sorry. We have moved on from the</p> <p>6 prior art. I have taken your lawyer's comment to</p> <p>7 heart. So put that out of your mind. Okay?</p> <p>8 I'm just asking you about what you wrote</p> <p>9 in Paragraph 27 about what the claims allow for.</p> <p>10 You used that.</p> <p>11 A. I think "allow for" also has a legal</p> <p>12 definition which I'm not sure of today.</p> <p>13 And I would actually want to ask Counsel</p> <p>14 for advice about whether or not that language is</p> <p>15 limiting. And if you'd allow that, I'd be happy</p> <p>16 to have a discussion.</p> <p>17 Otherwise, I can tell you that the claimed</p> <p>18 methods, as I wrote, can be used to correct errors</p> <p>19 and reduce background noise present in NGS,</p> <p>20 et cetera.</p> <p>21 Q. Okay. So sitting here today, you believe</p> <p>22 that when you wrote that sentence, it simply means</p>	<p style="text-align: right;">Page 144</p> <p>1 there are a series of independent claims as the</p> <p>2 first claim. And I'm not going to read them in</p> <p>3 great detail.</p> <p>4 But as an example, in the '858 patent,</p> <p>5 Claim 1, "What is claimed is:</p> <p>6 "A method for analyzing sequencing reads</p> <p>7 of double-stranded cell-free deoxyribonucleic acid</p> <p>8 (cfDNA) molecules from a sample of a subject,</p> <p>9 comprising."</p> <p>10 And it steps through a series of steps</p> <p>11 that describe an analysis that includes a number</p> <p>12 of different elements.</p> <p>13 In the '631 patent, "What is claimed is:</p> <p>14 "A method of generating high accuracy</p> <p>15 sequence reads of a population of double-stranded</p> <p>16 target nucleic acid molecules, comprising," and</p> <p>17 then it steps through a series of steps that go on</p> <p>18 for almost the length of an entire page column.</p> <p>19 '306 patent, "What is claimed is:</p> <p>20 "A method comprising," and then over about</p> <p>21 half the column length there are a series of steps</p> <p>22 that involve the analysis of cell-free DNA</p>

Page 145	Page 147
<p>1 molecules that include tagging, sequencing, other 2 processes.</p> <p>3 And what is claimed in the '221 patent, 4 Claim 1, "A method comprising," and then again we 5 step through a series of steps.</p> <p>6 So we have four patents. We probably have 7 two or three entire pages of claims in these 8 patents.</p> <p>9 In looking at my declaration -- and we're 10 referring to Paragraphs 25, 26, and 27 -- what we 11 have here, in probably a fifth of one of these 12 columns with these very long descriptions of the 13 claimed inventions in these four patents, is a 14 very brief summary of what these individual 15 patents are collectively describing.</p> <p>16 So providing a broad high-level summary of 17 the kind of analysis that we see in Figure 1 of 18 the Guardant patents that include a large number 19 of individual steps.</p> <p>20 So in asking me specific questions about 21 how the patents are limited or what it's directed 22 to, each one of these patents has different</p>	<p>1 And in general, the claim methods can be 2 used to generate accurate sequencing by correcting 3 errors and reducing background noise.</p> <p>4 Q. And that includes, for example, the '631, 5 which you just talked about. Right?</p> <p>6 MS. SCORDINO: Objection to form.</p> <p>7 A. I'm sorry. I mentioned the '631. That 8 was a mistake. I have too many documents in front 9 of me.</p> <p>10 And I understand that Guardant actually 11 copied the claims from some of these patents. So 12 apparently the '631 is largely a copy from '306, 13 so I'll set that aside.</p> <p>14 What I should have said is that -- I'll 15 look at Claim 1 here. This is the Guardant 16 patent.</p> <p>17 So if I can correct my previous answer, my 18 characterization of the '858 patent in its first 19 claim is correct. It's a method for analyzing 20 sequencing reads of double-stranded cell-free DNA 21 molecules from a sample.</p> <p>22 The '306 patent is a method comprising a</p>
Page 146	Page 148
<p>1 variations and describe different methods. And at 2 this moment in time, I'm not prepared to offer 3 in-depth opinions about any of them.</p> <p>4 However, these generally are directed to 5 collecting a bodily fluid sample from a patient, 6 extracting and isolating double-stranded DNA, 7 including cell-free DNA, from the sample, tagging 8 the double-stranded DNA with an adapter and bar 9 code, in which the Watson strand is 10 distinguishable from the Crick strand tag, 11 amplifying or copying the tagged DNA, sequencing 12 the amplified DNA to produce a set of sequence 13 reads, and then identifying true mutations in the 14 sequence reads.</p> <p>15 So each one of these has, as I mentioned, 16 a large number of steps and a variety of different 17 steps. And I don't think it's appropriate to try 18 to condense this, each of them, in a concise 19 summary as a way to try to limit those inventions.</p> <p>20 So yes, in general, the methods contain a 21 series of steps and different variations on the 22 steps. This is not exhaustive.</p>	<p>1 series of steps for doing an analysis.</p> <p>2 The '221 patent is a method comprising a 3 series of steps for doing an analysis.</p> <p>4 And the '063 patent is a method for 5 classifying consensus sequence generated from 6 sequencing reads derived from double-stranded 7 cell-free DNA molecules from a human subject 8 comprising, and then a series of steps.</p> <p>9 And to the best of my knowledge, these 10 claims weren't copied from somewhere else. These 11 were the original invention of the scientists at 12 Guardant.</p> <p>13 Q. What's that knowledge based on?</p> <p>14 A. I haven't been presented any evidence 15 suggesting these were copied from anyone else.</p> <p>16 Q. All right. Let's turn to Paragraph 28 17 from your declaration. And maybe we can move on. 18 It uses the phrase "allow for." And a 19 moment ago you told me you weren't sure what that 20 meant. Are you able to answer questions about 21 what this paragraph means without talking to your 22 attorney?</p>

<p style="text-align: right;">Page 149</p> <p>1 MS. SCORDINO: Objection to form.</p> <p>2 A. I can answer questions without rendering a</p> <p>3 legal opinion.</p> <p>4 Q. Okay. Great. I take it when you signed</p> <p>5 this declaration you understood its contents.</p> <p>6 Right?</p> <p>7 A. I definitely understood its contents.</p> <p>8 Yes.</p> <p>9 Q. And you think -- do you believe you</p> <p>10 continue to have an understanding of its contents</p> <p>11 today?</p> <p>12 A. So you're asking me about limitations</p> <p>13 placed on the claims of the Guardant patents based</p> <p>14 on a high-level summary of what's included in</p> <p>15 them.</p> <p>16 As I mentioned previously, the Guardant</p> <p>17 patents, the first independent claim in each of</p> <p>18 these Guardant patents, if we put them together</p> <p>19 collectively, would probably fill two full columns</p> <p>20 if not more. So full page, tiny type in the</p> <p>21 patents.</p> <p>22 Now you're asking me to try to read</p>	<p style="text-align: right;">Page 151</p> <p>1 discuss my declaration. And I'm happy to discuss</p> <p>2 it with --</p> <p>3 Q. That's not what I asked. I asked a</p> <p>4 different question.</p> <p>5 And my question is, so you told me that</p> <p>6 you understood the declaration when you signed it,</p> <p>7 which was a week or two ago.</p> <p>8 A. Yup.</p> <p>9 Q. And my follow-up question is, do you</p> <p>10 understand it today?</p> <p>11 A. I've been explaining to you today. I've</p> <p>12 spent hours with you explaining it to you today.</p> <p>13 Q. So is that a yes?</p> <p>14 A. I understand it and I understand the</p> <p>15 limitations of --</p> <p>16 Q. Thank you, thank you.</p> <p>17 A. -- what we're here today to discuss.</p> <p>18 Q. So you continue to understand it? I ask</p> <p>19 because I've used some of the language from your</p> <p>20 dec and you told me, "I don't know what that</p> <p>21 means, I've got to talk to my lawyer."</p> <p>22 I'm trying to understand where you and I</p>
<p style="text-align: right;">Page 150</p> <p>1 limitations into those claims when I told you</p> <p>2 previously I was not prepared to testify or to</p> <p>3 offer in-depth opinions on those.</p> <p>4 My understanding of the --</p> <p>5 Q. I'm going to -- Doctor, I did not ask you</p> <p>6 about the limitations of the claims. I had a</p> <p>7 question, and I'm going to reread the question.</p> <p>8 A. My understanding of the goal of today's</p> <p>9 deposition --</p> <p>10 MR. PICKARD: I move to strike as</p> <p>11 nonresponsive.</p> <p>12 Q. Here is my question.</p> <p>13 A. My understanding --</p> <p>14 Q. My question is very simple. Do you</p> <p>15 continue to understand what your declaration means</p> <p>16 today? Full stop.</p> <p>17 A. My understanding of the goal of today's</p> <p>18 deposition was to discuss the claim terms and how</p> <p>19 they're construed. So I am not prepared to</p> <p>20 provide an in-depth answer to questions about</p> <p>21 potential limitations on the claims.</p> <p>22 Now, you asked me if I'm prepared to</p>	<p style="text-align: right;">Page 152</p> <p>1 aren't connecting on the questions and answers.</p> <p>2 A. And I explained that to you. We talked</p> <p>3 about this as a high-level summary in a document</p> <p>4 that was not intended to provide any kind of</p> <p>5 guidance on potential limitations or prior art or</p> <p>6 other in-depth analysis of the Guardant patents.</p> <p>7 This document was developed -- my</p> <p>8 declaration was developed to try to provide</p> <p>9 context for certain claim terms that had been</p> <p>10 construed in which the two parties disagreed.</p> <p>11 Now you're asking me to do what really</p> <p>12 amounts to a more in-depth analysis, which was not</p> <p>13 part of this.</p> <p>14 This background was written -- I'll tell</p> <p>15 you what I understand. It was written to provide</p> <p>16 you and the court with some background about the</p> <p>17 overall feel and some background about the</p> <p>18 patents. It was not an in-depth analysis of the</p> <p>19 limitations of the claims.</p> <p>20 And my concern is that there are terms</p> <p>21 like "directed to," which I used here, which may</p> <p>22 have a specific legal context.</p>

<p style="text-align: right;">Page 153</p> <p>1 And if you'd like me to answer in greater 2 depth, I'd like to actually make sure that I'm not 3 testifying to something in which I may not have a 4 full legal understanding. 5 Q. Okay. So I think you know how this works. 6 You're under oath. I ask questions. You give 7 answers. I don't really care about what you think 8 the intent of today is. So we're going to go back 9 to the question and answer. Is that fair? 10 A. That's what I've been doing all day. 11 Q. All right. Well, I think we can disagree 12 about that. 13 A. That's fine. 14 Q. All right. So we agree that what you've 15 stated here at or about Paragraphs 25 to 28 16 provides what you call context for the other 17 opinions in your declaration. Right? 18 MS. SCORDINO: Objection to form. 19 A. So if we turn the page to page 6, there's 20 a heading which you may have missed, Heading 21 Number 4, "Background of the Technology." 22 So in providing the background over about</p>	<p style="text-align: right;">Page 155</p> <p>1 Since -- 2 Q. Given that, I'll withdraw the question 3 because you seem very worried and I don't want to 4 concern you. 5 So when you wrote "The claimed methods" in 6 the first three words of Paragraph 28, what were 7 you referring to? 8 A. So if you refer back, the claimed methods 9 are the claimed methods in these four Guardant 10 patents. 11 Q. What you call the Guardant asserted 12 patents. Right? 13 A. Yes. 14 Q. So when one performs the claimed methods, 15 do you agree that true mutations in a molecule 16 must inherently appear on both strands? 17 A. So there are four patents here. Each one 18 of the patents has many pages of claims. There's 19 a high-level summary of those claims here. 20 If we understand how these inventions 21 work, one of the things that we often discover in 22 doing analysis is that in the process of library</p>
<p style="text-align: right;">Page 154</p> <p>1 two pages, in providing a background I haven't 2 provided the kind of in-depth analysis you're 3 asking me to do. Providing a high-level summary. 4 And so if you're asking me to read into 5 this high-level summary, which is an abstraction 6 of many pages of claim language in four patents, 7 which honestly was not the subject of what we were 8 going to discuss today and honestly was not 9 something I reviewed in depth in preparation for 10 this deposition, which you asked me earlier, I'm 11 hesitant to provide answers which may -- without 12 having a chance to talk to Counsel, that may be 13 misread or misinterpreted. 14 Q. All right. Let's just see if we can agree 15 to some real basic stuff. 16 Paragraph 28, do you agree that "true 17 mutations in a molecule must inherently appear on 18 both strands" when one performs the claimed 19 methods of the Guardant asserted patents? 20 A. So you added some language to your 21 question which I believe has a legal context and 22 which I'm not prepared to offer an opinion on.</p>	<p style="text-align: right;">Page 156</p> <p>1 generation and sequencing, an apparent mutation 2 can occur, a sequence variation can occur on one 3 of the strands. 4 To truly identify as a true mutation, what 5 you want to see is that variant and its complement 6 on the other strand. 7 So sitting here today, as I told you, 8 without fully reviewing these, that at a high 9 level the claimed methods allow for comparison of 10 complementary strands. And since true mutations 11 in a molecule really must inherently appear on 12 both strands, the strand comparison allows true 13 mutations to be distinguished from sequencing 14 errors which occur on only one of the two strands. 15 So yes, I believe that at a high level the 16 Guardant claims allow for this kind of detection 17 of true mutations by seeing the variant and 18 getting confirmatory evidence on both strands. 19 Q. And if you see a variant on one strand but 20 you don't see its complement on the other, that's 21 indicative of a sequencing error. Right? Or 22 other error?</p>

Page 157	Page 159
<p>1 A. Potentially it's a sequencing error or an</p> <p>2 error that was introduced at another stage in the</p> <p>3 laboratory process.</p> <p>4 Q. Okay. And it's that approach of looking</p> <p>5 for the variant in both strands, variant and its</p> <p>6 complement, that allows the claimed methods to</p> <p>7 provide the necessary sensitivity and --</p> <p>8 specificity and sensitivity for accurate cancer</p> <p>9 detection. Right?</p> <p>10 A. So I think you're mischaracterizing the</p> <p>11 claimed inventions. The claimed inventions are</p> <p>12 not just that last step.</p> <p>13 The claimed invention is actually a whole</p> <p>14 series of processes. Remember, if you look at any</p> <p>15 of these patents, which I believe all share the</p> <p>16 same specification, if you look back at these, all</p> <p>17 of them have Figure 1.</p> <p>18 And Figure 1 provides a high-level summary</p> <p>19 of many different steps. There are laboratory</p> <p>20 steps and there are analytical steps that are</p> <p>21 described at a high level.</p> <p>22 And yes, a mutation should really occur in</p>	<p>1 However, as I was saying earlier before</p> <p>2 you asked the question, finding true mutations in</p> <p>3 both strands is a necessary but not sufficient</p> <p>4 condition for these Guardant asserted patents to</p> <p>5 work.</p> <p>6 So it's absolutely necessary, but you're</p> <p>7 not going to get there unless -- and I apologize</p> <p>8 for providing a high-level summary here, but</p> <p>9 unless you actually practice the invention in the</p> <p>10 Guardant patents.</p> <p>11 You can't take this DCS method</p> <p>12 necessarily, which wasn't really designed for</p> <p>13 doing any of this, and lay your claims on top and</p> <p>14 expect it to work.</p> <p>15 Q. Why did you apologize? I'm just a little</p> <p>16 confused by that.</p> <p>17 A. I'm sorry. I don't remember.</p> <p>18 Q. You said you apologize for providing a</p> <p>19 high-level summary. I don't know what you mean.</p> <p>20 Why are you sorry?</p> <p>21 A. Because you're asking me questions about</p> <p>22 this as if I performed an in-depth analysis. You</p>
Page 158	Page 160
<p>1 both strands. But actually being able to see that</p> <p>2 mutation and identifying it requires that you use</p> <p>3 some innovative and novel laboratory protocols.</p> <p>4 You can't just take a description of some</p> <p>5 protocol that hasn't really seen commercial</p> <p>6 success and tack on a series of claims and then</p> <p>7 try to believe that those claims are allowing you</p> <p>8 to do what the Guardant patent claims with the</p> <p>9 specifications that provide a great level of</p> <p>10 detail. And the claim language provides a great</p> <p>11 level of detail about both the laboratory and</p> <p>12 analytical methods that are involved.</p> <p>13 Q. Why do you need to see commercial success</p> <p>14 before you can do that?</p> <p>15 A. If someone had a great invention and they</p> <p>16 managed to market it, that's some evidence that at</p> <p>17 least their method works.</p> <p>18 Q. Do you know when the Guardant products</p> <p>19 came out relative to the priority date of the</p> <p>20 patents?</p> <p>21 A. I haven't done that analysis for the</p> <p>22 context of today's discussion.</p>	<p>1 asked me before about prior art analysis.</p> <p>2 You're asking me now about a one-paragraph</p> <p>3 summary of four inventions. And the first claim,</p> <p>4 which spans, if I take you to the first claim of</p> <p>5 each of the four patents, it spans more than a</p> <p>6 page of patent text.</p> <p>7 So I apologize because you seem to be not</p> <p>8 grasping the purpose of this high-level summary.</p> <p>9 And if I had made it clearer for you, maybe it</p> <p>10 would be easier for you to understand.</p> <p>11 Q. Why don't you turn to the '631 patent,</p> <p>12 please. It's Exhibit 2, I believe.</p> <p>13 Do I have that right?</p> <p>14 A. Yes.</p> <p>15 Q. Great. Okay. Please turn to Column 13</p> <p>16 for me, please. Let me know when you're there.</p> <p>17 A. I turned right there.</p> <p>18 Q. You'll see in that column there's a series</p> <p>19 of I guess you call them figures or pictures, if</p> <p>20 you will. Do you see those?</p> <p>21 A. Yes.</p> <p>22 Q. There is one at around line 30. Do you</p>

<p style="text-align: right;">Page 161</p> <p>1 see that?</p> <p>2 A. Yes, I do.</p> <p>3 Q. And you agree that's what the patent calls</p> <p>4 an adapter?</p> <p>5 A. So the text immediately preceding this</p> <p>6 describes sort of a synthesis method for</p> <p>7 generating an oligonucleotide that would loop back</p> <p>8 and self-hybridize that contains a uracil, so</p> <p>9 that's an RNA base instead of a DNA base, which</p> <p>10 can be cleaved with an enzyme.</p> <p>11 And as it says in I believe it's line 24,</p> <p>12 "The linker" -- above, the uracil in this</p> <p>13 construct -- "may then be cleaved, yielding a DCS</p> <p>14 adaptor."</p> <p>15 So the image in 30 is sort of a cartoon of</p> <p>16 one of their DCS adapters.</p> <p>17 Q. Okay. Great. And "DCS," that stands for</p> <p>18 duplex consensus sequencing? Do I have that</p> <p>19 right?</p> <p>20 A. I believe that's correct.</p> <p>21 Q. So the adapter shown there at or about</p> <p>22 Column 13, line 30, is an adapter for use in</p>	<p style="text-align: right;">Page 163</p> <p>1 such as" the "uracil."</p> <p>2 So there's nothing here telling me at all</p> <p>3 what those Xs and Ys are other than they're</p> <p>4 complementary to each other.</p> <p>5 Q. Okay. And the uses -- the use in the</p> <p>6 patent of the X and Y, you understand that that's</p> <p>7 to reflect that those four positions could be</p> <p>8 occupied by essentially any nucleotide and its</p> <p>9 complement on the opposite strand. Right?</p> <p>10 A. So you were asking questions just a moment</p> <p>11 ago about bar codes. And this shows one way of</p> <p>12 making a Y-shaped adapter. It doesn't show all</p> <p>13 ways of making Y-shaped adapters, and it doesn't</p> <p>14 actually tell me what type of Y-shaped adapter</p> <p>15 exists.</p> <p>16 If we look at most of the Y-shaped</p> <p>17 adapters which are included in or are described in</p> <p>18 '631 and other patents, these Y-shaped adapters,</p> <p>19 if we look at Figure 2, actually seem to be</p> <p>20 formed -- if I sort of took what's shown on</p> <p>21 page -- on Column 13, if I take that and abstract</p> <p>22 it, what they're showing me actually in Figure 2</p>
<p style="text-align: right;">Page 162</p> <p>1 duplex sequencing. Right?</p> <p>2 A. It's a cartoon of an adapter. They're</p> <p>3 showing a general way of constructing some of</p> <p>4 these adapters. And the XXX and YYY simply</p> <p>5 represent I believe complementary nucleotides.</p> <p>6 So they're not specifying what the</p> <p>7 nucleotides are. But if you make the</p> <p>8 single-stranded molecule with a uracil in the</p> <p>9 middle and allow it to self-hybridize and break</p> <p>10 the uracil, you can make what are referred to</p> <p>11 above in line 7 as Y-shaped SMI adapters.</p> <p>12 Q. And let's focus in on those Xs and Ys in</p> <p>13 that Y-shaped DCS adapter in Column 13.</p> <p>14 The four Xs and four Ys together, that's</p> <p>15 what the patent regards or refers to as a bar</p> <p>16 code. Right?</p> <p>17 MS. SCORDINO: Objection to form.</p> <p>18 A. There's no description actually anywhere</p> <p>19 in Column 13 referring to those with bar codes.</p> <p>20 If you look above starting in line 11, "In this</p> <p>21 schematic, X and Y represent complementary</p> <p>22 nucleotides, and U indicates a cleavable linker,</p>	<p style="text-align: right;">Page 164</p> <p>1 is the way in which they construct their Y-shaped</p> <p>2 adapters.</p> <p>3 So if I look here, I have the 5' and 3'</p> <p>4 ends of the Y, and then I have this complementary</p> <p>5 region and then I have this long string of Ns and</p> <p>6 then a fixed sequence at the end.</p> <p>7 So if I'm interpreting this -- and this</p> <p>8 isn't the entire process for making these Y-shaped</p> <p>9 adapters. But I think Figure 2 will help you</p> <p>10 better understand how they're made.</p> <p>11 Q. My question is not about how they're made.</p> <p>12 A. Yes, it is, because the X and Y are going</p> <p>13 to be these complementary pieces in here, not the</p> <p>14 bar codes, which would then be filled in with a</p> <p>15 polymerase --</p> <p>16 Q. I've moved on from the bar code. We're</p> <p>17 going to come back to it.</p> <p>18 My question is real simple. And that is</p> <p>19 simply, your understanding when the patent and</p> <p>20 that Y-shaped adapter had Xs and Ys there, what's</p> <p>21 intended by that is simply to reflect that each of</p> <p>22 those four positions could be made up of any of</p>

Page 165	Page 167
<p>1 the four nucleotides and their complements on the</p> <p>2 other strand. Right?</p> <p>3 A. So they tell us that in this context, in</p> <p>4 this schematic -- so not in general in the patent,</p> <p>5 but in this schematic, which is really just a</p> <p>6 cartoon that doesn't show you in nearly as much</p> <p>7 detail, say, as Figure 2, in this schematic X and</p> <p>8 Y represent complementary nucleotides.</p> <p>9 So you need complementary nucleotides in</p> <p>10 this component here in Figure 2 where the two</p> <p>11 pieces self-hybridize together.</p> <p>12 Q. Right. And I think I understand your</p> <p>13 issue. I'm not suggesting that -- we're talking</p> <p>14 about a particular example here in Column 13.</p> <p>15 Right?</p> <p>16 A. Yes.</p> <p>17 Q. And there are other examples. Right?</p> <p>18 A. There are a number of examples.</p> <p>19 Q. And some of them are different than what's</p> <p>20 described in Column 13. Right?</p> <p>21 MS. SCORDINO: Objection to form.</p> <p>22 A. I'd have to look at all the examples.</p>	<p>1 Q. All right. So in the particular example</p> <p>2 shown in the schematic in Column 13, can we agree</p> <p>3 that what is reflected by the use of the Xs and Ys</p> <p>4 in that Y-shaped adapter is those four positions</p> <p>5 can be occupied by any nucleotide and their</p> <p>6 corresponding complement on the other strand?</p> <p>7 A. So in this schematic, X and Y represent</p> <p>8 complementary nucleotides.</p> <p>9 I haven't read this through further to see</p> <p>10 if there are any additional limitations placed on</p> <p>11 X and Y. But they could be chosen such that --</p> <p>12 and you have to think about the order and</p> <p>13 orientation -- so that one of the Xs is -- in this</p> <p>14 schematic once it's finally put together, that the</p> <p>15 first X is complementary to the first Y, the</p> <p>16 second X is complementary to the second Y, the</p> <p>17 third to the third, and fourth to the fourth.</p> <p>18 Q. I want to make sure I understand or have</p> <p>19 your understanding of this example. If you look</p> <p>20 above, there's a schematic at about line 10. Do</p> <p>21 you see that?</p> <p>22 A. Yes, I do.</p>
Page 166	Page 168
<p>1 We're talking about this one example.</p> <p>2 Q. You're not sure, sitting here, whether</p> <p>3 there are different examples than what's in</p> <p>4 Column 13?</p> <p>5 MS. SCORDINO: Same objection.</p> <p>6 A. There are many examples. I'm -- if you'd</p> <p>7 like to talk about something really concrete, we</p> <p>8 can look at Figure 2 where --</p> <p>9 Q. I want to talk about the concrete example</p> <p>10 of Column 13. And I just want to make you</p> <p>11 comfortable.</p> <p>12 I'm not trying to suggest by my</p> <p>13 questioning that you're saying everything in the</p> <p>14 patent is what's described in 13. Let's just talk</p> <p>15 it's an example and it's just one of several.</p> <p>16 Can we stipulate to that?</p> <p>17 A. But it says "schematic." Okay? And the</p> <p>18 thing you have to understand is a schematic is not</p> <p>19 going to show full detail. It's going to be some</p> <p>20 sort of high-level, in this case, graphical</p> <p>21 representation that doesn't provide the full depth</p> <p>22 of what these Y-shaped adapters include.</p>	<p>1 Q. And it shows a linear oligonucleotide.</p> <p>2 Can we agree that's what's shown schematically?</p> <p>3 A. Yes. It's a linear oligo shown in</p> <p>4 line 10.</p> <p>5 Q. Okay. And there's another schematic at</p> <p>6 about line 20. Do you see that?</p> <p>7 A. Yes, I do.</p> <p>8 Q. And is it your understanding that at a</p> <p>9 high level -- I realize that's been problematic</p> <p>10 today -- that what's shown in that column is</p> <p>11 essentially three major steps in sequence with</p> <p>12 that schematic at line 10 as a first part or first</p> <p>13 step, line 20 as a second step, and line 30, that</p> <p>14 schematic, as the third step in this process that</p> <p>15 would yield the Y-shaped adapter?</p> <p>16 MS. SCORDINO: Objection to form.</p> <p>17 A. So what you see in line 10 is a linear</p> <p>18 oligonucleotide. Why? Because they're easy to</p> <p>19 synthesize. And with the uracil in the middle</p> <p>20 because that's cleavable and they refer to it as a</p> <p>21 linker. That is then allowed to self-hybridize.</p> <p>22 And again, this is a schematic. I would</p>

Page 169

1 assume that the self-hybridizing region would be
2 longer than four nucleotides, although that may be
3 what they choose.

4 You can also assume that there are
5 additional pieces added onto this that might
6 include an SMI adapter which isn't shown. Again,
7 this is a schematic.

8 And then down below, they show the result
9 of -- and I forget the name of the enzyme, which
10 excise is used -- but in which this U is excised
11 to yield the Y-shaped adapter.

12 But again, they are showing, which is sort
13 of curious, a series of bases that in their
14 schematic diagram would also probably be
15 complementary. And they're not showing the
16 additional SMI 12 nucleotide random piece of the
17 adapter, which is shown in Figure 2, which, you
18 know, to make it easy, would actually be added on
19 to one end of the adapter in line 10.

20 So it doesn't show the full construct.
21 It's simply to provide a schematic representation
22 of how one might make in part a Y-shaped adapter.

Page 170

1 Q. Great. And you mentioned a moment ago
2 hybridization. And that occurs by virtue of the
3 fact that the Xs and Ys are complementary to each
4 other? That allows for what the patent calls
5 self-annealing?

6 A. Self-annealing is the self-hybridization.
7 It's the hybridization of the molecule to itself.

8 And again, reflecting the fact that this
9 is a schematic, the full sequence isn't being
10 shown here, only this complementary piece. And
11 I'll refer you back to Figure 2 where the SMIs are
12 located.

13 And in fact, this is even incomplete
14 because we see a series of dashes on the top and
15 bottom strand which to make these adapters really
16 functional should also be complementary to each
17 other.

18 Q. And all right. If we look at Column 13,
19 line 15, the beginning of the sentence at the end
20 of that line, it says, "The oligonucleotide may be
21 designed with appropriate regions of
22 self-complementarity to anneal" --

Page 171

1 THE VIDEOGRAPHER: I'm sorry. Your
2 microphone is rustling. I didn't hear any of
3 that.

4 MR. PICKARD: Sorry. I'll start over. My
5 apologies.

6 Q. Column 13, line 15, the patent states,
7 "The oligonucleotide may be designed with
8 appropriate regions of self-complementarity to
9 anneal into the following form."

10 Did I read that correctly?

11 A. Yes, you did.

12 Q. And where it says "the oligonucleotide,"
13 it's referring to that schematic at line 10 of
14 Column 15. Correct?

15 A. So in line I believe it's 8, for example,
16 "an oligonucleotide may be prepared in the
17 following form."

18 And that's in line 10, that long linear
19 molecule, which can self-anneal if there are
20 appropriate regions where self-annealing or
21 hybridization can occur.

22 And as I pointed out earlier, this --

Page 172

1 again, recognizing this is a schematic, there are
2 a number of places where the schematic actually
3 doesn't make sense, if you want to dig into it.

4 If it's self-annealed, it wouldn't form a
5 hexagonal ring. It would actually come in and
6 form a partial loop with the Xs and Ys.

7 And in fact, in the regions which are
8 shown parallel to each other, all of those bases
9 there should be complementary.

10 Q. Thank you for that. I think that answered
11 a question, just not mine.

12 Can we agree when the sentence refers to
13 the oligonucleotide, it is the same
14 oligonucleotide that's shown at line 10, which
15 ultimately anneals as shown in line 20?

16 MS. SCORDINO: Objection to form.

17 A. So line 20, I just told you, it can't
18 fully -- it can't take on this form.

19 Q. I want to be clear. Line 20 is an
20 incorrect schematic. Is that your position?

21 A. It's a schematic. But depending on the
22 level of detail you want to look at, it's not

43 (Pages 169 to 172)

<p style="text-align: right;">Page 173</p> <p>1 going to form a hexagonal ring. It can't.</p> <p>2 Q. So that's just wrong when it shows a</p> <p>3 hexagonal --</p> <p>4 A. In this cartoon, the cartoon is meant to</p> <p>5 show -- the schematic is meant to show how one</p> <p>6 might take a linear molecule.</p> <p>7 And again, recognizing this is a cartoon</p> <p>8 and not faithful to what's actually happening but</p> <p>9 to give a high-level view of the process, that</p> <p>10 yes, this is meant to show the linear molecule</p> <p>11 self-hybridizing to form a structure, which has a</p> <p>12 loop, although not a closed loop, but a loop with</p> <p>13 two complementary strands.</p> <p>14 Q. And despite showing a closed loop, you</p> <p>15 agree that a skilled artisan would understand it</p> <p>16 wouldn't actually form that hexagonal cartoon, as</p> <p>17 you called it?</p> <p>18 MS. SCORDINO: Objection to form, outside</p> <p>19 the scope.</p> <p>20 A. A skilled artisan would also recognize the</p> <p>21 limitations of this and also recognize that, given</p> <p>22 the parallel lines here, there are additional X</p>	<p style="text-align: right;">Page 175</p> <p>1 illustrates" . . . "(SMI) adaptor synthesis</p> <p>2 according to one embodiment."</p> <p>3 However, it's worth noting that</p> <p>4 Figure 1 -- Figure 2 shows a synthesis. It</p> <p>5 actually doesn't show the synthesis but it shows</p> <p>6 the structure of the Y-shaped adapter. And that</p> <p>7 Figure 2, in fact, is consistent with the</p> <p>8 illustration shown in Figure 1 of the Y-shaped</p> <p>9 adapters being attached to the T-tailed DNA</p> <p>10 fragments that we were discussing earlier.</p> <p>11 And in fact, if we look at Column 19,</p> <p>12 Example 1 -- and this serves as a template for all</p> <p>13 of the examples actually provided in the patent --</p> <p>14 they actually show the -- state that the adapters</p> <p>15 were synthesized from two oligonucleotides</p> <p>16 designated as the primer strand and the template</p> <p>17 strand.</p> <p>18 And if you look at these, they in fact are</p> <p>19 two independent primers that would create, I</p> <p>20 believe, an asymmetrical Y-shaped adapter.</p> <p>21 So you're absolutely correct that Figure 2</p> <p>22 is one embodiment. And as far as I know, the</p>
<p style="text-align: right;">Page 174</p> <p>1 and Y bases which should have been omitted</p> <p>2 probably for simplification where</p> <p>3 complementarity would be necessary.</p> <p>4 And that in fact, referring back to</p> <p>5 Figure 2, that additional pieces of the</p> <p>6 oligonucleotides necessary to synthesize these</p> <p>7 Y-shaped adapters in additional steps haven't been</p> <p>8 shown.</p> <p>9 Q. Let's look at Column 3, line 63, from the</p> <p>10 '631 patent. We've been talking a lot about</p> <p>11 Figure 2. You agree Figure 2 is just -- it just</p> <p>12 relates to one embodiment of the '631 patent.</p> <p>13 Right?</p> <p>14 MS. SCORDINO: Objection to form.</p> <p>15 Q. I'll just direct you to the sentence that</p> <p>16 says, "FIG. 2 illustrates Single Molecule</p> <p>17 Identifier (SMI) adaptor synthesis according to</p> <p>18 one embodiment."</p> <p>19 So do you agree that Figure 2 just shows</p> <p>20 one embodiment?</p> <p>21 MS. SCORDINO: Objection to form.</p> <p>22 A. So you're correct in that it says, "FIG. 2</p>	<p style="text-align: right;">Page 176</p> <p>1 example in Column 19 that we're referring to is</p> <p>2 not -- is not widely used in the example or it's</p> <p>3 not used in the example in the patent.</p> <p>4 Q. Okay. We haven't been talking about</p> <p>5 Column 19, have we, you and I?</p> <p>6 A. Sorry. Column 13. I misread it.</p> <p>7 Q. All right. If you look at Column 13,</p> <p>8 line 34, it references "A double-stranded SMI</p> <p>9 hairpin." Do you see that?</p> <p>10 A. Yes, I do.</p> <p>11 Q. And "SMI" stands for single molecule</p> <p>12 identifier in the '631 patent. Right?</p> <p>13 A. So it's a double-stranded hairpin linker.</p> <p>14 But yes, SMI is single molecule identifier.</p> <p>15 Q. And earlier we were talking about what the</p> <p>16 X and Y represent. You agree that the patent</p> <p>17 states at about line 36, "For example, a set of</p> <p>18 nucleotides known" -- "of known sequence where X</p> <p>19 and Y represent the complementary SMI sequences</p> <p>20 can be synthesized on an array."</p> <p>21 Do you agree that's what the patent</p> <p>22 discloses?</p>

<p style="text-align: right;">Page 177</p> <p>1 A. So the problem with these schematics is</p> <p>2 that they're incomplete. Right? So a</p> <p>3 double-stranded SMI hairpin linker can be</p> <p>4 constructed by an analogous method to the one</p> <p>5 above we were just discussing but without the need</p> <p>6 for a cleavable linker.</p> <p>7 So in this case -- and I haven't read</p> <p>8 through the entire example. But again, this is a</p> <p>9 schematic which is showing -- if you like, I'll</p> <p>10 read through it, but is showing at least the</p> <p>11 process of allowing self-hybridization in a</p> <p>12 synthesized oligonucleotide to self-hybridize</p> <p>13 based on knowledge a priori of what the bases in</p> <p>14 those oligonucleotides are.</p> <p>15 However, if we look at the way in which</p> <p>16 these SMIs are used, the SMI itself is a</p> <p>17 randomized duplex tag.</p> <p>18 So those bases in the randomized portion</p> <p>19 of the tag, the SMI tag itself, the</p> <p>20 single-molecule identifier, are randomly inserted</p> <p>21 in the process of oligo synthesis.</p> <p>22 And just like I pointed out that that SMI</p>	<p style="text-align: right;">Page 179</p> <p>1 construction step.</p> <p>2 But in fact, as we can see if we look at</p> <p>3 Figure 1, and I think in my declaration I actually</p> <p>4 cite to a number of different external sources of</p> <p>5 information as well as the patent itself that</p> <p>6 demonstrate the SMI tag itself.</p> <p>7 It's a random set of oligonucleotides,</p> <p>8 including a presentation by Dr. Salk himself,</p> <p>9 which I had the pleasure of watching. I think it</p> <p>10 was AACR, the American Association of Cancer</p> <p>11 Research.</p> <p>12 But I watched his presentation. And even</p> <p>13 the mathematics there illustrates what his figures</p> <p>14 in the talk illustrated and what his figures in</p> <p>15 the patent illustrated, that there is this</p> <p>16 randomized duplex tag that's the SMI tag itself.</p> <p>17 So we're trying to draw conclusions about</p> <p>18 the construction of these -- what do they refer</p> <p>19 to? -- SMI hairpin adapters based on a schematic</p> <p>20 which anyone can see is incomplete.</p> <p>21 Q. That video of Dr. Salk that you took</p> <p>22 pleasure in reviewing, he was talking about a</p>
<p style="text-align: right;">Page 178</p> <p>1 tag is missing in the figure in line 20, the SMI</p> <p>2 tag is also missing in this figure in line 45.</p> <p>3 It's the linker, but it doesn't actually</p> <p>4 show the SMI tag itself, which we know from the</p> <p>5 patent is a random collection or a random set of</p> <p>6 oligonucleotides.</p> <p>7 If we had to synthesize each SMI</p> <p>8 independently with a known sequence, the cost</p> <p>9 would be prohibitive if we really wanted to have</p> <p>10 unique molecular identifiers.</p> <p>11 So the way in practice these are</p> <p>12 synthesized is using a random set of nucleotides</p> <p>13 as a bar code.</p> <p>14 Q. And so I want to make clear, part of the</p> <p>15 reason you make that conclusion is it would be</p> <p>16 cost-prohibitive to do otherwise than to use a</p> <p>17 randomized process?</p> <p>18 MS. SCORDINO: Objection to form.</p> <p>19 A. So one of the reasons why you would do</p> <p>20 that -- if I put random oligonucleotides in here,</p> <p>21 I have no way of knowing if they're going to</p> <p>22 hybridize. Right? This is part of the</p>	<p style="text-align: right;">Page 180</p> <p>1 commercial embodiment of TwinStrand's. Is that</p> <p>2 right?</p> <p>3 A. I don't recall exactly what he was</p> <p>4 describing. I do remember the structure of the</p> <p>5 oligonucleotide adapters. I recall him referring</p> <p>6 to -- I think he talks about 4 to the 12th and</p> <p>7 4 to the 24 different adapters.</p> <p>8 I watched it a couple weeks ago. So I</p> <p>9 don't recall exactly what the context of the</p> <p>10 presentation was. I do recall I watched it in</p> <p>11 particular to try to understand the term that he</p> <p>12 was -- to understand how degenerate and</p> <p>13 semi-degenerate sequences were being described in</p> <p>14 the context of creating SMI tags.</p> <p>15 Q. Interesting. So did you do any, like,</p> <p>16 side-by-side comparison of what Dr. Salk was</p> <p>17 talking about with any of the TwinStrand claims to</p> <p>18 see if what he was talking about was the claimed</p> <p>19 invention?</p> <p>20 MS. SCORDINO: Objection to form.</p> <p>21 A. The thing I recall is seeing what I</p> <p>22 believe were versions of the figures here with</p>

<p style="text-align: right;">Page 181</p> <p>1 versions of the figures he was presenting.</p> <p>2 And as I mentioned, my main focus in</p> <p>3 looking at that was really to understand how the</p> <p>4 SMI tags were constructed. I don't know how he</p> <p>5 might map these patents to the subject of what he</p> <p>6 was presenting. But based on the figures, I think</p> <p>7 there's a pretty clear correlation between the</p> <p>8 two.</p> <p>9 Q. So you don't know whether he mapped it?</p> <p>10 You didn't map it. Right?</p> <p>11 A. Actually, Dr. -- let me correct myself,</p> <p>12 please.</p> <p>13 Dr. Salk was talking directly about duplex</p> <p>14 consensus sequencing.</p> <p>15 Q. You didn't map any of his conversation to</p> <p>16 the claims in your declaration, did you?</p> <p>17 A. Not to the claims. But he was talking</p> <p>18 about duplex consensus sequencing. And this</p> <p>19 patent is about duplex consensus sequencing.</p> <p>20 I actually believe the title of this talk</p> <p>21 was something like -- I don't know if I have it</p> <p>22 listed here or not. I'm not going to dig through</p>	<p style="text-align: right;">Page 183</p> <p>1 means that there is a complementary randomized</p> <p>2 sequence, and in this case there are twelve N's,</p> <p>3 which means 4 to the 12th possible combinations."</p> <p>4 If we ligate one of these adapters on one</p> <p>5 end and one on the other end, we have 4 to the</p> <p>6 24th possible random combinations. And there is</p> <p>7 just simply no way the two molecules have the same</p> <p>8 label by random chance. Okay?</p> <p>9 So whether or not this is a commercial</p> <p>10 product or not, Dr. Salk himself in his own words</p> <p>11 describes that method as duplex consensus</p> <p>12 sequencing. Dr. Salk is one of the inventors on</p> <p>13 the '631 patent.</p> <p>14 And the figures map to Figure 1 in the</p> <p>15 patent.</p> <p>16 Q. Do you think Figure 1 limits the scope of</p> <p>17 the TwinStrand patent claims?</p> <p>18 MS. SCORDINO: Objection to form, calls</p> <p>19 for a legal conclusion.</p> <p>20 A. So I'm not prepared to offer a legal</p> <p>21 opinion on what the claims -- what the figures</p> <p>22 might limit the invention to.</p>
<p style="text-align: right;">Page 182</p> <p>1 it. I believe "duplex consensus sequencing" was</p> <p>2 in the title of the presentation, which would tell</p> <p>3 me he's describing what he describes here in the</p> <p>4 specification, duplex consensus sequencing.</p> <p>5 And in referring to this -- it's</p> <p>6 Paragraph 57 of my declaration. "I have also</p> <p>7 reviewed a 2019 AACR presentation given by</p> <p>8 Dr. Jesse Salk, 'TwinStrand Biosciences discusses</p> <p>9 Duplex Sequencing.'"</p> <p>10 And in the presentation, he talked about</p> <p>11 duplex consensus sequencing. And I give you time</p> <p>12 marks in the presentation.</p> <p>13 And Dr. Salk uses the same schematic from</p> <p>14 Figure 1 of the patent and confirms that the</p> <p>15 degenerate SMI tag is randomized.</p> <p>16 So this is actually mapped to the claim</p> <p>17 language. "He states that 'the way duplex</p> <p>18 consensus sequencing works is we have a unique</p> <p>19 label that is affixed to every single molecule, so</p> <p>20 that in this particular case, those "Ns" represent</p> <p>21 a random degenerate sequence' and 'the top</p> <p>22 sequence and the bottom sequence (N and N') just</p>	<p style="text-align: right;">Page 184</p> <p>1 I will say, though, the analysis that I</p> <p>2 did was not in the context of looking at claim</p> <p>3 limitations but, in this case, understanding what</p> <p>4 a degenerate sequence was.</p> <p>5 And as Dr. Salk himself tells us, that a</p> <p>6 random degenerate sequence is in one in which</p> <p>7 there are 12 Ns, which means that we don't know</p> <p>8 what the bases are. Because any N could be one of</p> <p>9 A, C, G, or T and there are 4 to the 12th possible</p> <p>10 combinations. Four nucleotides, 12 of them, 4 to</p> <p>11 the 12th power.</p> <p>12 Q. Can we agree there's more than one way to</p> <p>13 do duplex consensus sequencing?</p> <p>14 A. I don't know what you mean by that.</p> <p>15 Q. What part of that don't you know what I</p> <p>16 mean? Is it the "duplex consensus sequencing"</p> <p>17 phrase that's throwing you or some other part of</p> <p>18 the question?</p> <p>19 MS. SCORDINO: Objection to form, asked</p> <p>20 and answered.</p> <p>21 A. So more than one way to do duplex</p> <p>22 consensus sequencing? So would that include</p>

<p style="text-align: right;">Page 185</p> <p>1 things like running the sequence on an Illumina 2 sequencer or a PacBio sequencer? Sure, there are 3 two ways to do it. 4 Would it require -- could I use a Mac or a 5 PC to analyze the data? Sure, there are different 6 ways to do it. 7 So if you are asking me are there more 8 than one way, it would be useful if you could 9 point to different ways. 10 The examples -- the four examples in the 11 patent itself or the patents themselves and 12 Dr. Salk's description are consistent with an SMI 13 tag being comprised of a set of random degenerate 14 nucleotides. 15 Q. Fair enough. So why don't we look at 16 Column 3, line 44 from the '631 patent, which 17 states, "FIG. 1 illustrates an overview of Duplex 18 Consensus Sequencing." 19 Did I say that right? 20 A. Yes. 21 Q. And so the question, then, so Figure 1 22 shows a way of doing duplex consensus sequencing.</p>	<p style="text-align: right;">Page 187</p> <p>1 essentially consistent with the cartoon in 2 Figure 1. 3 Q. Okay. Fair enough. They're consistent. 4 Are they limited to what's shown in 5 Figure 1? 6 MS. SCORDINO: Objection to form. 7 A. So my understanding is "limited" is a term 8 of legal art, and I'm not prepared today to offer 9 opinions on potential limitations of the claims. 10 What we were talking about here, actually, 11 is claim construction. And that was our goal 12 today. And in particular, we were talking about 13 claim construction for degenerate sequences 14 because those are what the SMI tags consist of. 15 MR. PICKARD: All right. Why don't we do 16 a five-minute break. 17 THE VIDEOGRAPHER: The time is 2:38. 18 We're off the record. 19 (Recess from 2:38 p.m. to 3:00 p.m.) 20 THE VIDEOGRAPHER: We are back on the 21 record. The time is 3:00 p.m. 22 BY MR. PICKARD:</p>
<p style="text-align: right;">Page 186</p> <p>1 Fair? 2 A. It provides an overview. So all the steps 3 are not described in great detail, but it's sort 4 of a schematic overview of duplex schematic 5 sequencing. 6 Q. You tied what Dr. Salk did back to 7 Figure 1. I'd like to know are there any other 8 ways to do duplex consensus sequencing other than 9 what's shown in Figure 1? 10 MS. SCORDINO: Objection to form. 11 A. I think I answered your question. 12 Figure 1 is a cartoon. 13 I don't know what you mean by "other 14 ways." There are a variety of different methods 15 or ideas that are mentioned in passing. I think 16 there are one or two sentences about something in 17 the patent referred to as "the hybrid method." 18 And so I can assume the inventors 19 envisioned a variety of different ways of doing 20 it. I know that what's described in the examples 21 here and what was presented in Dr. Salk's 22 presentation at the 2019 AACR meeting are</p>	<p style="text-align: right;">Page 188</p> <p>1 Q. Dr. Quackenbush, if you could turn to 2 Column 6, line 59, in the '631 patent, which is 3 Exhibit 2 to this deposition. 4 A. You said line 59? 5 Q. Yes, Column 6, line 59. Are you there? 6 A. Yes. 7 Q. It says, "The first and/or second 8 degenerate or semi-degenerate nucleotide n-mer 9 sequences may be any suitable length to produce a 10 sufficiently large number of unique tags to label 11 a set of sheared DNA fragments from a segment of 12 DNA." 13 Did I read that correctly? 14 A. Yes, you did. 15 Q. Looking at that portion of the '631 16 patent, do you agree that the '631 patent uses 17 n-mers to ensure that every DNA fragment in the 18 sample is uniquely labeled? 19 A. Could you repeat the question, please? 20 Q. Sure. So again, directing your attention 21 to Column 6, lines 59 to 64, do you agree that the 22 '631 patent uses n-mers to ensure that every DNA</p>

<p style="text-align: right;">Page 189</p> <p>1 fragment in the sample is uniquely labeled?</p> <p>2 A. The language that you read is actually a</p> <p>3 little bit unclear, "The first and/or second</p> <p>4 nucleotide n-mer sequences may be any suitable</p> <p>5 length to produce a sufficiently" -- and I don't</p> <p>6 know what "sufficiently" means here --</p> <p>7 "sufficiently large number of unique tags to label</p> <p>8 a set of sheared DNA fragments from a segment of</p> <p>9 DNA."</p> <p>10 So the thing you probably recognize is</p> <p>11 that for nucleotides of any length, if we sequence</p> <p>12 the kind of SMI tags that are described in this</p> <p>13 patent and the canonical one which they refer to</p> <p>14 multiple times, including in Column 7, is one</p> <p>15 which is 12 nucleotides long.</p> <p>16 Those 12 nucleotides consist of 12 random</p> <p>17 degenerate nucleotides. So at any position, it's</p> <p>18 randomly chosen or randomly synthesized from an A,</p> <p>19 C, G, or T.</p> <p>20 So as Dr. Salk mentioned in his AACR</p> <p>21 presentation, the 4 to the 12th in each SMI, those</p> <p>22 don't get synthesized in a one-off fashion. They</p>	<p style="text-align: right;">Page 191</p> <p>1 And I think you refer to the example where</p> <p>2 there's 4 to the 24th distinct tags in a reaction.</p> <p>3 That's in that Salk video. Right? Do I have that</p> <p>4 right, Doctor?</p> <p>5 A. I think that's what Dr. Salk refers to.</p> <p>6 Yes.</p> <p>7 Q. And even in that example, there's a small</p> <p>8 but nonzero chance that you're going to get</p> <p>9 different parent polynucleotides that get tagged</p> <p>10 with the same SMI. Right?</p> <p>11 A. Multiple fragments could be tagged with</p> <p>12 the same SMI. Yes.</p> <p>13 Q. And am I right, in principle you can't</p> <p>14 really drive that risk to zero no matter how many</p> <p>15 distinct SMI tags you use in your method? Right?</p> <p>16 MS. SCORDINO: Objection to form.</p> <p>17 A. So you can describe it -- you could drive</p> <p>18 it asymptotically to zero. The longer the SMI</p> <p>19 tags are, the greater the chance that -- the</p> <p>20 smaller the chance that two fragments get the same</p> <p>21 tags.</p> <p>22 Q. Do we agree that the -- this example from</p>
<p style="text-align: right;">Page 190</p> <p>1 actually get synthesized in a large-scale</p> <p>2 sequencing reaction.</p> <p>3 And so what you see is that in the tube of</p> <p>4 oligonucleotides that you get, you actually have</p> <p>5 hundreds of thousands of -- typically hundreds of</p> <p>6 thousands of examples of each molecule.</p> <p>7 So there is some small random chance that</p> <p>8 multiple fragments can be tagged with the same SMI</p> <p>9 tag.</p> <p>10 Part of the reason they use two SMI tags</p> <p>11 is to increase that from 4 to the 12th to 4 to the</p> <p>12 24th, but there may still be instances in which</p> <p>13 molecules get the same tag.</p> <p>14 So the goal, in my understanding of what</p> <p>15 the SMIs are used for, is to try to uniquely label</p> <p>16 these.</p> <p>17 However, we were not provided any guidance</p> <p>18 for what a sufficiently large number of unique</p> <p>19 tags to label the set of sheared DNA fragments is.</p> <p>20 Q. So you mentioned there's a small random</p> <p>21 chance that multiple fragments can be tagged with</p> <p>22 the same SMI tag. I want to explore that a bit.</p>	<p style="text-align: right;">Page 192</p> <p>1 the Salk video with 4 to the 24th distinct SMIs,</p> <p>2 would you consider that a unique labeling</p> <p>3 approach?</p> <p>4 MS. SCORDINO: Objection to form.</p> <p>5 A. So if you turn to my declaration on</p> <p>6 page 24, about a third of the way down I write,</p> <p>7 "Significantly, while these specification</p> <p>8 passages" -- and it refers to a number of</p> <p>9 passages -- "describe 'unique' tagging, none of</p> <p>10 this discussion provides any clarity of the</p> <p>11 differences" between unique and non-unique</p> <p>12 tagging, "if" . . . "among unique, non-unique,</p> <p>13 substantially unique and sufficiently unique</p> <p>14 tagging" and what those differences really are.</p> <p>15 And the term "sufficiently" here stands</p> <p>16 out because I'm not, like I said earlier, sure</p> <p>17 exactly what they're referring to.</p> <p>18 The goal is for the tags to be as unique</p> <p>19 as possible. But again, we're not really provided</p> <p>20 with a great deal of guidance as to what level</p> <p>21 reaches "sufficiently unique."</p> <p>22 So I go on further, "Plaintiffs and</p>

<p style="text-align: right;">Page 193</p> <p>1 Dr. Erlich admit that the categories of 'unique'</p> <p>2 and 'non-unique' can overlap, and that 'unique'</p> <p>3 tags can be identical to each other in 'extremely</p> <p>4 rare circumstances'" . . . "Plaintiffs and</p> <p>5 Dr. Erlich further cite to the Miner reference" --</p> <p>6 which we haven't discussed, that Dr. Erlich refers</p> <p>7 to -- "and describe Miner as 'tagging a population</p> <p>8 of polynucleotide molecules with a highly diverse</p> <p>9 set of tags, such that the probability of two</p> <p>10 genomic fragments being tagged with the same</p> <p>11 molecular sequences is exceedingly improbable -- a</p> <p>12 .31% chance in one instance."</p> <p>13 So this was -- I don't know if in</p> <p>14 Dr. Miner's paper whether this is empirical data</p> <p>15 or the result of a calculation. I don't recall.</p> <p>16 But while 0.31 seems like it's small, one</p> <p>17 of the examples I gave is for an Illumina 550</p> <p>18 sequencer, which was a sequencer that was</p> <p>19 commercially available I believe in 2012. That</p> <p>20 sequencer can generate 400 million sequencing</p> <p>21 reads in a single run. So that is 0.31 percent of</p> <p>22 identical tags would actually yield 1.24 million</p>	<p style="text-align: right;">Page 195</p> <p>1 you consider that approach to be a unique one, one</p> <p>2 that involves unique tags?</p> <p>3 A. 4 to the 12th is what they talk about here</p> <p>4 too. If you recall, in column -- Column 6 going</p> <p>5 on to Column 7, "In one embodiment" -- and this is</p> <p>6 the one Dr. Salk discussed -- "the SMI sequence is</p> <p>7 a random" degenerate "n-mer sequence which is 12</p> <p>8 nucleotides in length. A 12 nucleotide SMI n-mer</p> <p>9 sequence that is ligated to each end of a target</p> <p>10 nucleic acid molecule, as described in the Example</p> <p>11 below, results in the generation of up to 4 to the</p> <p>12 24th" -- and they actually do the math for you, so</p> <p>13 2.8 times 10 to the 14th -- "distinct tag</p> <p>14 sequences."</p> <p>15 Depending on how many fragments you have,</p> <p>16 the number of fragments in your ligation reaction</p> <p>17 can exceed 2.8 times 10 to the 14th, in which case</p> <p>18 the number of molecules would be greater than the</p> <p>19 number of tags, which would require that the tags</p> <p>20 be reused.</p> <p>21 So in the patent and in Dr. Salk's video,</p> <p>22 they use this example. I don't recall whether</p>
<p style="text-align: right;">Page 194</p> <p>1 sequences having the same tags.</p> <p>2 So while the goal is to make them unique,</p> <p>3 I don't know if that's sufficiently unique, that's</p> <p>4 a sufficiently large number that they're</p> <p>5 sufficiently unique such that this 1.24 million --</p> <p>6 one and a quarter million molecules with the same</p> <p>7 tags would actually be significant or</p> <p>8 nonsignificant.</p> <p>9 Part of the problem is the patent really</p> <p>10 doesn't provide guidance for what "sufficient"</p> <p>11 really means here.</p> <p>12 Q. Right. And when you talk about</p> <p>13 "sufficiently," you're referring back to that</p> <p>14 Column 6 thing we looked at a moment ago. Right?</p> <p>15 A. So "sufficiently" does occur here. I</p> <p>16 don't know what a sufficiently large number is. I</p> <p>17 was not given guidance.</p> <p>18 Q. My question was about the Salk video that</p> <p>19 you talked about and you talk about in your</p> <p>20 declaration.</p> <p>21 That approach where he discusses having 4</p> <p>22 to the 12th and 4 to the 24th distinct SMIs, do</p>	<p style="text-align: right;">Page 196</p> <p>1 Dr. Salk refers to the number of tags being</p> <p>2 sufficiently unique or substantially unique.</p> <p>3 But again, the patent doesn't provide any</p> <p>4 guidance for that. If you happen to have a</p> <p>5 transcript of Dr. Salk's video, I'd be happy to</p> <p>6 read it over and see if there are any additional</p> <p>7 references.</p> <p>8 Q. Thank you for that.</p> <p>9 Would you consider -- would you call that</p> <p>10 approach a unique one in any context?</p> <p>11 MS. SCORDINO: Objection to form.</p> <p>12 A. Which approach?</p> <p>13 Q. The use of SMIs having 12 mers.</p> <p>14 A. So if I had one fragment I was going to</p> <p>15 label, it would definitely be unique. Beyond</p> <p>16 that, the goal may be to have unique tags. But</p> <p>17 what I would call it matters less than what the</p> <p>18 patent tells us.</p> <p>19 The patent talks about sufficiently</p> <p>20 unique, substantially unique, and doesn't tell us</p> <p>21 what level of uniqueness one has to have to be</p> <p>22 sufficiently or substantially unique.</p>

Page 197	Page 199
<p>1 Q. Would you please turn to Column 9 in the</p> <p>2 '631 patent. And starting at Column 9, line 9.</p> <p>3 Let me know when you're there.</p> <p>4 A. All right. I have it.</p> <p>5 Q. The patent states, "However described</p> <p>6 below, there are limited" -- "there are a limited</p> <p>7 number of shear points flanking any genomic</p> <p>8 position and thus the power to sequence deeply is</p> <p>9 increased via inclusion of the SMI tag. A hybrid</p> <p>10 method using a combination of sheared ends and a</p> <p>11 shorter n-mer tag (such as 1 or 2 or 3 or 4 or</p> <p>12 more degenerate or semi-degenerate bases) in the</p> <p>13 adapter may also serve as unique molecular</p> <p>14 identifiers."</p> <p>15 Did I read that correctly?</p> <p>16 A. Yes, you did.</p> <p>17 Q. Do you agree the '631 patent explains that</p> <p>18 the tags of the hybrid method are comprised of the</p> <p>19 combination of an n-mer tag and the sheared</p> <p>20 points?</p> <p>21 A. Would you repeat the question?</p> <p>22 Q. Do you agree the '631 patent explains that</p>	<p>1 actually limit the randomness of where these DNA</p> <p>2 fragments shear. And that's what the inventors</p> <p>3 are referring to here.</p> <p>4 So the inclusion of this short n-mer tag,</p> <p>5 and assuming we have four bases and they're</p> <p>6 degenerate, meaning random, 256 n-mers, with a</p> <p>7 limited number of shear points, may also serve as</p> <p>8 unique molecular identifiers.</p> <p>9 Now, it's worth noting that UMIs, unique</p> <p>10 molecular identifiers, and SMI, single molecule</p> <p>11 identifiers, are sometimes used interchangeably.</p> <p>12 And I'm not sure if this "unique molecular</p> <p>13 identifier" term appears elsewhere in the patent.</p> <p>14 If I could search, I would.</p> <p>15 But even though they're calling them</p> <p>16 unique, we're not -- it's very clear, given a</p> <p>17 limited number of shear points and at most 256</p> <p>18 n-mer tags, that all of the molecules themselves</p> <p>19 are going to have unique hybrid tags.</p> <p>20 And unfortunately, it's only these few</p> <p>21 sentences here in Column 9 that describes this</p> <p>22 hybrid method at all.</p>
Page 198	Page 200
<p>1 the tags of the hybrid method are comprised of the</p> <p>2 combination of an n-mer tag and the sheared</p> <p>3 points?</p> <p>4 A. So in Paragraph -- sorry -- Column 9,</p> <p>5 starting at line 9, it says, "A hybrid method</p> <p>6 using a combination of sheared ends and a shorter</p> <p>7 n-mer tag" -- and they talk about 1, 2, 3, or 4</p> <p>8 degenerate or semi-degenerate bases.</p> <p>9 So to give them the benefit of the doubt,</p> <p>10 let's say there are four degenerate bases. So</p> <p>11 they're all random. So there are 256 individual</p> <p>12 possibilities.</p> <p>13 The sentence immediately above this says,</p> <p>14 "However described below, there are a limited</p> <p>15 number of shear points flanking any given genomic</p> <p>16 position and thus the power to sequence deeply is</p> <p>17 increased via the inclusion using an SMI tag."</p> <p>18 So we have a limited number of shear</p> <p>19 points, and that has to do with the physical</p> <p>20 properties of DNA. We talked about the Covaris</p> <p>21 shearing being sort of random, but there are</p> <p>22 actually structural elements of the DNA which</p>	<p>1 So again, I would have to ask, as someone</p> <p>2 reading this short section in the context of the</p> <p>3 larger patent, whether that combination is</p> <p>4 sufficiently unique or substantially unique such</p> <p>5 that I could practice the invention.</p> <p>6 Q. Okay. I don't think I asked if it was</p> <p>7 unique or if it worked.</p> <p>8 Just simply, do you agree that the '631</p> <p>9 patent explains that the tags of the hybrid method</p> <p>10 are comprised of the combination of an n-mer tag</p> <p>11 and a shear point? Do you follow that question?</p> <p>12 A. Yes, I do.</p> <p>13 Q. Can you answer that one?</p> <p>14 A. I just did.</p> <p>15 Q. Okay. I'm not asking whether it works.</p> <p>16 I'm asking, do you agree that the tags of</p> <p>17 the hybrid method as described in the '631 patent</p> <p>18 are comprised of the combination of the n-mer tag</p> <p>19 and the shear points?</p> <p>20 MS. SCORDINO: Objection to form.</p> <p>21 Q. I don't think you did answer it. If you</p> <p>22 did, could you please repeat it.</p>

Page 201	Page 203
<p>1 A. I'd love to see the transcript because</p> <p>2 that was a good answer. If you want to read it,</p> <p>3 you could read it into the record.</p> <p>4 Essentially, if we're talking about the</p> <p>5 tags --</p> <p>6 Q. Actually, it starts at 178. Why don't you</p> <p>7 show me in there where you think you answered it.</p> <p>8 A. So from 178 -- I guess that's a timestamp.</p> <p>9 So from 178:12 down through 180:10.</p> <p>10 Q. And what did you say there?</p> <p>11 A. All right. I can read it again.</p> <p>12 "So in Paragraph" -- sorry -- "Column" --</p> <p>13 it came out as "slum." "Column 9, starting at</p> <p>14 line 9, it says, "A hybrid method using a</p> <p>15 combination of sheared ends in this shorter n-mer</p> <p>16 tag' -- and they talk about 1, 2, 3, or 4</p> <p>17 degenerate or semi-degenerate bases.</p> <p>18 "So to give them the benefit of the doubt,</p> <p>19 let's say there are four degenerate bases. So</p> <p>20 they're all random. So there are 256 individual</p> <p>21 possibilities.</p> <p>22 "The sentence immediately above this says,</p>	<p>1 of shear points, may also include as unique -- may</p> <p>2 also serve as unique molecular identifiers.</p> <p>3 "Now, it's worth noting that UMIs, unique</p> <p>4 molecular identifiers, and SMI, single molecule</p> <p>5 identifiers, are sometimes used interchangeably.</p> <p>6 And I'm not sure if this 'unique molecular</p> <p>7 identifier' term appears elsewhere in the patent.</p> <p>8 If I could search, I would.</p> <p>9 "But even though they're calling them</p> <p>10 unique, we're not -- it's very clear, given a</p> <p>11 limited number of shear points and at most 256</p> <p>12 n-mer tags, that all of the molecules themselves</p> <p>13 are going to have unique hybrid tags.</p> <p>14 "And unfortunately, it's only these few</p> <p>15 sentences in Column 9 that describe this hybrid</p> <p>16 method at all.</p> <p>17 "So again, I would have to ask, as someone</p> <p>18 reading this short section in the context of the</p> <p>19 larger patent, whether or not that combination is</p> <p>20 sufficiently unique or substantially unique such</p> <p>21 that I could practice this invention."</p> <p>22 So then you went on and you followed on</p>
Page 202	Page 204
<p>1 'However described below, there are a limited</p> <p>2 number of shear points flanking any given</p> <p>3 genomic" -- linked to -- "any given genomic</p> <p>4 position and thus the power to sequence deeply is</p> <p>5 increased by the inclusion of an SMI tag."</p> <p>6 Sorry. I'm reading the transcript.</p> <p>7 Q. Right. And there you were just quoting</p> <p>8 the patent.</p> <p>9 A. I was trying to quote this.</p> <p>10 "So we have a limited number of shear</p> <p>11 points, and that has to do with the physical</p> <p>12 properties of DNA. We talked earlier about the</p> <p>13 Covaris shearing being sort of random, but there</p> <p>14 are actually structural elements of the DNA which</p> <p>15 actually limit the randomness of where these DNA</p> <p>16 fragments shear. And that's what the inventors</p> <p>17 are referring to here" -- the limited number of</p> <p>18 shear points.</p> <p>19 "So the inclusion of this short n-mer tag,</p> <p>20 and assuming we have four bases and that they're</p> <p>21 degenerate, meaning" -- again, as I mentioned</p> <p>22 previously -- "256 n-mers, with a limited number</p>	<p>1 asking me about whether or not the tags include.</p> <p>2 The '631 patent explains that the tags of the</p> <p>3 hybrid method are comprised of the combination of</p> <p>4 an n-mer tag and shear point.</p> <p>5 And I believe your confusion in asking</p> <p>6 this question comes down to understanding what the</p> <p>7 tags are supposed to do.</p> <p>8 The tags are supposed to be used to group</p> <p>9 sequences together in the duplex consensus</p> <p>10 sequencing method.</p> <p>11 So if we want to group them together, we</p> <p>12 want to group together the sequence from each</p> <p>13 molecule. And remember we talked about</p> <p>14 amplification, other things happening in the</p> <p>15 process of sequencing.</p> <p>16 We want to be able to track each DNA</p> <p>17 sequence back to a molecule. Essentially kind of</p> <p>18 counting molecules and looking at molecules and</p> <p>19 grouping molecules together.</p> <p>20 And the tags have to be sufficiently</p> <p>21 unique to be able to group them. So when you ask</p> <p>22 me about the tags, I think your confusion is</p>

<p style="text-align: right;">Page 205</p> <p>1 you're forgetting that the tags have to be</p> <p>2 sufficiently unique to practice the invention.</p> <p>3 So are the inventors here saying you could</p> <p>4 use some combination of SMI tags and the sheared</p> <p>5 ends but, in fact, this is the only mention of</p> <p>6 this. We're given no guidance whatsoever.</p> <p>7 How long are these fragment ends we're</p> <p>8 supposed to use? "Sheared ends" or "fragment</p> <p>9 ends," it's an indefinite term in the patent.</p> <p>10 And if we look beyond that indefinite term</p> <p>11 for those -- for the invention to be practiced,</p> <p>12 the tags themselves have to be sufficiently</p> <p>13 unique. And we're not given guidance as to how --</p> <p>14 whether or not those would be sufficiently unique.</p> <p>15 Q. All right. So I think I understand.</p> <p>16 So your point is you just can't tell</p> <p>17 whether what the patent describes as the hybrid</p> <p>18 method at Column 9, whether the tags of that</p> <p>19 method are comprised of the n-mer tags and the</p> <p>20 shear points? You just don't know how long they</p> <p>21 need to be?</p> <p>22 MS. SCORDINO: Objection to form.</p>	<p style="text-align: right;">Page 207</p> <p>1 call it here? The sheared ends. And whether or</p> <p>2 not those are sufficiently unique.</p> <p>3 So are they a tag? Absolutely. You're</p> <p>4 100 percent correct. Are they an SMI tag that can</p> <p>5 be used to practice the claimed invention in the</p> <p>6 '631 patent? That's not clear.</p> <p>7 Q. All right. So with that same statement in</p> <p>8 the spec in mind from Column 9 that we've been</p> <p>9 talking about, do you agree that the '631 patent</p> <p>10 teaches that the hybrid method, using a</p> <p>11 combination of sheared ends and the shorter n-mer</p> <p>12 tag in the adapter, it may serve as a unique</p> <p>13 molecular identifier?</p> <p>14 A. So could you repeat the question, please?</p> <p>15 Q. Do you agree that the '631 patent teaches</p> <p>16 that the hybrid method, using a combination of</p> <p>17 sheared ends and the shorter n-mer tag in the</p> <p>18 adapter, that may serve as a unique molecular</p> <p>19 identifier?</p> <p>20 A. So the patent says that a combination of</p> <p>21 sheared ends and the short n-mer tag in the</p> <p>22 adapter may serve as a unique molecular</p>
<p style="text-align: right;">Page 206</p> <p>1 A. So again, if I wasn't clear --</p> <p>2 Q. You weren't.</p> <p>3 A. The tags of the patent are tags which are</p> <p>4 used to group sequences together. All right?</p> <p>5 The whole duplex consensus sequencing</p> <p>6 method is predicated on grouping sequences</p> <p>7 together.</p> <p>8 The reason is if I take the same parent</p> <p>9 DNA molecule and I carry it through a laboratory</p> <p>10 protocol and I sequence it, in that laboratory</p> <p>11 protocol, the enzymes may make mistakes. I may</p> <p>12 introduce errors. And what I want to be able to</p> <p>13 do, according to the DCS method, is group</p> <p>14 sequences together, build consensus sequences, and</p> <p>15 then do a series of comparisons. Right?</p> <p>16 To do that, I have to be able to group my</p> <p>17 molecules together appropriately. Okay? So these</p> <p>18 sentences do say that you could use an SMI tag</p> <p>19 that consists of a random oligonucleotide tag</p> <p>20 together with the fragment ends.</p> <p>21 But we're given absolutely no guidance as</p> <p>22 to how long those fragment ends are. What do we</p>	<p style="text-align: right;">Page 208</p> <p>1 identifier.</p> <p>2 I wouldn't say it teaches that because</p> <p>3 we're not provided any guidance whatsoever as to</p> <p>4 how to practice the invention in that case because</p> <p>5 we don't know, we're not given any parameters</p> <p>6 whatsoever about the fragment ends, how long they</p> <p>7 are.</p> <p>8 The patent might also say that this</p> <p>9 combination could be used as a table lamp, but</p> <p>10 there's no guidance in the patent as to how one</p> <p>11 might practice that invention. So I wouldn't say</p> <p>12 it teaches how to use it as a table lamp either.</p> <p>13 And I'm sorry for the absurd example.</p> <p>14 But saying this teaches how to use these</p> <p>15 just because it says that, to me, I couldn't read</p> <p>16 this and use what they claim without further</p> <p>17 guidance as to how long these fragment ends have</p> <p>18 to be and how to use them.</p> <p>19 Q. All right. Let's take a look at Example 3</p> <p>20 from the '631 patent. If you could turn to the</p> <p>21 top of Column 26, please. Let me know when you're</p> <p>22 there. Starting about line 10, "Data Analysis."</p>

<p style="text-align: right;">Page 209</p> <p>1 A. Sure.</p> <p>2 Q. The patent states, "The first 10</p> <p>3 nucleotides of each sequencing read pair,</p> <p>4 corresponding to the randomly sheared DNA ends,</p> <p>5 were combined, such that the first 10 nucleotides</p> <p>6 of read 1, referred to as A, was combined with the</p> <p>7 first 10 nucleotides of read 2, referred to as B,</p> <p>8 to yield an SMI tag of form AB."</p> <p>9 Did I read that correctly?</p> <p>10 A. Yes. I believe you did.</p> <p>11 Q. And that sentence is talking about</p> <p>12 grouping based just on the sheared ends in that</p> <p>13 example. Right?</p> <p>14 MS. SCORDINO: Objection to form.</p> <p>15 A. So in Column 26, this is Example 3, and</p> <p>16 this is demonstration of error correction by DCS</p> <p>17 using randomly sheared DNA ends, single molecule</p> <p>18 identifiers.</p> <p>19 And they talk about applying this in the</p> <p>20 <i>Saccharomyces cerevisiae</i> genome, which is yeast.</p> <p>21 You can look it up. And that genome is 12</p> <p>22 megabases in length, 12 million base pairs.</p>	<p style="text-align: right;">Page 211</p> <p>1 MR. PICKARD: All right. I think I may be</p> <p>2 done. Let's take a short break just so I can</p> <p>3 confer with my colleagues.</p> <p>4 THE WITNESS: Thank you.</p> <p>5 THE VIDEOGRAPHER: The time is 3:36.</p> <p>6 We're off the record.</p> <p>7 (Recess from 3:37 p.m. to 3:50 p.m.)</p> <p>8 THE VIDEOGRAPHER: We are back on the</p> <p>9 record. The time is 3:50.</p> <p>10 BY MR. PICKARD:</p> <p>11 Q. So, Dr. Quackenbush, from the time you</p> <p>12 were sworn in under oath this morning to now, have</p> <p>13 you discussed your testimony with anyone today?</p> <p>14 A. No, I haven't.</p> <p>15 MR. PICKARD: All right. Pass the</p> <p>16 witness.</p> <p>17 MS. SCORDINO: I have no questions for the</p> <p>18 witness.</p> <p>19 THE VIDEOGRAPHER: The time is 3:50.</p> <p>20 We're off the record.</p> <p>21 (Whereupon the deposition</p> <p>22 was concluded at 3:50 p.m. EDT)</p>
<p style="text-align: right;">Page 210</p> <p>1 The human genome is 3 billion bases long.</p> <p>2 So it's 2.5 times 10 to the 8th, which is</p> <p>3 250 million times the size of these genes.</p> <p>4 So they're telling us that 10 nucleotides</p> <p>5 of sequence may be sufficient to be an SMI tag</p> <p>6 without any other random sequence attached in the</p> <p>7 tiny yeast genome.</p> <p>8 But I have no guidance whatsoever in how</p> <p>9 to apply this in a genome that's 250 million times</p> <p>10 larger.</p> <p>11 If my goal is to produce a diagnostic for</p> <p>12 yeast, then maybe the patent teaches me how to do</p> <p>13 that. If my goal is to produce a diagnostic for</p> <p>14 humans, I have no guidance from the patent</p> <p>15 whatsoever as to what may be sufficient.</p> <p>16 In fact, if I think about this and if</p> <p>17 10 nucleotides are what I need for yeast, if I</p> <p>18 need something longer for a genome that's</p> <p>19 250 million times the size, then I may need</p> <p>20 something which is longer than the length of</p> <p>21 sequence I could have generated in 2012 when this</p> <p>22 patent was first filed.</p>	<p style="text-align: right;">Page 212</p> <p>1 COMMONWEALTH OF MASSACHUSETTS</p> <p>2 SUFFOLK, SS.</p> <p>3</p> <p>4 I, Michelle Keegan, Registered Merit Reporter</p> <p>5 and Notary Public in and for the Commonwealth of</p> <p>6 Massachusetts, do hereby certify that JOHN</p> <p>7 QUACKENBUSH, PH.D., the witness whose deposition</p> <p>8 is hereinbefore set forth, was duly sworn by me</p> <p>9 and that such deposition is a true record, to the</p> <p>10 best of my ability, of the testimony given by the</p> <p>11 witness.</p> <p>12 I further certify that I am neither related to</p> <p>13 or employed by any of the parties in or counsel to</p> <p>14 this action, nor am I financially interested in</p> <p>15 the outcome of this action.</p> <p>16 In witness whereof, I have hereunto set my hand</p> <p>17 and seal this 13th day of September, 2022.</p> <p>18</p> <p>19 Notary Public</p> <p>20 My commission expires:</p> <p>21 May 15, 2026</p> <p>22</p>

53 (Pages 209 to 212)

Page 213	Page 215
<p>1 John Quackenbush, Ph.D., c/o DLA PIPER LLP 2 33 Arch Street, 26th Floor Boston, Massachusetts 02110-1447</p> <p>3</p> <p>4 Case: TwinStrand Biosciences, Inc., et al. v. Guardant Health, Inc. Date of deposition: September 9, 2022 Deponent: John Quackenbush, Ph.D.</p> <p>5</p> <p>6 Please be advised that the transcript in the above referenced matter is now complete and ready for signature. 7 The deponent may come to this office to sign the transcript, 8 a copy may be purchased for the witness to review and sign, 9 or the deponent and/or counsel may waive the option of 10 signing. Please advise us of the option selected. 11 Please forward the errata sheet and the original signed 12 signature page to counsel noticing the deposition, noting the 13 applicable time period allowed for such by the governing 14 Rules of Procedure. If you have any questions, please do 15 not hesitate to call our office at (202)-232-0646.</p> <p>16</p> <p>17</p> <p>18 Sincerely, 19 Digital Evidence Group 20 Copyright 2022 Digital Evidence Group 21 Copying is forbidden, including electronically, absent 22 express written consent.</p>	<p>1 Digital Evidence Group, LLC 2 1730 M Street, NW, Suite 812 3 Washington, D.C. 20036 4 (202)232-0646</p> <p>5</p> <p>6 ERRATA SHEET</p> <p>7</p> <p>8 Case: TwinStrand Biosciences, Inc., et al. v. Guardant Health, Inc. 9 Witness Name: John Quackenbush, Ph.D. 10 Deposition Date: September 9, 2022 11 Page No. Line No. Change 12 13 14 15 16 17 18 19 20 21 22</p> <p style="text-align: center;">Signature _____ Date _____</p>
<p style="text-align: center;">Page 214</p> <p>1 Digital Evidence Group, L.L.C. 1730 M Street, NW, Suite 812 2 Washington, D.C. 20036 (202) 232-0646</p> <p>3</p> <p>4 SIGNATURE PAGE Case: TwinStrand Biosciences, Inc., et al. v. Guardant Health, Inc. 5 Witness Name: John Quackenbush, Ph.D. Deposition Date: September 9, 2022</p> <p>6</p> <p>7 I do hereby acknowledge that I have read and examined the foregoing pages of the transcript of my deposition and that:</p> <p>8</p> <p>9 (Check appropriate box): () The same is a true, correct and 10 complete transcription of the answers given by me to the questions therein recorded. 11 () Except for the changes noted in the attached Errata Sheet, the same is a true, 12 correct and complete transcription of the 13 answers given by me to the questions therein 14 recorded.</p> <p>15</p> <p>16 _____ 17 DATE WITNESS SIGNATURE</p> <p>18</p> <p>19</p> <p>20</p> <p>21 _____ 22 DATE NOTARY</p>	



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

Case IPR2019-00652
Patent No. 9,834,822

DECLARATION OF DR. JOHN QUACKENBUSH

GUARDANT - EXHIBIT 2025
Foundation Medicine, Inc. v. Guardant Health, Inc.
IPR2019-00652

TABLE OF CONTENTS

I.	QUALIFICATIONS	1
II.	SCOPE OF WORK.....	4
III.	LEGAL STANDARDS	5
IV.	LEVEL OF ORDINARY SKILL	6
V.	BACKGROUND	8
	A. Cellular DNA and cell-free DNA.....	8
	B. Next generation sequencing	9
	C. Error correction techniques introduce cost and complexity.....	11
VI.	CITED REFERENCES	13
	A. Fan (EX1048).....	13
	B. Forshew (EX1004)	13
	C. Schmitt (EX1011 and EX1047)	14
VII.	THE '822 PATENT	17
VIII.	CLAIM CONSTRUCTION	21
IX.	THE PETITION MATERIALS DO NOT ESTABLISH UNPATENTABILITY OF THE CHALLENGED CLAIMS	25
	A. Schmitt does not disclose a method for non-uniquely tagged parent polynucleotides.....	25
	i. Petitioner's contrived scenario does not support its assertion that Schmitt teaches non-uniquely tagging.....	26
	ii. Schmitt exclusively teaches unique tagging methods	29

B.	Neither Schmitt nor any combination of references teaches a method for converting cell-free DNA into tagged parent polynucleotides.....	34
C.	The petition materials do not establish that a skilled artisan would have wanted to combine Schmitt with either Fan or Forshew	36
D.	The petition materials do not establish that the Schmitt methods would reasonably be applicable to cell-free DNA	39
E.	Schmitt is not applicable to cell-free DNA	45
F.	The petition materials do not establish that dependent claims 2-13 and 17-20 are unpatentable	49
i.	Claim 2 is not unpatentable.....	50
ii.	Claim 5 is not unpatentable.....	51
iii.	Claim 9 is not unpatentable.....	51
iv.	Claim 12 is not unpatentable.....	52
v.	Claim 13 is not unpatentable.....	54
X.	OBJECTIVE INDICIA CONFIRM THE PATENTABILITY OF THE CHALLENGED CLAIMS	54
A.	Long-Felt Need.....	59
B.	Commercial Success.....	60
XI.	CONCLUDING STATEMENTS.....	62

I, John Quackenbush, declare as follows:

I. QUALIFICATIONS

1. I have been retained by Counsel on behalf of Guardant Health, Inc. to provide opinions in this matter related to my experience and expertise. My opinions are based on my skills, knowledge, training, education, and experience in matters of this nature, and my examination of the materials utilized in preparing this report.

2. I am a Henry Pickering Walcott Professor of Computational Biology and Bioinformatics and Chair of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health. I am also Director of the MS Program in Computational Biology and Quantitative Genetics and Director of the Big Data to Knowledge Training Program. In addition, I hold appointments as Professor of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute and at the Channing Division of Network Medicine of Brigham and Women's Hospital.

3. In addition to my academic appointments, I co-founded Genospace LLC. Genospace produces software solutions to operationalize precision medicine through the integration of clinical and genomic data and its presentation to clinical and research users in an intuitive format. Genospace was purchased by Hospital Corporation of America in January of 2017.

4. In addition to my academic and research responsibilities, over the years I have taken significant regional and national research leadership responsibilities. I have served on the Scientific Advisory Board of the St. Jude's Children's Research Hospital and the Board of Scientific Counselors of the Environmental Protection Agency. I have also served on numerous scientific review panels for the National Institutes of Health, the National Science Foundation, the Department of Energy, the National Aeronautics and Space Administration, the Wellcome Trust, Genome British Columbia, Genome Canada, the National Sciences and Engineering Council of Canada, and the European Union. And I have served on numerous study panels for the National Research Council, the National Academy of Sciences, and the Institute of Medicine.

5. I have presented more than 300 talks, courses, and workshops since joining the Harvard School of Public Health and Dana-Farber in 2005. I have also taught numerous courses and workshops on the analysis of genomic data and served as an organizer of the EMBO course on DNA microarray analysis for more than 5 years.

6. Prior to joining the faculty at Dana-Farber and Harvard, I was a Professor of Chemical Engineering at the University of Maryland from 2003-2005; an Investigator with The Institute for Genomic Research from 2002-2006; a Professor in the Department of Biochemistry at The George Washington

University from 2000 – 2005; a Lecturer in The Department of Biostatistics at The Johns Hopkins University from 1998 – 2005; an Associate Investigator at The Institute for Genomic Research from 1997 – 2001; and an Assistant Investigator at The Institute for Genomic Research in 1997.

7. I received my Ph.D. in Theoretical Particle Physics at the University of California, Los Angeles in 1990. I also hold a Master of Science in Physics from University of California, Los Angeles and a Bachelor of Science in Physics from the California Institute of Technology.

8. I have studied, taught, practiced, and conducted research involving the use of genomic technologies, including DNA sequencing and DNA microarrays, and involving computational analysis of data related to genomic technologies. I have expertise in genomic technologies, computational analysis, and modeling of a plant, animal, and microbial systems with an emphasis on the study of human diseases, such as cancer.

9. I have received numerous awards and honors including being recognized as a White House Open Science Champion of Change, an Australia Fellow, and a Distinguished International Advisor for the International Conference of BioInformatics and BioEngineering sponsored by the Institute of Electrical and Electronics Engineers.

10. I have published more than 290 peer reviewed scientific papers that have been cited more than 71,000 times. I have had continuous grant support for my research from the National Institutes of Health and other organizations for nearly twenty-seven years. In 2018, I received an NCI Outstanding Investigator Career Award, a seven-year research grant recognizing a lifetime record of substantial contributions to the field.

11. A copy of my Curriculum Vitae, attached as EX2026, contains further details on my education, experience, publications, and other qualifications to render an expert opinion in this matter.

II. SCOPE OF WORK

12. I understand that a petition was filed with the United States Patent and Trademark Office for inter partes review of U.S. Patent No. 9,834,822 (“the ’822 patent,” EX1001).

13. I further understand that the Patent Trial and Appeal Board (“PTAB” or the “Board”) has decided to institute inter partes review of claims 1–13 and 17–20 of the ’822 patent under 35 U.S.C. § 103 based on the disclosures of U.S. Patent No. 9,752,188 (“the Schmitt patent,” EX1011), Schmitt, et al., “Detection of Ultra-rare Mutations by Next-generation Sequencing” (“Schmitt 2012,” EX1047), Fan, et al., “Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood” (“Fan,” EX1048), and Forshew, et al., “Noninvasive

Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA” (“Forsheew,” EX1004).

14. I receive \$750 per hour for my services. I am also being reimbursed for reasonable and customary expenses associated with my work in this investigation. My compensation is not contingent on the outcome of this matter or the specifics of my testimony.

III. LEGAL STANDARDS

15. I have been advised that a claimed invention is not patentable under 35 U.S.C. § 103 if it is obvious. A patent claim is unpatentable if the claimed invention would have been obvious to a person of ordinary skill in the field at the time the claimed invention was made. This means that even if all requirements of the claim cannot be found in a single prior art reference that would anticipate the claim, a person of ordinary skill in the relevant field who knew about all this prior art would have come up with the claimed invention.

16. I have further been advised that the ultimate conclusion of whether a claim is obvious should be based upon several factual determinations. That is, a determination of obviousness requires inquiries into: (1) the level of ordinary skill in the field; (2) the scope and content of the prior art; (3) what difference, if any, existed between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness.

17. I have been advised that, in determining the level of ordinary skill in the field that someone would have had at the time the claimed invention was made, I should consider: (1) the levels of education and experience of persons working in the field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology.

18. I have been advised that a patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was independently known in the prior art. In evaluating whether such a claim would have been obvious, I may consider whether there is a reason that would have prompted a person of ordinary skill in the field to combine the elements or concepts from the prior art in the same way as in the claimed invention.

19. I have also been advised, however, that I must be careful not to determine obviousness using the benefit of hindsight; many true inventions might seem obvious after the fact.

20. Finally, I have been advised that any obviousness rationale for modifying or combining prior art must include a showing that a person of ordinary skill would have had a reasonable expectation of success.

IV. LEVEL OF ORDINARY SKILL

21. I have been advised that, in determining the level of ordinary skill in the art that someone would have had at the time the claimed invention was made, I

should consider: (1) the levels of education and experience of persons working in the field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology. I have been advised that an invention must be evaluated not through the eyes of the inventor, who may have been of exceptional skill, but as by one of ordinary skill in the art.

22. According to Dr. Gabriel, “a person of ordinary skill in the art, as of September 4, 2012, would have had a Ph.D. in genetics, molecular biology, bioinformatics or a related field, and at least five years of research in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics. The person of ordinary skill in the art would have had knowledge of DNA sequencing, including next generation sequencing (NGS) and related sequencing methods, and related sample preparation techniques, bioinformatics methods for grouping and comparing sequence reads and mapping sequence reads onto genomes, and methods for identifying genetic variants in a sample.” EX1002, ¶72.

23. Dr. Gabriel describing a person of exceptional skill, not a person of ordinary skill in the art.

24. In addition, Dr. Gabriel’s description omits relevant knowledge that a person of ordinary skill in the art would have had concerning the types of mutations that drive cancer and are consequential for the treatment of cancer.

Furthermore, a person of ordinary skill in the art would have known that different sample types have different challenges and considerations. For example, such a skilled artisan would have known that just because a technique is designed for cellular DNA does not necessarily make it well suited to cell-free DNA — a fundamentally different sample type.

25. Regardless of which definition is applied the challenges fail. Even applying Dr. Gabriel's perspective, the asserted prior art references do not render the claims obvious.

V. BACKGROUND

A. Cellular DNA and cell-free DNA

26. The ability to analyze tumor markers in cell-free DNA (“cfDNA”) is significant. Unlike cellular DNA, cfDNA is typically present in such low concentrations that detection and analysis was difficult with prior techniques. *E.g.*, EX1004 at 32 (Table S6) (disclosing samples containing between 0.9 and 17.9 ng cfDNA); EX1048 at 16270 (disclosing samples containing between 1 and 8 ng cfDNA); EX1001, 33:12-17 (teaching that prior art library preparation methods were low efficiency and required “greater than 1 microgram of DNA as input material.”).

27. Additionally, cfDNA is highly fragmented which compounds the difficulty of NGS library preparation. These short fragments of cfDNA require

distinct isolation procedures as compared to cellular DNA. EX1056 at 433 (“cfDNA assay issues”).

28. Absent information to the contrary, a person of ordinary skill in the art would not expect a method designed for cellular DNA to be applicable to cfDNA. *E.g.*, EX2003 at 3 (“Furthermore, the sensitivity to detect variants from low purity samples will be limited by the total yield or genome equivalents of *cfDNA* that are available for sequencing. Thus, the accurate profiling of tumor DNA or RNA in a sample that contains non-tumor DNA or RNA is challenging and *requires specialized methods...*”) (internal citations omitted).

B. Next generation sequencing

29. Next Generation Sequencing (“NGS”) has been used to accurately identify a wide array of human genetic aberrations. Most NGS-based studies and diagnostic assays do not use a barcode-based error correction method. This is because the error rate associated with NGS is sufficiently low such that it does not significantly affect interpretation of the resulting data. *See, e.g.*, Fan (EX1004).

30. For example, some NGS-based diagnostic techniques are not used to identify sequence variation. Applications such as fetal aneuploidy detection rely on counting NGS reads associated with a particular chromosome and simply do not analyze or report sequence variants. Such applications are insensitive to sequencing errors. Accordingly, fetal aneuploidy detection methods, such as

reported by Fan (EX1004), typically do not employ any error correction method.

See also EX1050.

31. Other NGS applications cannot tolerate a 1% error rate, such as applications that use NGS to diagnose rare mutations, because these methods require a relatively high degree of sequence fidelity. Accordingly, error correction methods, including redundant sequencing of samples and molecular barcoding, are typically used.

32. Forshew, for example, relies on redundant sequencing to distinguish between sequencing errors and true point mutations (*i.e.*, single nucleotide variants) in the sample DNA. *E.g.*, EX1004 at 19 (“A point mutation was called in a sample if it ranked among the 6 loci with highest non-reference frequency in both duplicates, and was represented by at least 10 reads in each.”).

33. Schmitt, for example, uses a molecular barcoding approach to error correction. In this method, individual polynucleotide molecules are tracked through the sample preparation and sequencing processes. Molecular barcoding allows for identification and grouping of sequence reads derived from PCR duplication of a sample polynucleotide molecule. *E.g.*, EX1011, Fig. 3, 4:4-29. These groups of sequence reads are typically referred to as “families” and represent the PCR progeny of a common parent polynucleotide molecule in the original sample.

C. Error correction techniques introduce cost and complexity

34. The petition materials seem to assume that barcode-based error correction is always desirable. *E.g.*, EX1002, ¶¶99 (“Because Schmitt’s DCS approach can have a ‘general role in next generation DNA sequencing,’ the person of ordinary skill in the art would consider Schmitt to provide the explicit motivation to apply the DCS approach for sequencing cell-free DNA as taught by Fan.”), ¶109 (“[I]t is my opinion that a person of ordinary skill in the art would have been motivated to combine the teachings of Schmitt and Forshew because both disclose methods of ‘deep sequencing’ to detect low frequency mutations.”). This is not the case. Error correction techniques add cost, complexity, and often result in losses of sample DNA.

35. Error correction typically requires sequencing of amplicons derived from the original sample polynucleotide. EX1057 at 4 (“DS is a uniquely sensitive method that is capable of detecting and quantifying mutations that occur at extremely low frequencies; however, this ability comes at a cost. Owing to the method’s reliance on sequencing multiple PCR duplicates of both DNA strands, DS requires much larger sequencing capacity than conventional NGS to produce a given depth of sequencing. At present, the use of current NGS technology with DS to sequence large genomes or genome targets > 1-2 Mbp in size to a high depth of

coverage is prohibitively expensive”). That is, error correction requires sequencing of multiple copies of the target sequence.

36. Error correction methods also require additional bioinformatic steps which further adds to the cost and complexity. *E.g.*, EX1011, 4:4-29.

37. A person of ordinary skill in the art would have understood that some barcode techniques can skew test results. For reasons not completely understood, disparities in performance are often observed among different barcodes. This is particularly problematic with degenerate barcodes.

38. Finally, the sample preparation steps involved in error correction schemes often lose a considerable amount of sample. EX1057 at 5 (“[W]hen feasible, it is most convenient to start with excess amounts of DNA to allow for easy quantification of the DNA throughout the initial sample preparation steps and to account for expected sample loss at the enzymatic and purification steps.”).

39. Sample loss may be tolerable when working with samples containing large amounts of DNA (*e.g.*, microgram quantities), but is not acceptable when working with samples that contain only a minute amount of DNA. EX1001, 60:50-61 (“Unlike conventional sequencing library preparation protocols, whereby the majority of extracted circulating DNA fragments are lost due to inefficient library conversion, our Digital Sequencing Technology workflow enables the vast majority of starting molecules to be converted and sequenced. This is critically

important for detection of rare variants as there may only be a handful of somatically mutated molecules in an entire 10 mL tube of blood. The efficient molecular biology conversion process developed enables the highest possible sensitivity for detection of rare variants.”).

VI. CITED REFERENCES

A. Fan (EX1048)

40. Fan discloses detection of fetal aneuploidy in maternal plasma samples using shotgun sequencing. *E.g.*, EX1048 at 16266 (“Shotgun Sequencing of Cell-free Plasma DNA”). Fan does not disclose detecting sequence variants in maternal plasma samples. Rather Fan discloses determining fetal aneuploidy by detecting an excess of NGS reads associated with a given chromosome. EX1048 at 16267-68 (Detection of Fetal Aneuploidy).

41. Fan does not disclose tagging sample DNA nor does Fan disclose a method for correcting sequencing errors. EX1048 at 16270 (“Sample Processing and DNA Quantification”), 16271 (“Data Analysis”).

B. Forshew (EX1004)

42. Forshew discloses detection of mutant alleles in plasma samples. *E.g.*, EX1004 at Table 1, 3 (“Quantitative limitations of mutation detection”). Forshew uses deep sequencing and replicate analysis to avoid false positives resulting from sequencing errors. EX1004 at 9 (“Duplicate sequencing of each sample is used to avoid false positives stemming from PCR errors.”), 10 (“Higher read depth or

fidelity, additional replicates, or improved algorithms could allow for enhanced mutation detection without change to protocols.”), 19 (“A point mutation was called in a sample if it ranked among the 6 loci with highest non-reference frequency in both duplicates, and was represented by at least 10 reads in each.”).

43. Forsheew discloses accurate detection of mutant alleles at frequencies as low as 2%. EX1004 at abstract.

44. To the extent Forsheew teaches tagging, it is the tagging of amplicons for the purpose of multiplex analysis. EX1004 at 2 (“Finally, sequencing adaptors and sample-specific barcodes were attached to the harvested amplicons in a further PCR.”), 9 (“Sample barcodes and high throughput PCR reduce the per sample costs to a range where this may be widely applicable.”).

C. Schmitt (EX1011 and EX1047)

45. The Schmitt patent (EX1011) and Schmitt 2012 (EX1047) (collectively, “Schmitt”)¹ disclose “Duplex Sequencing” which purports to reduce error through analysis of both strands of a DNA duplex. EX1047 at Abstract

¹ The petition asserts that the Schmitt patent (EX1011) and Schmitt 2012 (EX1047) teach “the same DCS method.” Pet. 28. Petitioner relies nearly exclusively on the Schmitt patent, however, since both references disclose the same DCS method, Patent Owner’s responsive arguments apply equally to both.

("[Duplex Sequencing] greatly reduces errors by independently tagging and sequencing each of the two strands of a DNA duplex. As the two strands are complementary, true mutations are found at the same position in both strands.").

46. The method of Schmitt requires flooding the sample with "SMI tags" or "n-mers" to ensure that every DNA fragment in the sample is uniquely labeled. These tags," allow for the tagging of every parent polynucleotide molecule with a different barcode. *E.g.*, EX1011, 3:46-53; 6:59-63; 18:36-41 ("Because the use of SMI tags ... allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence."); EX1047 at 14509 ("The sequences of uniquely tagged PCR duplicates are then compared to create a PCR consensus sequence.").

47. Schmitt groups PCR progeny into families solely by virtue of the SMI tag. *E.g.*, EX1011, 4:4-9 ("FIG. 3 illustrates error correction through Duplex Consensus Sequencing (DCS) analysis according to one embodiment. (a-c) shows sequence reads (brown) sharing a unique set of SMI tags are grouped into paired families"), 18:36-41 ("Because the use of SMI tags ... allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence."), 20:50-52 ("Reads having common (i.e., identical) SMI

sequences were grouped together, and were collapsed to generate a consensus read.”).

48. All disclosed embodiments of Schmitt rely solely on SMI tags for grouping, including the hybrid method. For example, Schmitt explains, that the tags of the “hybrid method” are comprised of the combination of an n-mer tag and the shear points. EX1011, 9:9-13 (“A hybrid method using a combination of sheared ends and a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases) in the adaptor may also serve as unique molecular identifiers.”).

49. Because the SMI tag provides the sole basis for grouping sequence reads, each SMI tag must be unique. EX1011, 18:36-37 (“Because the use of SMI tags (or ‘double-stranded SMI sequences’) allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence. This approach would thereby minimize the loss of data by overcoming the intrinsic limitations of using shear points to identify PCR duplicates.”), 3:47-49 (“Because every adaptor contains a unique, double-stranded, complementary n-mer random tag on each end...”), 6:59-63 (“The first and/or second degenerate or semi-degenerate nucleotide *n-mer sequences may be any suitable length to produce a sufficiently large number of unique tags* to label a set of sheared DNA fragments

from a segment of DNA.”), 18:36-41 (“Because the use of SMI tags ... allows every molecule to be *uniquely labeled* prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence.”), 21:59-61 (“The sequences of *uniquely tagged PCR duplicates* are subsequently compared in order to create a PCR consensus sequence.”) (emphases added).

50. Because the SMI tag provides the sole basis for grouping sequence reads, each SMI tag must be unique. EX1011, 3:47-49, 6:59-63, 18:36-41, 21:59-61. Moreover, polynucleotides that are not uniquely tagged cannot be properly grouped and analyzed and must be discarded.

VII. THE '822 PATENT

51. The method of the '822 patent uniquely identifies parent polynucleotide molecules and is able to do so using only a small handful of barcodes. *E.g.*, EX1001, 41:25-28 (“Improvements in sequencing can be achieved as long as at least some of the duplicate or cognate polynucleotides bear unique identifiers, that is, bear different tags.”), 41:31-34 (“For example, a sample comprising about 10,000 haploid human genome equivalents of cfDNA can be tagged with about 36 unique identifiers. The unique identifiers can comprise six unique DNA barcodes.”).

52. The disclosed method, in part, takes advantage of the inventor's insight that polynucleotide molecules in a sample that map to different positions of a reference sequence are distinguishable on this basis alone. *E.g.*, EX1011, 39:12-18 (“[B]arcodes may be ligated to individual molecules such that the combination of the bar code and the sequence it may be ligated to creates a unique sequence that may be individually tracked.”); 40:31-39; 40:61-67.

53. In the '822 patent methods, the only polynucleotide molecules in a sample that must be distinguished with barcodes are those that map to the same start and stop position of the reference sequence—these are referred to as “cognates.” Cognates are polynucleotides that map to the same position in the reference sequence but are derived from different copies of the genome. EX1001, 40:4-8 (“In a sample comprising fragmented genomic DNA, e.g., cell-free DNA (cfDNA), from a plurality of genomes, there is some likelihood that more than one polynucleotide from different genomes will have the same start and stop positions (‘duplicates’ or ‘cognates’).”).

54. The inventor of the '822 patent determined empirically that the number of cognates in a sample is proportional to the size distribution of the polynucleotide fragments and the number of genomic equivalents—that is, the number of haploid genome copies present in the sample. EX1001, 39:24-29 (“It has been empirically determined that in a sample of about 10,000 haploid genome

equivalents of human DNA, there are about 3 duplicate polynucleotides beginning at any given position. Thus, such a collection can contain a diversity of about 6×10^{10} - 8×10^{10} (about 60 billion-80 billion e.g., about 70 billion (7×10^{10})) differently sequenced polynucleotide molecules.”); *see also id.*, 40:31-38.

55. The '822 patent distinguishes between (a) total polynucleotide fragments in a sample, (b) polynucleotides that map to a given mappable position in the reference genome, and (c) cognates or duplicates.

56. For example, cfDNA has a peak size of about 160 nucleotides. EX1001, 40:11-14. A “cfDNA [sample] from a genome of about 3 billion bases (e.g., the haploid human genome) may be comprised of almost 20 million (2×10^7) polynucleotide fragments.” *Id.*, 40:14-17. Each of the 20 million polynucleotide fragments in a sample comprising *one* haploid genome equivalent (*i.e.*, 3 billion bases of the human genome), is unique — that is, there are no cognates.

57. However, if the number of haploid genome equivalents is increased to 10,000, there is a possibility for cognates in the sample. The '822 patent discloses that when the sample has 10,000 genome equivalents, 3 cognates are typically found at any given mappable base position.

A sample of about 30 ng DNA can contain about 10,000 haploid human genome equivalents. ... A sample containing about 10,000 (10^4) haploid genome equivalents of such DNA can have about 200 billion (2×10^{11}) individual polynucleotide molecules. It has been

empirically determined that in a sample of about 10,000 haploid genome equivalents of human DNA, there are about 3 duplicate polynucleotides beginning at any given position.

EX1001, 40:18-27; *see also id.*, 40:36-61 (disclosing that in samples comprising 3000 genomic equivalents about 92% of polynucleotide fragments can be correctly identified without a barcode).

58. According to the '822 patent, the number of tags used in the claimed method depends—not on the total fragments in a sample—but on a subpopulation of fragments that map to a given position in the reference genome and the expected number of cognates.

This invention provides methods and compositions in which a population of polynucleotides in a sample of fragmented genomic DNA is tagged with n different unique identifiers, wherein n is at least 2 and no more than $100,000 * z$, wherein z is a measure of central tendency (e.g., mean, median, mode) of an expected number of duplicate molecules having the same start and stop positions.

EX1001, 41:6-13.

59. Because only a small number of barcodes are employed using the disclosed non-unique tagging method, these barcodes may be selected and tested in advance. *E.g.*, EX1011, 41:31-36 (“For example, a sample comprising about 10,000 haploid human genome equivalents of cfDNA can be tagged with about 36 unique identifiers. The unique identifiers can comprise six unique DNA barcodes.

Attached to both ends of a polynucleotide, 36 possible unique identifiers are produced.”).

60. According to the '822 patent, the ability to use a well-characterized set of barcodes allows for better detection of rare variants in samples comprising cfDNA.

Unlike conventional sequencing library preparation protocols, whereby the majority of extracted circulating DNA fragments are lost due to inefficient library conversion, our Digital Sequencing Technology workflow enables the vast majority of starting molecules to be converted and sequenced. This is critically important for detection of rare variants as there may only be a handful of somatically mutated molecules in an entire 10 mL tube of blood. The efficient molecular biology conversion process developed enables the highest possible sensitivity for detection of rare variants.

EX1001, 60:50-61.

VIII. CLAIM CONSTRUCTION

61. Both Dr. Gabriel and the Board’s institution decision state that the '822 patent provides an express definition for the term “non-uniquely tagged.” That is, both indicate the '822 patent expressly defines the term in explaining that parent polynucleotides “can be non-uniquely tagged, that is, the number of different identifiers can be at least 2 and fewer than the number of polynucleotides that map to the mappable base position.” EX1002, ¶75 (citing EX1001, 41:42-46).

62. The Board adopted this as an express definition:

In the context of “non-unique” identifiers, the ’822 patent follows the words “non-uniquely tagged” with “*that is*, the number of different identifiers can be at least 2 and fewer than the number of polynucleotides that map to the mappable base position.”

Paper 12 at 9 (citing EX1001, 41:42-46) (emphasis in original). The Board went on to state that “[w]e read this description in the ’822 patent forth an express definition of ‘non-uniquely tagged.’” Paper 12 at 10.

63. I agree with Dr. Gabriel and the Board that above definition for the term “non-uniquely tagged” is appropriate. I take issue with the analysis in the petition materials and the Board’s institution decision for never applying this interpretation when assessing the cited art.

64. Specifically, the petition materials and the Institution Decision, instead of applying what is identified as an express definition, ignore the phrase “that map to the mappable base position” in order to conclude that “non-uniquely tagged” is found in the cited art. *See* EX1002, ¶75; Paper 12 at 10 (“[W]e further agree with Petitioner that, because the number of different identifiers is fewer than the number of parent polynucleotides, not every parent polynucleotide is tagged with a unique identifier.”). Thus, the petition materials and the Institution Decision erroneously focused on an entire population of polynucleotides in a sample, which

is far more expansive than “polynucleotides that map to the mappable base position.”

“Mappable base position”

65. I agree with Dr. Gabriel that a person of ordinary skill in the art would have understood that “mappable base position” is a position in the reference sequence to which polynucleotide molecules can be confidently mapped. EX2027, ¶¶67; EX2022, 23:22-24:13, 30:4-18; EX1001, 41:42-46; *see also id.*, 35:1-11.

66. According to the express definition of “non-uniquely tagged,” the number of different identifiers is determined by the number of polynucleotides that map to the mappable base position.

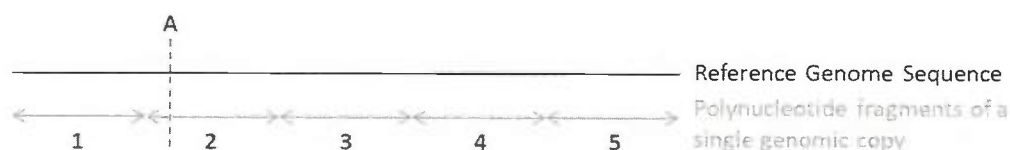
A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least [] 2 and fewer than the number of polynucleotides that map to the mappable base position.

EX1001, 41:42-47.

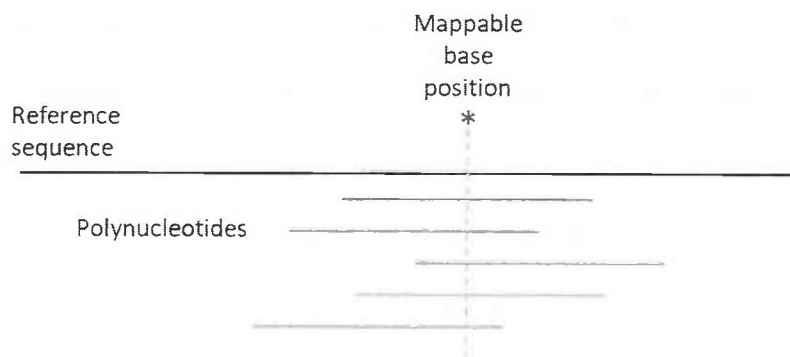
67. The number of polynucleotides in a sample is different than the number of polynucleotides in a sample that map to the mappable base position. The number of copies of the genome retained in the sample impacts the number of polynucleotides that map to a given mappable base position.

68. For example, for illustrative purpose, consider a single copy of a genome that is fragmented into five polynucleotides, all of which are confidently

mappable to the reference sequence. Such a sample includes five polynucleotides. Yet, at any mappable base position of the reference sequence (*e.g.*, tumor marker locus “A,” below), there is only one polynucleotide fragment (fragment “2” in this example).



69. As another example, for illustrative purpose, consider a sample comprised of five haploid copies of the human nuclear genome that are fragmented into 200 base pair polynucleotides. The entire sample comprises about 75 million polynucleotide fragments $((3 \text{ billion base pairs} \times 5 \text{ copies})/200)$. However, at any given mappable base position there are at most only 5 polynucleotides. The 65,536 possible unique tags from a 4-mer tag sequence might be less than the entire number of polynucleotides in the sample, but much larger than the five polynucleotides that map to a given mappable base position.



IX. THE PETITION MATERIALS DO NOT ESTABLISH UNPATENTABILITY OF THE CHALLENGED CLAIMS

70. The petition challenges claims 1-13 and 17-20 of the '822 patent as unpatentable over Schmitt in view of Schmitt 2012, further in view of Fan or Forsheew. Pet. 30. The petition fails at least because Schmitt does not teach “non-uniquely tagged parent polynucleotides” as required by claim 1. Furthermore, none of Schmitt, Schmitt 2012, Fan, and Forsheew teaches tagging of cell-free DNA molecules.

71. Furthermore, the petition fails to establish motivation to combine the references as proposed with a reasonable expectation of success. Moreover, it is my opinion that Schmitt is not reasonably applicable to cfDNA.

A. Schmitt does not disclose a method for non-uniquely tagged parent polynucleotides

72. It is my opinion that Schmitt does not teach “non-uniquely tagged parent polynucleotides,” as that term is used in the '822 patent. I have reviewed the cited references, but Schmitt is silent regarding a sub-population of fragments in a sample that map to a given mappable base position. The absence of such content from Schmitt is unsurprising as it would be of no value in the DCS method. As discussed further herein, Schmitt’s DCS method tags its sample such that each polynucleotide is uniquely identifiable with a different SMI tag. See e.g., EX1011, 3:46-53; 6:59-63; additional discussion herein. Information about the number of

fragments in subpopulations of the sample do not advance this objective. In fact, it is not clear that the number of polynucleotides in subpopulations mapping to different mappable base positions is information that is determinable in the context of Schmitt.

i. Petitioner's contrived scenario does not support its assertion that Schmitt teaches non-uniquely tagging

73. Petitioner constructs a scenario based on a series of unexplained assumptions:

Schmitt's "hybrid" approach for tagging DNA fragments results in non-uniquely tagged parent polynucleotides. In this embodiment, if the tag sequence is a 4-mer, for example, then the total number of possible unique tag sequences that may be attached on both ends is only 65,536. A human genome has about 3 billion base pairs, and Schmitt teaches selection of fragments in the optimal range of 200-500 base pairs, which would result in millions of fragments per genome. Given that there are no more than 65,536 possible tag sequences in Schmitt's "hybrid" approach, probability dictates that each tag sequence will be ligated more than once, which means that each tag sequence is non-unique relative to a fragmented genome or to naturally fragmented cfDNA, which has an average size of about 140 to 170 base pairs.

EX1002, ¶127 (internal citations and footnote omitted). This scenario does not support Petitioner's assertion that Schmitt teaches non-uniquely tagging.

74. First, the number of polynucleotides that map to a mappable base position is different than the total number of polynucleotides in a sample, and would require multiple copies of similarly mappable fragments in a sample from multiple genome copies. The petition materials assume a sample comprising fragments of a *one* haploid human genome (*i.e.*, 3 billion base pairs). That is, there could be no more than one polynucleotide at any given mappable base position and every polynucleotide is unique without any tags being used. *See* Section VIII.

75. Second, when there is only one polynucleotide at any given mappable base position, it is impossible to tag the sample with at least 2 and fewer than the number of polynucleotides that map to the mappable base position. EX1001, 41:42-47 (“A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least [] 2 and fewer than the number of polynucleotides that map to the mappable base position.”).

76. To the extent that Petitioner might argue that additional copies of the genome would be analyzed, the proposed 65,536 n-mers would need to be used to tag an even greater number of genome copies—e.g., at least 65,537 copies of the haploid human genome—in order for the number of tags to be less than polynucleotides mappable to a given position.. That is, there would need to be more copies of the human genome than tags. EX1001, 41:42-47 (“A set of

polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least [] 2 and fewer than the number of polynucleotides that map to the mappable base position.”).

77. This discussion is of course meant to be illustrative. In reality, a vastly greater number of genome copies would be required to even approximate the number of tags available. As discussed elsewhere herein, Schmitt’s method involves discarding large portions of sample and data, and employs a highly inefficient tagging scheme. *See* Section IX.D. and IX.E. Schmitt’s process of random fragmentation and discarding most polynucleotides alone would result in only a minute fraction of genome copies in a sample producing a polynucleotide that maps to a given mappable base position.

78. If 65,537 haploid copies of the human nuclear genome were sequenced, this would represent a target size of about 10^{14} base pairs (*i.e.*, 65,537 copies x 3,000,000,000 base pairs). This would represent an extraordinary amount of sequencing, far in excess of what is typically conducted even in present day experiments.

79. This is also far in excess of what is contemplated in Schmitt. Schmitt does not disclose sequencing targets as large as the entire 3 billion base pair haploid human genome, much less 65,537 copies of said genome. Instead, Schmitt

discloses the benefits of applying DCS to much smaller targets. EX1011, 24:7-11 (“Current experiments are being performed on vastly smaller target DNA molecules (ranging from ~300 bp to ~20 kb in size). Use of smaller DNA targets will allow for much greater sequencing depth, and far more accurate assessment of the background mutation rate of the assay.”).

80. Moreover, in a later publication by the inventors of the Schmitt patent, the DCS method was characterized as being “prohibitively expensive” for genome targets in excess of 1-2 Mbp. EX1057 at 4. That is, DCS is prohibitively expensive for targets *three orders of magnitude smaller* than a one copy of the haploid human genome.

ii. Schmitt exclusively teaches unique tagging methods

81. The purported invention of the Schmitt patent is expressly identified as methods involving unique single molecule identifier (“SMI”) or n-mer tags, which are critical to Schmitt’s grouping of amplicons and consensus sequence construction. This is repeatedly expressed throughout the Schmitt patent. *E.g.*, EX1011, 4:6-7 (“sequence reads ... sharing a unique set of SMI tags are grouped into paired families”), 3:47-49 (“Because every adaptor contains a unique, double-stranded, complementary n-mer random tag on each end...”), 6:59-63 (“The first and/or second degenerate or semi-degenerate nucleotide n-mer sequences may be any suitable length to produce a sufficiently large number of unique tags to label a

set of sheared DNA fragments from a segment of DNA.”), 18:36-41 (“Because the use of SMI tags ... allows every molecule to be uniquely labeled prior to PCR duplication, true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence.”), 21:59-61 (“The sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence.”).

82. Despite this disclosure in Schmitt, the petition materials assert that n-mer tags used in the “hybrid method” of Schmitt are not “unique” because that embodiment necessarily employs fewer barcodes than total polynucleotide fragments. Pet. 43-44 (citing EX1011, 9:1-13, Figure 4); Paper 12 at 18-19. In my opinion, this is incorrect for a number of reasons, including those discussed further below.

83. As discussed, Petitioner’s argument ignores the undisputed express definition of “non-uniquely tagged,” in the ’822 patent. In particular, the petition materials address an entire population of polynucleotides in a sample, rather than “polynucleotides that map to the mappable base position.”

84. Additionally, the argument in the petition materials makes a number of assumptions not supported in the cited reference. For example, the petition materials assume a combination of more fragments in a sample (i.e., millions of fragments) than SMI tags (i.e., 65,536 tags).

85. But Schmitt does not describe sequencing and analysis of the samples that are the size of an entire human genome as the petition materials assume in its hypothetical. As indicated above, Schmitt discloses applying DCS to much smaller targets — “ranging from ~300 bp to ~20 kb in size.” EX1011, 24:7-11. Assuming such targets are sheared into 200 bp fragments, *id.*, 19:65-66, a target of 300 bp to 20,000 bp would at best generate between 1 and 100 fragments. That is, far fewer fragments than “millions of fragments” and certainly less than tags generated by a 4-mer.

86. Furthermore, Schmitt never instructs that the number of n-mer tags should be less than the polynucleotides in a sample. I have reviewed the cited references, and find that Schmitt states just the opposite. That is, where Schmitt does relate the number of barcodes to polynucleotide fragments in a sample it instructs that the barcodes should be in excess of the sample fragments. *See, e.g.*, EX1011, 3:47-53 (“Because every adaptor contains a unique, double-stranded, complimentary n-mer random tag on each end (n-mer =12 bp according to one embodiment), every DNA fragment becomes labeled with two distinct SMI sequences...”), 6:59-62 (“The first and/or second degenerate or semi-degenerate nucleotide n-mer sequences may be any suitable length to produce a sufficiently large number of unique tags to label a set of sheared DNA fragments from a segment of DNA.”). The instructions of Schmitt in this regard are in the general

context of the DCS method employing n-mer or SMI tags. There is no instruction to the contrary.

87. The reference in the petition to an embodiment that does not use any n-mer tag does not warrant reaching any other conclusion. Pet. 43 (citing EX1011, 9:1-4 as providing an embodiment that “does not strictly require the use of an SMI tag, as the sheared ends can be used as identifiers to differentiate unique individual molecules from PCR duplicates”). While Schmitt mentions such a possibility, it then goes on to identify such an approach as limited and advocates for inclusion of an SMI tag. EX1011, 9:7-10 (“there are a limited number of shear points flanking any given genomic position and thus the power to sequence deeply is increased via inclusion of an SMI tag.”).

88. An embodiment that does not tag polynucleotides at all is outside the scope of claims requiring “non-uniquely **tagged** parent polynucleotides.” Schmitt’s hybrid method uses SMI tags as molecular identifiers. EX1011, 9:9-13 (“A hybrid method using a combination of sheared ends and a shorter n-mer tag”).

89. As indicated above, in the embodiments where Schmitt does include an n-mer/SMI tag, Schmitt instructs using a sufficiently large number of tags. Limiting n-mer tags as suggested in the petition materials would be contrary to the express instruction of Schmitt, and counterintuitive considering that Schmitt (as

discussed herein) critically relies on unique tagging in order to group amplicons for building consensus sequences.

90. Finally, the petition materials assert that “Schmitt’s ‘hybrid method’ is nearly identical to an embodiment of the ’822 patent.” EX1002, ¶130. In my opinion, that is incorrect.

91. As I explain above, the ’822 patent discloses a non-unique tagging method that relies on both mapping position and identifiers (*e.g.*, barcodes) to distinguish parent polynucleotide molecules. The ’822 patent discloses that a much smaller number of tags may be used such that at least some of the cognates— that is, polynucleotide molecules that map to the same position in the reference sequence but are derived from different copies of a genome — are distinguishable. EX1001, 40:4-8, 41:25-28; *see also* Section VII.

92. Schmitt’s hybrid method takes a fundamentally different approach that critically relies on random shearing of cellular DNA. EX1011, 9:9-13.

93. The methods of the ’822 patent do not and cannot employ the shearing method of Schmitt. The random shearing method of Schmitt (*i.e.*, acoustic shearing) is incompatible with cfDNA.

B. Neither Schmitt nor any combination of references teaches a method for converting cell-free DNA into tagged parent polynucleotides

94. The claims of the '822 patent require “converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides,” yet the petition materials assert that this limitation is taught by Schmitt’s disclosure of the so-called “hybrid” method. EX1002, ¶131. I disagree.

95. It is my opinion that a skilled artisan would not have understood Schmitt or any reasonable combination of Schmitt, Schmitt 2012, and Fan or Forshew to teach “converting the population of cfDNA molecules into a population of ... tagged parent polynucleotides.”

96. As discussed elsewhere herein, various aspects of Schmitt’s DCS method are incompatible with cfDNA analysis. As such, Schmitt’s methods could not be applied to cfDNA in this capacity without fundamental modifications to the DCS method. For example, Schmitt describes the hybrid method as tagging randomly sheared cellular DNA. EX1011, 9:9-10 (“A hybrid method using a combination of sheared ends and a shorter n-mer tag...”). Indeed, Schmitt is directed exclusively to cellular DNA samples. *E.g.*, EX1011, 4:55-56 (“Fig. 5 illustrates duplex sequencing of *human mitochondrial DNA*.”), 5:12 (“Fig. 7 illustrates duplex sequencing of *M13mp2 DNA*.”), 23:4-5 (“Genomic DNA was isolated from *normal human colonic mucosa*...”), 25:63-64 (“Genomic DNA

was isolated from a derivative of *Saccharomyces cerevisiae*....”) (emphasis added). Such shearing is not compatible with cfDNA analysis.

97. Schmitt 2012 is also directed exclusively to cellular DNA. *E.g.*, EX1047 at 14508 (“We apply the method to directly assess the frequency and pattern of random mutations in *mitochondrial DNA from human cells*.”), 14511 (“[W]e isolated *mitochondrial DNA from human brain tissue*...”), S11 (“M13mp2 DNA was isolated *from E. coli*...” (emphasis added).

98. Fan does not teach converting cell-free DNA into tagged parent polynucleotides at least because it does not disclose tagging of any kind.

99. Forshew does not disclose converting cell-free DNA into tagged parent polynucleotides. To the extent that Forshew discloses tagging at all, it is a PCR-based approach for tagging amplicons with a sample identification barcode. EX1004 at 9 (“Our TAm Seq method uses a combination of short amplicons, two step amplification, sample barcodes, and high throughput PCR.”); see also EX1002, ¶95.

100. The petition materials do not point to any prior art disclosure of converting *cfDNA* into tagged parent polynucleotides. Nor do the petition materials explain how the combination of Schmitt, Schmitt 2012, and Fan or Forshew teach this limitation – it does not.

101. As I explain below, a person of ordinary skill in the art would have understood that the tagging method of Schmitt is not reasonably applicable to cfDNA. *See* Section IX.E.

C. The petition materials do not establish that a skilled artisan would have wanted to combine Schmitt with either Fan or Forshe

102. The petition materials allege that “a POSA would have been motivated to apply Schmitt’s DCS method for aneuploidy analysis (as taught by Fan using fetal cfDNA) or for cancer mutation analysis (as taught by Forshe using circulating tumor DNA).” EX1002, ¶98. I disagree. The petition materials offer only mischaracterizations and flawed logic in support of reason to combine. As I discuss in detail below, a person of ordinary skill in the art would not have wanted to use DCS for either fetal aneuploidy detection or cancer mutation analysis in circulating tumor DNA.

103. For reason to combine Schmitt and Fan, the petition materials offer the false assertion that Schmitt “explicitly” contemplates application of DCS for prenatal screening for fetal aneuploidy. EX1002, ¶99 (citing EX1011, 1:28-55). A person of ordinary skill in the art would not understand this passage to be contemplating application of DCS to fetal aneuploidy detection. Rather, Schmitt is merely disclosing that next-generation sequencing (“NGS”) has been used by others to detect fetal aneuploidy.

104. The petition materials also define the term “deep sequencing” as “the ‘unique’ ability of massively parallel DNA sequencing to detect minor variants within heterogeneous mixtures.” EX1002, ¶99. Furthermore, the petition materials suggest that Fan discloses a method for “deep sequencing.” *Id.* (“Schmitt provides the explicit motivation to combine with Fan. When discussing ‘deep sequencing’ (... Schmitt specifically cites Fan...”); see also Paper 12 at 24 (quoting Pet. 32) (“Petitioner contends that Schmitt ‘provides explicit motivation to combine’ with the teachings of Fan, because Schmitt cites to Fan when discussing ‘deep sequencing’—i.e., the use of massively parallel sequencing to detect minor variants within heterogeneous mixtures.”).

105. Even accepting the petition’s definition of “deep sequencing,” Fan does not disclose such a method. Minor variants are not detected with Fan’s method. No sequence information (*e.g.*, identification of single nucleotide variants) is provided by Fan’s method. Rather, Fan detects fetal aneuploidy by counting mapped reads and determining if there is an excess number of reads relative to a reference data set for a given chromosome. EX1048 at 16267-68 (“Detection of Fetal Aneuploidy).

106. Moreover, there would be no good reason to apply Schmitt’s DCS method to detecting fetal aneuploidy, such as disclosed by Fan. Schmitt discloses that it is desirable to use error correction to detect “rare variants” such as single

nucleotide variants in “heterogeneous populations.” EX1011, 2:56-62. But rare variants are not detected by Fan. No sequence information (*e.g.*, identification of single nucleotide variants) is provided by Fan’s method. Rather, Fan detects fetal aneuploidy by counting mapped reads and determining if there is an excess number of reads relative to a reference data set for a given chromosome. EX1048 at 16267-68 (“Detection of Fetal Aneuploidy”).

107. Consequently, application of Schmitt’s DCS method to aneuploidy detection would needlessly increase the expense and complexity of the method. *E.g.*, EX1057 at 4 (“DS is a uniquely sensitive method that is capable of detecting and quantifying mutations that occur at extremely low frequencies; however, this ability comes at a cost. Owing to the method’s reliance on sequencing multiple PCR duplicates of both DNA strands, DS requires much larger sequencing capacity than conventional NGS to produce a given depth of sequencing.”).

108. Second, a person of ordinary skill in the art would not have been motivated to apply Schmitt’s DCS method to cancer mutation analysis in circulating tumor DNA.

109. For reason to combine Schmitt and Forshew, the petition materials assert that “because both [references] disclose methods of ‘deep sequencing’ to detect low frequency mutations.” EX1002, ¶109. The Board also stated that “that Schmitt’s DCS method was a reasonable substitute for the deep sequencing

techniques used in the prior art — such as those techniques Fan and Forsheew used for prenatal cfDNA screening and for tumor cfDNA screening.” Paper 12 at 26. As an initial matter, Schmitt’s DCS method is not a “deep sequencing” technique but rather a method for correcting errors in NGS reads. EX1011, Abstract.

Consequently, Schmitt cannot be viewed as a “substitute” for deep sequencing.

110. It is my opinion that a person of ordinary skill in the art would have considered Schmitt poorly suited for cfDNA analysis.

D. The petition materials do not establish that the Schmitt methods would reasonably be applicable to cell-free DNA

111. The petition materials assert that there would be a reasonable expectation of success in combining Schmitt, Schmitt 2012, and Fan or Forsheew. I have reviewed those arguments and disagree. Many of the arguments presented in support of this assertion are either not supported, irrelevant, or wrong.

112. For example, the petition materials also assert that a “person of skill in the art would have known that next generation sequencing technologies, including barcode tag-based approaches to sequencing, had been used successfully to detect rare mutations in both cellular and cell-free DNA.” EX1002, ¶118 (citing EX1049; EX1059 at 2). Neither cited exhibit uses the Schmitt method. Furthermore, exhibit 1049 does not disclose methods directed to cfDNA, instead it discloses PCR-based methods for barcoding cellular DNA. Exhibit 1059 does not disclose detection of rare mutations, rather it describes a method for detecting fetal aneuploidy by

counting sequencing reads. That is, neither reference is relevant to whether the Schmitt could be used to convert cfDNA into tagged parent polynucleotides.

113. The petition materials assert that “the DCS method does not require substantive modification of existing sequencing workflows and can serve as a general technique for next generation sequencing.” EX1002, ¶114 (citing EX1011, 18:44-61). I do not understand what Petitioner means by “general” applicability of Schmitt to NGS workflows or why this is relevant to an expectation of success.

114. The petition materials assert that “a person of ordinary skill in the art reasonably would have expected the DCS method, as described by both Schmitt and Schmitt 2012, to be sensitive enough to detect rare mutations irrespective of the source of the DNA to be sequenced.” EX1002, ¶115. In support of this assertion, the petition materials point exclusively to application of DCS to cellular samples. EX1047 at 14511 (identifying mutation in plasmid DNA); EX1011, 30:7-10 (same); EX1056 at 14290 (same). Using DCS to identify mutation in plasmid DNA does not address the applicability of DCS to cfDNA.

115. The petition materials assert that a skilled artisan would have had “a reasonable expectation of success because the claims of the ’822 patent recite only well-known sample preparation, sequencing and analysis steps” and “Schmitt discloses every one of these same basic steps, namely generating sequence reads by tagging fragmented DNA with barcodes, amplifying the tagged DNA, and

sequencing the amplified DNA.” EX1002, ¶116. This is incorrect, the ’822 patent does not recite only “well-known” steps. As I explain above, multiple elements of claim 1 are not found in the prior art.

116. The petition materials rely on the assertion that “[a] person of ordinary skill in the art also would have recognized that the tagging, amplifying, and sequencing steps described by Schmitt would operate in the same or an equivalent manner whether one was starting with cellular DNA or cell-free DNA.” EX1002, ¶118. Not so, as I discuss in more detail below, a person of ordinary skill in the art would not understand Schmitt to operate in the same way with cfDNA. *See* Section IV.E.

117. For example, the petition materials assert that “a person of skill in the art would have recognized that the claimed methods are equally applicable to cell-free DNA and cellular DNA.” EX1002, ¶118. The claimed methods are not the same as the Schmitt method. The Schmitt method differs in a number of ways and, and as discussed herein, include a number of aspects that would be recognized as inapplicable to cfDNA.

118. The petition materials further assert that “[t]he size of the cellular genomic DNA fragments that Schmitt sequenced and analyzed is similar to the naturally fragmented size of cfDNA.” EX1002, ¶118. Not so, in fact, Schmitt discloses the opposite — that is, discarding fragments of similar size to cfDNA.

Schmitt describes the optimal range of fragment sizes for DCS is 200-500 bp. EX1011, 19:65-66, 22:43-46. Schmitt describes removing fragments that are larger than 500 bp and smaller than 200 base pairs prior to tagging fragments. EX1011, 19:65-20:15 (describing “size selecting” fragments in the range of 200-500 bp prior to attaching tags), 22:43-54 (same).

119. The petition materials assert that the purpose of the shearing step is to make fragments that are “compatible with amplification and NGS sequencing.” EX1002, ¶118. Schmitt also discloses that the SMI tag of the hybrid method comprises the randomly sheared ends. EX1011, 9:9-13 (“A hybrid method using a combination of sheared ends and a shorter n-mer tag”). As discussed elsewhere herein, such shearing would be recognized as not compatible with cfDNA analysis.

120. Finally, the petition materials point to Krimmel (EX1060) as allegedly demonstrating successful application of Schmitt’s method to cfDNA. EX1002, ¶119 (citing EX1060, Abstract, 6006). I have reviewed this reference, and petitioner’s assertion is simply untrue. That is, Krimmel (EX1060) applies DCS to cellular DNA, not cfDNA. EX1060 at Abstract (“Our aim was to determine whether duplex sequencing could detect extremely rare *cancer cells* present in peritoneal fluid from women with high-grade serous ovarian carcinomas (HGSOCs).”), (“Our results demonstrate the ability of duplex sequencing to detect rare *cancer cells* ...”), 6005 (“We reasoned that peritoneal fluid is an optimal

clinical biopsy for high sensitivity early detection of ovarian cancer because HGSOC disseminates early and preferentially to the peritoneal cavity, suggesting that *cancer cells* may be more abundant in peritoneal fluid...”), 6006 (“Our goal was to provide proof of principle of the ability of duplex sequencing to detect very rare *cancer cells* ...”), (“Peritoneal fluid was centrifuged, and DNA was extracted from the *cell pellet*, obtaining an average of 11.9 µg of DNA.”), 6009 (“[D]uplex sequencing demonstrated here could also be applicable to the identification of *cancer cells* from other cancer types ...”), 6010 (“DNA was extracted from peripheral whole blood and peritoneal fluid sample *cell pellets* ...”).

121. Moreover, Krimmel’s samples contain microgram quantities of cellular DNA. EX1060 at 6010 (“For peritoneal fluid libraries, up to 10 µg of genomic DNA (mean 5.4 µg) was used. For peripheral blood libraries, 3.5 µg of starting DNA was used. DNA was sonicated, end repaired, a tailed, and ligated with duplex sequencing adaptors.”). That is, Krimmel applies DCS to samples that contain orders of magnitude more DNA than the amount of cfDNA that can reasonably be obtained from a patient.

122. Finally, that the DCS method disclosed in the Schmitt references is inefficient and poorly suited for limited amounts of DNA, such as cfDNA samples, is well documented in the literature, including by the inventors of DCS. For

example, Perakis, et al. concluded that “prospects of success” in applying DCS to cfDNA were limited:

Although [Schmitt] used this approach for selective enrichment of small genomic regions, the original protocol has not yet been used with ctDNA. Prospects of success are limited since the method is relatively inefficient when limited amounts of input DNA—as it is most likely the case for cfDNA—are used.

EX2002 at 102.

123. Newman, et al. came to the same conclusion:

Although duplex barcoding achieves better error suppression than single-stranded barcoding methods, it is relatively inefficient and thus suboptimal for the limited cfDNA quantities obtainable in a clinical setting.

EX2039 at 548.

124. Kamps-Huges, et al. further commented on the necessity for “extremely high” DNA input amounts:

Molecular barcoding has shown promise in drastically lowering the limit of detection for variants in NGS data. However, the proof of principle experiments demonstrating high accuracy at ultralow allele frequencies have required extremely high read depths and DNA inputs while demonstrating efficacy only over very small genomic regions.

EX2040 at 2 (citing Schmitt 2012).

125. Wang, et al., addressed the “critical losses” of template DNA:

For instance, Duplex Sequencing creates high quality DCSs with exceedingly low error rates but at the expense of inefficient processes leading to critical losses of template DNA molecules.

EX2041 at 10. The issue of sample loss was even addressed by the inventors of DCS:

[I]t is most convenient to start with excess amounts of DNA to allow for easy quantification of the DNA throughout the initial sample preparation steps and to account for expected sample loss at the enzymatic and purification steps.

EX1057 at 5.

126. That the DCS method disclosed by the Schmitt references is poorly suited for cfDNA samples.

E. Schmitt is not applicable to cell-free DNA

127. In my opinion, a person skilled in the art would not view Schmitt as teaching, or even contemplating, application of its methods to cfDNA. In my opinion, there are several aspects of the Schmitt method that would be recognized as poorly suited for, even incompatible with, cfDNA analysis.

128. Cellular DNA samples are discussed throughout Schmitt and each of examples addresses cellular samples. Example 1 applies the method to cellular DNA isolated from “normal human colonic mucosa.” EX1011, 23:4-5. Example 2 applies the method to “human mitochondrial DNA” isolated from cells. *Id.*, 4:55-

56, 24:64-65. Example 3 applies the method to DNA isolated from yeast cells. *Id.*, 25:63-64. Example 4 applies the method to plasmid DNA isolated from bacterial cells. *Id.*, 5:12, 27:37-38. Schmitt does not even mention applying DCS to cfDNA, let alone provide any corresponding analysis.

129. Schmitt characterizes the optimal size of polynucleotide fragments for its method to be different than the fragment sizes that would be reflected in cfDNA samples. For example, Schmitt instructs selection of fragments in the optimal range of 200-500 base pairs. EX1011, 19:65-66 (identifying “the optimal range of ~200-500 bp” for its DCS method), 22:43-46.

130. The average size of cfDNA fragments is about 140 to 170 base pairs. Schmitt instructs that fragments of less than 200 base pairs (*e.g.*, fragments about 140 to 170 base pairs) should be discarded in the sample preparation steps of the DCS method. EX1011, 19:63-20:4 (“DNA fragments larger than the optimal range of ~200-500 bp were removed....”), (“this step allows fragments of approximately 200 bp or greater to bind to the beads.”), 22:43-46 (describing “size-selection for fragments in the range of ~200-500 bp by size-selective binding to Ampure XP beads.”). Discarding fragments outside the optimal range of about 200-500 base pairs is not compatible with cfDNA analysis as it would result in discarding a large portion of a cfDNA sample.

131. Schmitt instructs additional steps that discard sample and data during processing and analysis, that further indicate its methods is poorly suited for working with the minute sample quantities in cfDNA analysis. EX1011, 20:42-43 (describing “filtering out reads that lack the expected fixed sequence at positions 13-17.”), 20:47-50 (“The first 4 nucleotides located following the adaptor sequence were also removed...”), 20:53-55 (“Sequencing positions were discounted if the consensus group covering that position consisted of fewer than 3 members...”), 20:65 (“Discard reads that do not have the 5 nt fixed reference...”), 21:4-18 (“Discard SMI’s with inadequate complexity.... Remove the 5 nt fixed reference sequence.... Trim an additional 4 nt from the 5’ ends of each read pair (sites of error prone end repair) Only score positions with identical sequence among both DCS partners.”). Further, Schmitt critically relies on randomly generated SMI tags—but such tags further result in significant data loss.

132. Schmitt explains that approximately 1% of bases are incorrectly identified by NGS. EX1011, 1:64-2:4 (“Polymerase mistakes during pre-amplification generate point mutations resulting from base mis-incorporations and rearrangements due to template switching [26, 27], cluster amplification, cycle sequencing and image analysis, approximately 1% of bases are incorrectly identified, depending on the specific platform and sequence context [2, 28].”). These errors are incorporated throughout the polynucleotide fragment, including in

the SMI tag and shear points. Since every fragment in Schmitt includes two tags (one at each end), even a relatively low rate of 1% will result in errors in about every fourth sequence read of Schmitt.

133. Base misincorporation errors in the SMI tag (or shear points) cannot be corrected. Rather, an error in the SMI tags would prevent the grouping of the polynucleotide into the appropriate family as required by Schmitt. *E.g.*, EX1011, Fig. 3, 4:4-29. As a result, polynucleotides with sequence errors in the SMI tag cannot be used for error correction and must be discarded.

134. In view of inefficiencies in the method and steps requiring discarding significant amounts of sample and data, Schmitt requires large amounts of cellular DNA in its assays. EX1011, 19:18-19, 19:58. While cellular DNA might be available in such large quantities, cfDNA is not.

135. Additional aspects of Schmitt's method are not compatible with cfDNA analysis. As discussed above, Schmitt's method also relies on a random fragmentation process that generates sheared ends. In particular, Schmitt instructs generating sheared ends by acoustic shearing of cellular DNA. Acoustic shearing results in a random distribution of sequences at the ends of polynucleotide molecules. EX1011, 9:9-13 ("A hybrid method using a combination of sheared ends and a shorter n-mer tag"), 19:58-60 ("DNA was ... *sheared* on the Covaris AFA system").

136. Schmitt's shearing method is not compatible with cfDNA. Cell-free DNA is already fragmented and has a peak size of around 160 nucleotides. Further reductions in size (e.g. by shearing), would result significant destruction of fragments and loss of material that is already present in only minute quantities. The smaller fragments would also be even more difficult to isolate and sequence.

137. Moreover, while cfDNA is fragmented, the fragments do not resemble those generated by Schmitt's shearing process. As indicated above, cfDNA fragments are smaller than the optimally sized fragments (*i.e.*, ~200-500 base pairs) generated and isolated in Schmitt's method. Additionally, cfDNA is not randomly fragmented as would be generated by Schmitt's shearing process, but instead represent a more patterned fragmentation. Cell-free DNA is produced enzymatically in cells which results in a much lower diversity of sequences at the termini as compared to acoustically sheared cellular DNA.

138. A person skilled in the art would not view Schmitt as teaching, or even contemplating, application of its methods to cfDNA. Rather, a person of ordinary skill in the art would have considered Schmitt's method wholly unsuited for cfDNA analysis.

F. The petition materials do not establish that dependent claims 2-13 and 17-20 are unpatentable

139. It is my opinion that claims 2-13 and 17-20 are not obvious for the same reasons identified above with respect to claim 1 for each of the grounds of

challenge. Additional reasons why some of claims 2-13 and 17-20 are not unpatentable are discussed below.

i. Claim 2 is not unpatentable

140. Claim 2 further requires “detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant.”

141. The petition materials assert that Schmitt “explicitly” teaches that DCS can detect copy number variation (“CNV”). EX1002, ¶157. But the petition materials fail to point to any disclosure of detection of CNVs — because there is none. Instead, the petition materials point to disclosure of “single molecule counting for accurate determination of DNA or RNA copy number.” EX1002, ¶158 (citing EX1011, 18:3-21).

142. The petition materials appear to be suggesting that the single molecule counting method of Schmitt could be used in an analogous manner to the unrelated disclosure of Kivioja used to detect whole chromosome aneuploidy. EX1002, ¶¶158-159. Even if true, this does not establish that Schmitt teaches CNV detection explicitly or otherwise.

143. The petition materials also assert that “person of ordinary skill in the art would have understood that different types of mutations could be identified from the same data set.” EX1002, ¶160 (EX1005, Figure 3; EX1067; EX1068).

What these “different types” of mutations are is unexplained. Furthermore, none of the references cited by the petition materials disclose application of the Schmitt method to detection of “at least one single nucleotide variant, at least one gene fusion and at least one copy number variant.”

ii. Claim 5 is not unpatentable

144. Claim 5 further requires “making the base call comprises voting, averaging, maximum a posteriori or maximum likelihood detection, dynamic programming, Bayesian methods, hidden Markov methods or support vector machine methods.”

145. The petition materials point to no disclosure in Schmitt of using voting, averaging, maximum a posteriori or maximum likelihood detection, dynamic programming, Bayesian methods, hidden Markov methods or support vector machine methods to make base calls. Instead, Petitioner merely states these methods were known in the art. EX1001, ¶167. Nowhere is it explained why a person of ordinary skill in the art would have wanted to apply one of the recited methods to the Schmitt with a reasonable expectation of success.

iii. Claim 9 is not unpatentable

146. Claim 9 further requires the mapping step to “us[es] information about a length of each of the sequence reads.”

147. Schmitt does not disclose using information about length of each of the sequence reads. Instead, the petition materials merely assert that “[a] person of ordinary skill in the art would have understood that aligning (i.e., mapping) reads with the Burrows-Wheeler aligner uses information about a length of each of the sequence reads.” EX1002, ¶173 (citing EX1077 at 1757). The petition does not explain what aspect of the BWA algorithm that allegedly provides this teaching.

iv. Claim 12 is not unpatentable

148. Claim 12 further requires that “the population of polynucleotides is tagged with n different unique identifiers, wherein n is no more than $100 \cdot z$, wherein z is a mean of an expected number of duplicate molecules having the same start and stop positions in the sample.”

149. Petitioner’s arguments for claim 12 are based largely on information that would not have been available to a person prior to the time of the ’822 patent. None of the cited references disclose the expected number of duplicate molecules in a sample much less a tagging scheme based on such a number. As discussed above, the expected number of duplicates in a given amount of cfDNA was empirically determined by the inventor of the ’822 patent. EX1001, 40:18-27; *see also id.*, 40:36-61. Likewise, a tagging scheme based on the number of duplicates in a sample is novel to the ’822 patent. EX1001, 41:6-13.

150. The argument in the petition materials for claim 12 is based entirely on the disclosure of the '822 patent. These materials even acknowledge reliance on the empirical data novel to the '822 patent.

The specification of the '822 patent defines “z” as a “measure of central tendency (e.g., mean, median, mode) of an expected number of duplicate molecules having the same start and stop positions” and states that “[i]t has been empirically determined that in a sample of about 10,000 haploid genome equivalents of human DNA, there are about 3 duplicate polynucleotides beginning at any given position.” EX1001, 40:24-27; 41:10-13.

EX1002, ¶178.

151. Using the '822 patent's disclosure, Petitioner then calculates the expected number of duplicates in a 20 ng sample:

Fan and Forshew disclose cfDNA amounts between 1-20 ng. EX1048, 16270, Table S1; EX1004, Table S6. A sample of 20 ng of DNA contains about 6,060 haploid genome equivalents, which would have approximately 1-2 duplicate polynucleotides beginning at any given position.

EX1002, ¶179. No explanation is given for selecting a 20 ng sample size as opposed to any other value in the 1-20 ng range that is identified. However, had Petitioner selected 1 ng, for example, there would have been little to no duplicate polynucleotides.

152. The petition materials further assert that “in view of Schmitt’s disclosure of using 1, 2, 3, or 4 n-mer tags in its “hybrid” approach, a person of ordinary skill in the art would have tried each of these alternatives, and it would only have been a matter of routine experimentation for them to do so.” EX1002, ¶180. The petition materials do not explain what is being optimized or why it would be routine.

v. Claim 13 is not unpatentable

153. Claim 13 further requires that the bodily sample comprise “no more than 100 nanograms of polynucleotides.”

154. Schmitt discloses using 3 µg of human colonic mucosa DNA. EX1011, 19:18-19, 19:58. That is, Schmitt uses samples that contain more than 300-fold more cellular DNA than the maximum amount of cfDNA required by claim 13.

155. The petition materials do not establish that a person of ordinary skill in the art would have had a reasonable expectation of success using a minute quantity of cfDNA.

X. OBJECTIVE INDICIA CONFIRM THE PATENTABILITY OF THE CHALLENGED CLAIMS

156. I have been asked to review materials describing the Guardant360 assay in view of the challenged ’822 patent claims. As set forth in further detail

below, the Guardant360 assay embodies the claims of the '822 patent and provides further evidence supporting the patentability of those claims.

157. Guardant360 is a “liquid biopsy” assay that provides clinically actionable sequence information from cfDNA molecules obtained from a routine blood draw from cancer patients. EX2034 at 4. The assay sequences a panel of genes commonly mutated in cancer and detects genetic aberrations such as single nucleotide variants (SNVs), indels, gene fusions, and copy number variants (CNVs). EX2029 at 5 (Figure 1). Guardant360 provides highly sensitive and accurate detection of genetic aberrations using a non-unique barcoding scheme in concert with bioinformatic algorithms specific for SNVs, indels, gene fusions, and CNVs. *Id.*; *see also* EX2030 at 3542-3544.

158. In my opinion, the Guardant360 test embodies the claims of the '822 patent. Guardant360 converts cfDNA obtained from a patient into non-uniquely tagged parent polynucleotides which are then amplified and sequenced. EX2029 at 5, 17-18; EX2030 at 3539, 3540, 3542, 3544. The resulting reads are then mapped to a reference genome and grouped into families based on start and stop position and identifier sequence. EX2029 at 19; EX2030 at 3540-3541. Finally, at each genetic locus sequence reads are collapsed to generate a base call and the frequency of one or more bases at each locus is determined. EX2029 at 19; EX2030 at 3544.

159. As further illustrated in the claim charts below, the Guardant360 assay practices at least claim 1 of the '822 patent.

Claim 1 ('822 patent)	Guardant 360
<p>1. A method, comprising:</p> <p>a) providing a population of cell free DNA ("cfDNA") molecules obtained from a bodily sample from a subject;</p>	<p>EX2029 at 17 ("The Guardant360 cfDNA NGS panel identifies SNVs via sequencing of 54 genes spanning approximately 78,000 base pairs, including complete exon coverage in all exons in 18 genes and the critical exons in 36 genes (gene list in S1 Table) as well as copy number variations (CNVs) in ERBB2, EGFR, and MET.")</p> <p>EX2029 at 18 ("Two 10mL tubes of whole blood were collected per individual in Streck Cell-Free DNA Blood Collection (Streck) tubes, which contain a proprietary formaldehyde-free preservative that stabilizes white blood cells, preventing the release of genomic DNA and allowing isolation of high-quality cfDNA")</p> <p>EX2029 at 5 (Figure 1) ("Workflow for the Guardant360 cell-free circulating DNA NGS genomic profile.")</p> <p>EX2030 at 3539 ("Purpose: To analytically and clinically validate a circulating cell-free tumor DNA sequencing test for comprehensive tumor genotyping and demonstrate its clinical feasibility.")</p> <p>EX2030 at 3540 ("Blood draw, shipment, and plasma isolation"), ("cfDNA extraction, library preparation, and sequencing")</p> <p>EX2030 at 3542 (Figure 1) ("DS-based cfDNA assay workflow")</p>
<p>b) converting the population of cfDNA molecules into a</p>	<p>EX2029 at 18 ("Isolated cfDNA fragments are subsequently converted to digital sequence</p>

<p>population of non-uniquely tagged parent polynucleotides, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a cfDNA molecule of the population of cfDNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes;</p>	<p>libraries. Briefly, in the digital sequencing workflow, non-unique oligonucleotide heptamer barcodes are ligated to each half of individual double-stranded cfDNA”)</p> <p>EX2030 at 3540 (“Five to 30 ng of extracted cfDNA (66% of samples processed with 30 ng input) was labeled with nonrandom oligonucleotide barcodes (IDT, Inc.) and used to prepare sequencing libraries”)</p> <p>EX2030 at 3544 (“Briefly, cfDNA is extracted from stabilized whole blood, labeled at high efficiency with nonrandom oligonucleotide adapters (‘molecular barcodes’), and used to prepare sequencing libraries, which are then enriched using hybrid capture and sequenced (Fig. 1).”)</p>
<p>c) amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides;</p>	<p>EX2029 at 18 (“These digital sequence libraries are amplified”)</p> <p>EX2030 at 3540 (“Five to 30 ng of extracted cfDNA (66% of samples processed with 30 ng input) was labeled with nonrandom oligonucleotide barcodes (IDT, Inc.) and used to prepare sequencing libraries”)</p>
<p>d) sequencing the population of amplified progeny polynucleotides to produce a set of sequence reads;</p>	<p>EX2029 at 5 (Figure 1) (“Workflow for the Guardant360 cell-free circulating DNA NGS genomic profile.”)</p> <p>EX2030 at 3540 (“Five to 30 ng of extracted cfDNA (66% of samples processed with 30 ng input) was labeled with nonrandom oligonucleotide barcodes (IDT, Inc.) and used to prepare sequencing libraries, which were then enriched by hybrid capture (Agilent Technologies, Inc.), pooled, and sequenced by paired-end synthesis (NextSeq 500 and/or HiSeq 2500, Illumina, Inc.).”)</p>

e) mapping sequence reads of the set of sequence reads to one or more reference sequences from a human genome;	<p>EX2029 at 19 (“First, 150bp paired-end reads are aligned to the reference genome.”), (“Because digital sequencing enables tracking and quantification of all unique cfDNA fragments overlapping a given genomic site, PCR duplicates and artifacts of amplification during library preparation can easily be removed.”)</p> <p>EX2030 at 3540-41 (“Processed reads were then aligned to hg19 using BWA-MEM (arXiv:1303.3997v2) and used to build double-stranded consensus representations of original unique cfDNA molecules using both inferred molecular barcodes and read start/stop positions. SNVs were detected by comparing read and consensus molecule characteristics ...”)</p>
f) grouping the sequence reads into families, each of the families comprising sequence reads comprising the same identifier sequence and having the same start and stop positions, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;	<p>EX2030 at 3540-41 (“Processed reads were then aligned to hg19 using BWA-MEM (arXiv:1303.3997v2) and used to build double-stranded consensus representations of original unique cfDNA molecules using both inferred molecular barcodes and read start/stop positions. SNVs were detected by comparing read and consensus molecule characteristics ...”)</p>
g) at each genetic locus of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus; and	<p>EX2029 at 19 (“Custom scripts are then used to (a) remove spurious variants (“noise”) created by sequencing errors, (b) identify all germline single nucleotide polymorphisms (SNPs) and somatic single nucleotide variants (SNVs), and (c) call somatic SNVs, while removing erroneous variants resulting from sequencing errors, DNA damage, strand bias, etc.”)</p>

	EX2030 at 3544 (“Sequencing reads are then used to reconstruct each individual cfDNA molecule present in the original patient sample with high-fidelity using proprietary double-stranded consensus sequence representation.
h) determining a frequency of one or more bases called at the locus from among the families.	EX2029 at 19 (“The fractional concentration or mutant allele fraction for a given mutation is calculated as the fraction of circulating tumor DNA harboring that mutation in a background of wild-type cfDNA fragments at the same nucleotide position.”) EX2030 at 3544 (Figure 3) (“Somatic variant detection performance”)

A. Long-Felt Need

160. Conventional tumor-based genotyping assays are limited in the number of genes interrogated, require invasive biopsies, and often take upwards of 15 days before results are generated. EX2031, 1-2; *see also* EX2032, 1. However, using cfDNA to detect early stage cancers presents unique challenges. EX2033, 16. Early attempts to use cfDNA lacked the necessary sensitivity and specificity for diagnosing and characterizing cancers. EX2033, 16 (describing limits in clinical applications and lack of genomic sensitivity).

161. Precision oncology “focus[es] on matching cancer patients to personalized treatments based on the underlying molecular profile of their tumors.” EX2034, 1. The industry has long faced “a critical need to expand the scope of precision oncology to enable precise detection, monitoring and selection of the

appropriate intervention as early in the disease state as possible.” EX2034, 1. That is, “[d]espite improvements to clinical outcomes and oncology drug development ... precision oncology has not significantly impacted earlier stage cancer care.” EX2034, 6. “Many early stage cancer patients receive only non-targeted chemotherapy post-surgical resection of the tumor in the adjuvant setting and ad-hoc, symptomatic monitoring for recurrence. For early detection of cancer ... the current standard of care is comprised of single protein biomarker tests or radiographic imaging, which can have challenges with high false positive rates.” EX2034, 6. The Guardant360 assay provides a solution to the challenge of non-invasive detection of cancer.

162. In January 2018, the Guardant360 test was granted Breakthrough Devices designation by the FDA. EX2034, 27; *see also* EX2036, 1. The Breakthrough Device designation is a prioritized review of products that “provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.” EX2035, 1. Further, the designation is a recognition that the product “demonstrates the potential to address unmet medical needs for such a disease or condition.” 21 U.S.C. § 356(b)(1).

B. Commercial Success

163. The claimed invention, as embodied by Guardnt360, has seen widespread adoption in the industry. “Since its introduction in 2014, the

Guardant360 assay has been ordered more than 70,000 times to help inform which therapy may be effective for advanced-stage cancer patients with solid tumors. More than 80 peer-reviewed studies have been published addressing its analytical validity, clinical validity, and clinical utility in multiple tumor types.” EX2036, 2; see also EX2034, 13 (Guardant360 has been used “by more than 6,000 oncologists across dozens of cancer types, by more than 50 biopharmaceutical companies and by all 28 NCCN centers.”).

164. The prevalence of Guardant360 has made it one of the “two most common commercially used liquid biopsies” EX2037, 988. Notably, the other most common liquid biopsy test is FoundationACT (EX2037, 988) – I understand that Patent Owner has alleged in district court that FoundationACT infringes the ’822 patent, among other patents owned by Patent Owner. That is, the innovation of the ’822 patent has market dominance, accounting for all the most common liquid biopsy methods available. EX2037, 988.

165. Reflecting the innovation of the ’822 patent, Guardant360 is a commercial success. *See* EX2032, 2-3 (attributing Guardant’s financial growth and success to its genomic tests, including Guardant360). Sales of Guardant360 “accounted for primarily all of [Guardant’s] revenue for the years ended December 31, 2016 and 2017, respectively, and a majority of [Guardant’s] revenue for the year ended December 31, 2018.” EX2034, 33. Guardant360 is expected to

“continue to account for the substantial majority of [Guardant’s] revenue going forward.” EX2034, 33. In 2019, Guardant’s “[r]evenue was \$60.8 million, a 181% increase from a year ago”. Guardant’s revenue also experienced a “year-over-year increase of more than 125%.” EX2032, 2. Guardant also had “total revenues of \$54.0 million for the quarter ended June 30, compared to \$19.4 million in the same period of 2018, handily beating the \$36.4 million that Wall Street had predicted on average.” EX2038, 1.

166. The commercial success of Guardant360 is also evidenced by the growth in Guardant’s stock price. Specifically, Guardant’s “stock price has doubled [in 2019] and has nearly tripled since the company started trading publicly on Oct. 4, 2018.” EX2032, 1.

XI. CONCLUDING STATEMENTS

167. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

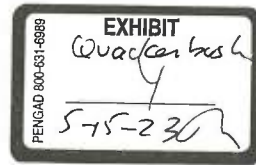
168. I declare that all statements made herein of my knowledge are true,
and that all statements made on information and belief are believed to be true, and
that these statements were made with the knowledge that willful false statements
and the like so made are punishable by fine or imprisonment, or both, under
Section 1001 of Title 18 of the United States Code.

Dated: December 4, 2019

By: 
John Quackenbush

Digitally signed by
John Quackenbush
Date: 2019.12.04
19:38:07 -08'00'

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE



TWINSTRAND BIOSCIENCES, INC. &
UNIVERSITY OF WASHINGTON,

Plaintiffs and
Counterclaim Defendants,

v.

GUARDANT HEALTH, INC.,

Defendant and
Counterclaim Plaintiff.

C.A. No. 21-1126-GBW-SRF

JURY TRIAL DEMANDED

Expert Report
of
John Quackenbush, Ph.D. on Invalidity
of U.S. Patent Nos. 10,287,631; 10,689,699; 10,752,951; and 10,760,127

April 7, 2023

A handwritten signature in black ink, appearing to be 'J. Quackenbush'.

John Quackenbush, Ph.D

[REDACTED]

POSA to determine whether the specification describes an invention understandable to that skilled person and show that the inventor actually invented the claimed invention.

38. I also understand that patent claims are invalid if they are not sufficiently supported by the specification. I also understand that the specification must provide sufficient written description such that a POSA can understand that the inventor was in possession of the claimed invention. I also understand that if a claim is amended during prosecution to include subject matter, limitations, or terminology not present in the application as filed, one may conclude that the claimed subject matter is not described in that application.

39. I understand that a patent must include claims that particularly point out and distinctly claim the subject matter of the invention. I also understand that a patent is indefinite if its claims, read in the light of the specification and the prosecution history, fail to inform with reasonable certainty those skilled in the art about the scope of the invention. I understand that a claim term is indefinite if the meaning of that term is not reasonably ascertainable to a POSA when read in light of the patent claims, the patent specification, and the patent file history.

40. I understand that a claim element may be expressed as a means or step for performing a specified function without the recital of a definite structure or materials for performing the step in the claim language, and the claim should be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof. I understand that where a patent does not disclose a corresponding definite structure or materials for performing the steps, the claims may be invalid for indefiniteness.

41. I understand that a patent claim may be declared invalid for lack of enablement. I have been informed that this standard is also set forth in 35 U.S.C. § 112, first paragraph, which has been reproduced below:

[REDACTED]

291. Finally, the full scope of the “amplifying” limitations in claims 1 and 20 are not enabled. None of the asserted dependent claims limit the scope of the amplifying step and are similarly not enabled. This step encompasses amplification by rolling circle replication. As I have been informed, the PTAB noted in its institution decision in IPR2022-00817, the teaching in Travers ’075 of rolling circle amplification meets this limitation. *See Guardant Health, Inc. v. University of Washington*, IPR2022-00817, Paper 14 at 19 (PTAB, Oct. 13, 2022).

292. In addition, as discussed above with the ’631, ’699, and ’951 patents, the specification of the ’127 patent fails to adequately describe how a POSA would obtain accurate sequence information *without* performing the Duplex Consensus Sequencing step of creating a separate consensus for each strand. *See, e.g.*, Paragraph 179.

2. Indefiniteness

293. The method claimed by the ’127 patent includes functional steps, for example, the “confirming,” “comparing,” and “analyzing” steps of claim 1. The specification of the ’127 patent does not disclose a corresponding structure or steps. Thus it is my opinion that the claims are invalid for indefiniteness.

294. The specification of the ’127 patent includes, in Figure 10, Python code for pairing single-strand consensus sequences with their strand-mate. The code provided in Figure 10 discloses selecting single-strand consensus sequences based on a stringent filter and forming duplex consensus sequences from the filtered single-strand consensus sequences. The filtering step retains pairs of single-strand consensus sequences that have an exact complementary match in their SMI sequences. Figure 10 further describes forming duplex consensus sequences from filtered single-strand consensus sequences. Duplex consensus sequences include nucleotides that perfectly agree between a pair of single-strand consensus sequences. Where a pair of single-

[REDACTED]

strand consensus sequences do not agree an “N” is included. This code describes operations on single-strand consensus sequences which are distinct from sequence reads and so does not correspond to the “confirming,” “comparing,” and “analyzing” steps of claim 1.

295. The specification states that confirming the presence of a true mutation when the mutation is present on both of the target nucleic acid strands and appears in all members of a paired target nucleic acid family may be performed in some embodiments, but does not disclose corresponding steps for this confirmation:

In further embodiments, the method confirms the presence of a true mutation by (i) identifying a mutation present in the paired target nucleic acid strands having one or more nucleotide positions that disagree; (ii) comparing the mutation present in the paired target nucleic acid strands to the error corrected double-stranded consensus sequence; and (iii) confirming the presence of a true mutation when the mutation is present on both of the target nucleic acid strands and appears in all members of a paired target nucleic acid family.

’127 Patent, 3:39-3:48.

This error corrected double-stranded consensus sequence may be used in a method for confirming the presence of a true mutation (as opposed to a PCR error or other artifactual mutation) in a target nucleic acid sequence. According to certain embodiments, such a method may include identifying one or more mutations present in the paired target nucleic acid strands that have one or more nucleotide positions that disagree between the two strands, then comparing the mutation present in the paired target nucleic acid strands to the error corrected double-stranded consensus sequence. The presence of a true mutation is confirmed when the mutation is present on both of the target nucleic acid strands and also appear in all members of a paired target nucleic acid family.

Id. at 16:44-16:58.

296. The specification states that comparing the sequence of the two single strand consensus sequences arising from a single duplex DNA molecule may be performed in the DCS stage, but does not disclose corresponding steps for this comparing:

The DCS stage includes steps of comparing the sequence of the two single strand consensus sequences arising from a single duplex DNA molecule, and

[REDACTED]

further reducing sequencing or PCR errors by considering only sites at which the sequences of both single-stranded DNA molecules are in agreement.

Id. at 16:21-16:26.

According to certain embodiments, such a method may include identifying one or more mutations present in the paired target nucleic acid strands that have one or more nucleotide positions that disagree between the two strands, then comparing the mutation present in the paired target nucleic acid strands to the error corrected double-stranded consensus sequence.

Id. at 16:48-16:55.

297. The specification notes that data were analyzed by Single Strand Consensus Sequencing (SSCS), but does not disclose corresponding steps for this analyzing step:

The data were then analyzed by Single Strand Consensus Sequencing (SSCS), using the unique SMI tag affixed to each molecule to group PCR products together in order to create a consensus of all PCR products that came from an individual molecule of single-stranded DNA. This resulted in a mutation frequency of 6.4E-05, suggesting that ~98% of sequencing errors are corrected by SSCS.

Id. at 27:63-28:2.

The data was then analyzed by consensus sequencing (FIG. 9).

Id. at 30:8-30:9.

298. Therefore, the specification of the '127 patent does not disclose a corresponding structure or steps for the "confirming," "comparing," and "analyzing" steps of claim 1. Thus it is my opinion that the claims are invalid for indefiniteness.

C. Invalidity under §101: Lack of Patentable Subject Matter

299. It is my opinion that the asserted claims of the '127 patent are directed to a natural law or abstract idea. The '127 patent, like the other Asserted TwinStrand Patents, is directed to a method of sequencing DNA to identify variants, such as mutations. Specifically, the '127 patent applies a solution that was made up of well-known steps. First, barcode adaptors are attached to fragments of double-stranded DNA. Next, the adaptor-DNA molecules are amplified to produce

[REDACTED]

“analyzing” steps of claim 1. These steps are all abstract ideas performed using generic computers.

303. It is thus my opinion that the asserted claims of the '127 patent claim unpatentable subject matter.

304. I declare under penalty of perjury that the foregoing is true and correct.

Date: April 7, 2023

Respectfully submitted,



[Dr. John Quackenbush]