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UNITED STATES PATENT AND TRADEMARK OFFICE

08:19:57

ILLUMINA INC.,	)	
	)	
Petitioner,	)	IPR2024-00964
	)	
v.	)	
	)	
MOLECULAR LOOP	)	
BIOSCIENCES, INC.,	)	
	)	
Patent Owner.	)	
_____	)	

VIDEOTAPED DEPOSITION OF PAUL SPELLMAN, PH.D.

April 9, 2025

9:00 a.m.

REPORTED BY:

Tammy Moon, CSR No. 13184, RDR, CRR

Henderson Legal Services

202-220-4158

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IPR2024-00964

Illumina Inc., v. Molecular Loop Biosciences, Inc.

Molecular Loop's Exhibit 2002

Ex. 2002, Page 1

1 APPEARANCES:

2 FOR PETITIONER ILLUMINA INC.:

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12 ALSO PRESENT: MARCUS BURCH, ILLUMINA

13 FRANK QUIRARTE, THE VIDEOGRAPHER

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INDEX TO EXAMINATION

PAUL SPELLMAN, PH.D.

Wednesday, April 9, 2025

Tammy Moon CSR No. 13184, RPR, CRR

WITNESS: PAUL SPELLMAN, PH.D.

EXAMINATION

MR. MATTY

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1 INDEX TO PREVIOUSLY-MARKED EXHIBITS

2 PAUL SPELLMAN, PH.D.

3 Wednesday, April 9, 2025

4 Tammy Moon CSR No. 13184, RPR, CRR

5 REFERENCED	DESCRIPTION	PAGE
6 Exhibit 1001	US Patent No. 11,768,200	9
7 Exhibit 1003	Declaration of Paul T.	7
8	Spellman, Ph.D.	
9 Exhibit 1004	Article " A	65
10	pyrosequencing-tailored	
11	nucleotide barcode design	
12	unveils opportunities for	
13	large-scale sample	
14	multiplexing"	
15 Exhibit 1005	Article "Microbiome profiling	128
16	by Illumina sequencing of	
17	combinatorial sequence-tagged	
18	PCR products"	
19 Exhibit 1017	Article "Reducing the impact of	100
20	PCR-mediated recombination in	
21	molecular evolution and	
22	environmental studies using a	
23	new-generation high-fidelity	
24	DNA polymerase"	

25

1 INDEX TO PREVIOUSLY-MARKED EXHIBITS

2 PAUL SPELLMAN, PH.D.

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5	Exhibit 1018	Article "DNA recombination	105
6		during PCR"	

7	Exhibit 1019	Article "DNA damage promotes	108
8		jumping between templates	
9		during enzymatic amplification"	

10	Exhibit 1020	Article "Template-switching	113
11		during DNA synthesis by thermus	
12		aquaticus DNA polymerase I"	

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1 Wednesday, April 9, 2025, 9:00 a.m. 09:00:28

2 THE VIDEOGRAPHER: Good morning, ladies and
3 gentlemen. We're going on video record. The time 09:00:33
4 is approximately 9:00 a.m. Today's date is 09:00:33
5 April 9th, 2025. 09:00:37

6 This is the video deposition of Dr. Paul 09:00:39
7 Spellman. It's in the matter of Illumina 09:00:43
8 v. Molecular Loop Biosciences, Inc. It's Case 09:00:51
9 No. IPR2024-00964. 09:00:53

10 This deposition is taking place at 3300 09:00:58
11 Hill View Avenue in Palo Alto, California. My name 09:01:03
12 is Frank Quirarte. I'm your legal videographer 09:01:05
13 today, representing Henderson Legal Services. 09:01:08

14 At this time, will counsel and all present 09:01:11
15 please identify yourself for the record. 09:01:13

16 MR. MATTY: Brian Matty, from Desmarais 09:01:15
17 LLP, on behalf of the patent owner, Molecular Loop. 09:01:18

18 MR. RAICH: Bill Raich of Finnegan for 09:01:21
19 petitioner, Illumina. With me today is my colleague 09:01:24
20 Yoonjin Lee, also of Finnegan, and Marcus Burch of 09:01:27
21 Illumina. 09:01:30

22 THE VIDEOGRAPHER: Madam Court Reporter, 09:01:30
23 will you please state your appearance and swear in 09:01:31
24 the witness. 09:01:34

25 THE REPORTER: My name is Tammy Moon, 09:01:35

1 Certified Stenographic Reporter 13184. I am a
2 code-compliant reporter, and as such, this
3 transcript will be handled pursuant to the Code of
4 Civil Procedure 2025.550. 09:01:44

5 PAUL SPELLMAN, PH.D.,
6 called as a witness, having been duly sworn,
7 testified as follows: 09:01:56

8 THE WITNESS: I do. 09:01:56

9 EXAMINATION BY MR. MATTY, COUNSEL FOR PATENT OWNER
10 MOLECULAR LOOP BIOSCIENCES 09:01:58

11 MR. MATTY: 09:01:58

12 Q. Good morning, Dr. Spellman. You understand 09:01:58
13 you have taken an oath to tell the truth today just 09:02:01
14 as if you were in front of a judge or a jury? 09:02:04

15 A. Yes. 09:02:06

16 Q. And you know you are being videotaped 09:02:06
17 today, right? 09:02:09

18 A. Yes. 09:02:10

19 Q. Is there any reason you can't give full and 09:02:10
20 truthful answers to my questions today? 09:02:13

21 A. No. 09:02:16

22 Q. I see you have brought some documents in 09:02:16
23 with me -- with you. Could you hand those to me. 09:02:18

24 A. Absolutely. 09:02:19

25 (Reference to previously-referenced Exhibit

1	1003.)	09:02:56
2	Q. Give those back to you. Thank you, sir.	09:02:56
3	So you've brought in two declarations that you have	09:02:58
4	signed in these matters, right?	09:03:02
5	A. Counsel provided me clean copies of the two	09:03:03
6	declarations in suit, yes.	09:03:06
7	Q. Right. And we are here for two IPRs. You	09:03:06
8	understand Illumina is challenging the validity of	09:03:10
9	two Molecular Loop patents, right?	09:03:14
10	A. Correct.	09:03:15
11	Q. And those declarations that are in front of	09:03:15
12	you, you understand, were submitted in support of	09:03:17
13	Illumina's petitions in these cases, right?	09:03:20
14	A. Correct.	09:03:22
15	Q. The Molecular Loop patents that are at	09:03:23
16	issue in these cases are about maintaining	09:03:27
17	identification of nucleic acid templates during	09:03:32
18	multiplex sequencing reactions. You know that,	09:03:34
19	right?	09:03:37
20	A. The parent specification is very -- is	09:03:37
21	relatively broad and is, broadly speaking, about	09:03:40
22	maintaining integrity of sequencing actions.	09:03:45
23	Q. And it specifically talks about maintaining	09:03:50
24	integrity of identification of nucleic acids, right?	09:03:55
25	A. May I please have a copy of the	09:03:59

1 **specification?** 09:04:02

2 **(Reference to previously-marked Exhibit 1001.)** 09:04:02

3 Q. Sure. I'm handing you Exhibit 1001 from 09:04:02

4 the -- I'll call it the 964 IPR, which is the '852 09:04:21

5 patent. Do you have that in front of you? 09:04:26

6 A. **I do.** 09:04:27

7 Q. All right. So my question was the 09:04:28

8 Molecular Loop patents at issue in these cases talk 09:04:32

9 about maintaining integrity of identification of 09:04:35

10 nucleic acids, right? 09:04:41

11 A. **That is the title of the patent, yes.** 09:04:43

12 Q. And it talks about maintaining the 09:04:44

13 integrity of identification during multiplex 09:04:47

14 sequencing reactions, right? 09:04:50

15 A. **Correct.** 09:04:51

16 Q. Maybe now that I have the patent in front 09:04:51

17 of you, if I refer to the Molecular Loop patents 09:04:55

18 today as the "'852 patent" and the "'200 patent," 09:04:57

19 you'll understand what I'm talking about, right? 09:05:01

20 A. **I believe so, yes.** 09:05:03

21 Q. Okay. Now, the concept of multiplex 09:05:05

22 sequencing reactions that these patents talk about, 09:05:08

23 that refers to pooling multiple samples and running 09:05:11

24 them together through a sequence, right? 09:05:13

25 A. **The initial background section describes** 09:05:38

10

1 the ability to multiplex samples. The broader 09:05:41
2 phrasing, "multiplex sequencing," can -- can be more 09:05:44
3 broad scope than that, but the -- the section in the 09:05:50
4 background specifically refers to multiplex samples. 09:05:52

5 Q. Okay. Maybe I'll just ask for in your own 09:05:55
6 words, from your experience. What are multiplex 09:05:58
7 sequencing reactions? What does that mean to you? 09:06:03

8 A. Well, I think it depends. It can be -- it 09:06:05
9 can be very broad. So I would use the specification 09:06:08
10 to guide myself in this case. 09:06:11

11 Q. Okay. And in your view, from having 09:06:12
12 reviewed the specification in this case, what are 09:06:26
13 the multiplex sequencing reactions that are 09:06:32
14 discussed in the Molecular Loop patents? 09:06:34

15 A. You would like me to summarize the 09:06:37
16 specification? 09:06:39

17 Q. Just as -- as they relate to multiplex 09:06:40
18 sequencing reactions -- your understanding of what 09:06:44
19 that is in the context of these patents. 09:06:47

20 A. So without limiting myself to later 09:06:58
21 sections the document, in Column 1, line 31: "The 09:07:00
22 ability to multiplex samples, i.e., pool different 09:07:04
23 patient samples, is important for decreasing costs 09:07:08
24 and increasing the throughput of sequencing by 09:07:11
25 synthesis platforms." 09:07:15

11

1 The next paragraph, at line 35, discusses 09:07:16
2 multiplex sequencing -- an issue in multiplex 09:07:20
3 sequencing is maintaining accurate identification of 09:07:24
4 samples through the sequencing process. 09:07:26

5 So, you know, I could read that whole 09:07:29
6 paragraph very carefully if you would like. I can 09:07:31
7 also summarize it more deeply. I'm happy to 09:07:34
8 continue if you would like. 09:07:37

9 Q. That's okay. Let me also hand you the 09:07:38
10 second patent, the '200 patent. This is 09:07:52
11 Exhibit 1001 in the 965 IPR -- 09:07:58

12 A. Thank you. 09:08:02

13 Q. -- just so you have it in front of you. 09:08:03
14 Now, you have given opinions in these cases that the 09:08:05
15 '852 patent covers what you refer to as "unique dual 09:08:07
16 indexing," true? 09:08:11

17 A. In paragraph 111, I discuss unique -- that 09:08:58
18 I require unique accommodations, two or more 09:09:05
19 identifiers. I do have discussion on unique dual 09:09:05
20 indexing and document in a separate place if you 09:09:08
21 would like me to find it. 09:09:11

22 Q. Let's go back to my question: In your 09:09:12
23 opinion, the claims of the '852 patent cover what 09:09:14
24 you refer to as "unique dual indexing," true? 09:09:16

25 A. So in paragraph 126 of my declaration, on 09:09:53

12

1 page 66, I have a discussion about Parameswaran in 09:09:56
2 this case and how it discloses the -- the sample 09:10:00
3 associated with two uniquely designed 10-nucleotide 09:10:05
4 barcodes to facilitate unambiguous assignment of 09:10:10
5 a -- nucleic acid sequences from a mixture of 09:10:13
6 libraries from 48 different samples. That would be 09:10:14
7 unique dual indexing. 09:10:18

8 Q. Okay. My question wasn't about 09:10:19
9 Parameswaran, so I'll go back again. In your 09:10:23
10 opinion, the claims of the '852 patent cover what 09:10:26
11 you refer to as "unique dual indexing," true? 09:10:29

12 A. So in paragraph -- page 34, paragraph 70, 09:11:16
13 continuing onward, I have a discussion of dual 09:11:21
14 indexing. And then in paragraph 71, unique dual 09:11:23
15 indexing -- unique dual indexing using two 09:11:27
16 identifier sequences per sample to -- and not 09:11:31
17 permitting an identifier sequence to be used with 09:11:36
18 more than one sample. 09:11:37

19 So in that context, the Parameswaran 09:11:38
20 discussion I brought up for -- is an example of 09:11:44
21 prior art, and this '852 patent would be -- would 09:11:47
22 cover unique dual indexing. 09:11:52

23 Q. Okay. I'm not sure why we're going back to 09:11:57
24 Parameswaran. I'll just give you a yes-or-no 09:11:59
25 question: Do the claims of the '852 patent cover 09:12:01

13

1 unique dual indexing, in your opinion? 09:12:08

2 **A. The final clause of the first -- so what is** 09:12:12

3 **claimed to Claim 1, the preamble, and then** 09:12:20

4 **incorporating at least two members of a plurality of** 09:12:25

5 **identifier sequences wherein -- blah, blah, blah --** 09:12:28

6 **wherein said two members constitute a distinct pair,** 09:12:32

7 **that would include unique distinct pairs, unique** 09:12:37

8 **dual indexing.** 09:12:42

9 Q. Okay. I'm not sure what the answer to the 09:12:43

10 question is, though. Does that mean that, yes, the 09:12:45

11 claims cover unique dual indexing for the '852 09:12:47

12 patent? 09:12:51

13 **A. Unique dual indexing would be included, but** 09:12:51

14 **it is not limited to.** 09:12:54

15 Q. What other types of indexing do the claims 09:12:58

16 of the '852 patent cover, in your opinion? 09:13:02

17 **A. The distinct pairs do not need to be** 09:13:04

18 **unique.** 09:13:07

19 Q. So the '852 patent could cover other dual 09:13:07

20 indexing methods other than unique dual indexing, in 09:13:17

21 your opinion? 09:13:21

22 **A. Yes.** 09:13:21

23 Q. Do you have any examples of other types of 09:13:21

24 dual indexing methods other than unique dual 09:13:27

25 indexing that the '852 claims cover, in your 09:13:31

14

1 opinion? 09:13:38

2 A. As long as it facilitated the rest of the 09:13:38

3 workflow, any -- any configuration of dual indexes 09:13:41

4 that facilitated the rest of the workflow would be 09:13:48

5 covered, in my opinion. 09:13:51

6 Q. So the '852 patent claims would cover 09:13:52

7 nonunique dual indexing, in your opinion? 09:13:55

8 MR. RAICH: Object to the form of the 09:13:57

9 question. 09:14:00

10 THE WITNESS: Not all nonunique dual 09:14:00

11 indexing. But in some cases, yes. 09:14:05

12 MR. MATTY: 09:14:07

13 Q. What cases are you thinking? 09:14:07

14 A. So the '852 patent does not require that 09:14:10

15 all chimeric molecules are excluded. And, 09:14:15

16 therefore, any configuration of dual indexes that 09:14:22

17 allows you to reject chimeric molecules but not all 09:14:26

18 chimeric molecules would be covered under the 09:14:30

19 claims. 09:14:34

20 Q. Do you have any specific examples of 09:16:32

21 nonunique dual indexing that are covered by the '852 09:16:34

22 patent claims, in your view? 09:16:41

23 A. Are you asking about in my declarations, or 09:16:41

24 can I provide you an example? 09:16:44

25 Q. Either. 09:16:45

15

1 A. When utilizing dual indexes, sometimes one 09:16:49
2 can be unique, as in Parameswaran, or sparse or 09:16:54
3 saturated. In the case of a saturated dual indexing 09:17:01
4 scheme, the strategy provided in the '852 patent 09:17:08
5 cannot work. 09:17:10

6 But in the situation that is sparse, where 09:17:12
7 not all possible pairs are utilized in the multiplex 09:17:16
8 tagging process, then any unexpected unutilized pair 09:17:25
9 that is observed is evidence for template crossover 09:17:28
10 reaction, as described in the specification. 09:17:36

11 So with a large number of barcodes in the 09:17:40
12 forward and reverse orientation, even with a very 09:17:43
13 large number of multiplex samples, if the matrix of 09:17:46
14 N squared is sparsely covered, a very large fraction 09:17:52
15 of template crossover bins can be detected and 09:17:57
16 rejected even though a barcode is used more than 09:18:01
17 for -- for more than one sample. 09:18:06

18 Q. Okay. Do the claims of the '200 patent 09:18:08
19 cover nonunique dual indexing, in your view? 09:18:11

20 A. Yes. 09:18:31

21 Q. And do the claims of the '200 patent cover 09:18:32
22 nonunique dual indexing in your view? 09:18:36

23 A. Can you repeat the question. 09:19:06

24 Q. Do the claims of the '200 patent cover 09:19:07
25 nonunique dual indexing, in your view? 09:19:10

16

1 A. Yes.

2 Q. All right. What did you do to prepare for 09:19:12

3 your deposition today? 09:19:36

4 A. Met with counsel, read my declarations, 09:19:39

```
5 read papers that had been referenced and documents 09:19:42
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```
6 referenced in the case, reread -- reread various -- 09:19:46
```

7 reread those documents on my own time, discussed 09:19:52

8 them with counsel. 09:19:55

9 Q. Who did you meet with? 09:19:56

A. Those present.

11 Q. Anyone else? 09:19:58

[illegible]

13 Q. How long did you meet? 09:20:00

A. Over the past three days.

15 Q. Did you speak with anyone other than 09:20:06

16 attorneys to prepare for your deposition today? 09:20:08

17 **A. No.** 09:20:10

18 Q. Have you spoken with anyone from Illumina 09:20:10

19 over the course of your work in this case? 09:20:15

A. Just the attorneys present.

21 Q. Just Mr. Burch? 09:20:20

22 **A.** Yeah. 09:20:23

23 Q. The documents that you reviewed to prepare 09:20:23

24 for today -- did you review any documents that you 09:20:27

25 hadn't reviewed -- let me start that over. 09:20:30

17

1 In preparing for your deposition today, did 09:20:33
2 you review any documents that you hadn't reviewed 09:20:36
3 before you submitted your declarations in this case? 09:20:39

4 **A. I don't believe so, but I'm not certain.** 09:20:43

5 Q. Have you reviewed the petitions that 09:20:45
6 Illumina submitted in these cases? 09:20:48

7 **A. I don't believe I've reviewed them myself,** 09:20:51
8 **no.** 09:20:54

9 Q. Have you reviewed the preliminary responses 09:20:54
10 that Molecular Loop filed in these cases? 09:20:58

11 **A. I don't believe I've seen them.** 09:21:00

12 Q. Have you reviewed the board's institution 09:21:01
13 decisions in these cases? 09:21:04

14 **A. I don't believe I've seen institution** 09:21:05
15 **decisions.** 09:21:07

16 Q. In your work on these matters, have you 09:21:08
17 reviewed any documents other than the exhibits that 09:21:12
18 are listed as materials considered in your 09:21:17
19 declaration? 09:21:20

20 **A. I don't believe so.** 09:21:20

21 Q. All right. I want to go through just a 09:21:21
22 couple general concepts that I think are relevant to 09:21:33
23 the opinions here. You are familiar with 09:21:37
24 pyrosequencing, true? 09:21:40

25 **A. Yes.** 09:21:41

18

1 Q. Can you describe for me how pyrosequencing 09:21:41
2 works to sequence DNA? 09:21:46

3 A. I have a lengthy discussion of it in my 09:21:47
4 declarations. The broad scheme, as implemented in 09:21:50
5 the Roche 454, is to utilize beads and emulsion PCRs 09:21:59
6 to spatially constrain on the 2D surface of the bead 09:22:05
7 clonally amplified PCR products that are conjugated 09:22:12
8 to the 2D surface and then using specific chemistry 09:22:17
9 that detects the emitted -- the emitted reagents 09:22:21
10 during the sequencing reaction as light to detect 09:22:28
11 individual bases. 09:22:30

12 Each base is sequentially flowed over a 09:22:31
13 flow cell containing the beads after the emulsion 09:22:35
14 PCR is broken. And it's all covered in my 09:22:39
15 declaration such that individual bases are sequenced 09:22:43
16 one at a time. There are interesting quirks of 454 09:22:46
17 compared to other sequencing by synthesis methods, 09:22:50
18 including Sanger sequencing and Illumina and others. 09:22:54

19 Q. You said "emulsion PCR." What's emulsion 09:22:56
20 PCR? 09:23:01

21 A. One of the challenges -- well, perhaps 09:23:02
22 always the challenge in clonally amplified 09:23:04
23 sequencing is creating copies of DNA when the signal 09:23:10
24 sensitivity is relatively poor and one needs a way 09:23:14
25 to create many copies of that. Historically, that 09:23:19

19

1 would have been done by cloning or PCR in an 09:23:26
2 individual PCR reaction. 09:23:31

3 An emulsion PCR is analogous to a multiplex 09:23:32
4 PCR -- or sorry -- a plate-based PCR with many 09:23:38
5 wells, except the wells are created with what is 09:23:42
6 called micelles, where individual beads nucleate a 09:23:46
7 small reaction via a vessel that is bounded by -- an 09:23:51
8 aqueous reaction vessel bounded by oil such that 09:23:57
9 these very small reaction chambers facially 09:24:01
10 constrain the individual PCR reactions from one 09:24:04
11 another as if they were individual tubes. 09:24:07

12 Different sequencing technologies using 09:24:10
13 applications solve these problems in different 09:24:13
14 methods. 09:24:16

15 Q. Okay. And in pyrosequencing, that emulsion 09:24:17
16 PCR takes place in a device that's separate from 09:24:19
17 where the DNA sequences. Is that true? 09:24:22

18 A. That it happens in 454 on a separate 09:24:28
19 device? I'd have to check. I don't know that it 09:24:31
20 intrinsically has to. One could imagine a device 09:24:34
21 that does it all. 09:24:38

22 So, you know, I'm prepared -- I would be 09:24:39
23 prepared to stipulate that the 454 does it on one 09:24:41
24 device and then moves it to another. I haven't used 09:24:44
25 one in a long time, but the broad concept wouldn't 09:24:47

20

1 **require it.** 09:24:51

2 Q. Okay. When is the last time you used a 09:24:51

3 pyrosequencing? 09:24:56

4 A. **My laboratory used the Ion Torrent** 09:24:56

5 **platform, which is a follow-on technology to the** 09:25:01

6 **454, circa 2011/2012 until, say, 2015, perhaps.** 09:25:03

7 Q. And for you personally, when's the last 09:25:09

8 time you personally, hands-on, used a 09:25:11

9 pyrosequencing? 09:25:14

10 A. **I don't believe I've ever personally used** 09:25:15

11 **the 454 or the Ion Torrent. That was in my** 09:25:17

12 **laboratory. I purchased and provided -- you know, I** 09:25:21

13 **supervised.** 09:25:23

14 Q. When's the last time you used an Illumina 09:25:23

15 sequencer? 09:25:26

16 A. **Again, I don't think I've ever personally** 09:25:27

17 **utilized the Illumina sequencer. It's the basis for** 09:25:30

18 **my laboratory's research from the period 2007 until** 09:25:34

19 **2000- -- you know, we still use it today. But,** 09:25:42

20 **again, as a -- as a professor, one often does not** 09:25:44

21 **directly do the work.** 09:25:49

22 Q. Okay. Going back to pyrosequencing, after 09:25:50

23 the emulsion PCR, you said that there's a flow cell, 09:26:01

24 and the bases are flowed over one at a time. Can 09:26:07

25 you describe to me what the flow cell looks like? 09:26:11

21

1 **A. My understanding is the flow cell has** 09:26:15
2 **capture sites for individual beads that are packed** 09:26:18
3 **into these sort of very small chambers, and then** 09:26:23
4 **there is a detection platform for collecting light** 09:26:26
5 **emitted from those.** 09:26:30

6 **Q. And the beads are what contain the** 09:26:32
7 **amplified DNA, right?** 09:26:34

8 **A. The beads that seeded the emulsion PCR --** 09:26:37
9 **surface of the beads have copies of the DNA from the** 09:26:42
10 **emulsion, yes.** 09:26:45

11 **Q. Okay. And so those beads go each into a** 09:26:46
12 **well on the flow cell -- or at least the intent is** 09:26:50
13 **one bead per flow cell well, right?** 09:26:52

14 **A. Roughly speaking. I think it's more** 09:26:56
15 **complicated than that because it's a random process.** 09:26:58
16 **And the goal is to get every well filled with a** 09:27:01
17 **bead, but I think you are doing really well when you** 09:27:04
18 **hit 90 percent.** 09:27:07

19 **Q. So you might have some wells that don't get** 09:27:08
20 **a bead. You might have some wells that get two** 09:27:11
21 **beads. But generally, as much as possible, you want** 09:27:14
22 **one bead of DNA per well in pyrosequencing, true?** 09:27:18

23 **A. Yes. Absolutely. And one template per** 09:27:21
24 **bead in pyrosequencing.** 09:27:23

25 **Q. And by "template," you mean the DNA that** 09:27:23

22

1 was amplified in emulsion PCR? 09:27:26

2 A. Correct. It is possible to see more than 09:27:28

3 one DNA molecule per bead, and then you get a 09:27:31

4 complex mixture or perhaps even a chimera. 09:27:35

5 Q. And when this sequencing is happening, what 09:27:38

6 else is in that well with that DNA bead? 09:27:43

7 A. My understanding, there are some reagents 09:27:46

8 that are -- I'm not -- how it works exactly, that -- 09:27:48

9 I cannot tell you what else is in there. Things to 09:27:51

10 facilitate the sequencing process -- these are 09:27:55

11 commercial platforms. 09:27:57

12 Q. Okay. But within each well on the flow 09:27:58

13 cell in pyrosequencing, there is a bead of DNA 09:28:01

14 that's sort of free floating and then other reagents 09:28:06

15 for the reaction that ultimately emit light when 09:28:10

16 bases are added one by one. Is that a fair summary? 09:28:16

17 A. I don't think the beads are free floating 09:28:20

18 in the sense that they -- you know, if they diffused 09:28:23

19 out, that would be extremely bad. So, no, they're 09:28:26

20 spatially constrained in a way that locks them in. 09:28:30

21 Q. They stay within the well? 09:28:32

22 A. Yes. 09:28:34

23 Q. Sort of like a ball pit, almost? 09:28:34

24 A. Yeah. The physics of a ball pit and the 09:28:36

25 physics of these microsurfaces are not equivalent. 09:28:39

23

1 **So I think it would be a bad characterization to** 09:28:43
2 **describe it that way. I suspect there are other** 09:28:46
3 **much more complicated forces than gravity** 09:28:48
4 **constraining the beads in the well.** 09:28:51

5 Q. Okay. For the reagents that are in the 09:28:51
6 well, are those also in beads, or are those just 09:28:53
7 separate liquids? 09:28:56

8 A. **I believe it is both.** 09:28:57

9 Q. Okay. 09:28:59

10 A. **If I understand it correctly.** 09:28:59

11 Q. Are you familiar with the primers that are 09:29:01
12 used for pyrosequencing? 09:29:03

13 A. **There -- which primers?** 09:29:06

14 Q. Well, can you generally describe for me the 09:29:08
15 primers that are used for pyrosequencing? 09:29:12

16 A. **So the bead, as I understand it, has** 09:29:15
17 **primers attached to it to facilitate. And those** 09:29:19
18 **will be, you know, some set of primers that -- that** 09:29:23
19 **bind to the prepared templates. One might attach** 09:29:29
20 **other primers to your prepared templates to** 09:29:34
21 **facilitate that interaction.** 09:29:36

22 Q. Have you ever designed primers for 09:29:38
23 pyrosequencing? 09:29:41

24 A. **As I've said, my laboratory utilized the** 09:29:43
25 **Ion Torrent extensively. Tim Butler, he's got a** 09:29:46

24

1 **number of papers and my -- supervised this, and so** 09:29:51

2 **he and I would have gone over that process.** 09:29:55

3 Q. Tim Butler was one of your students who got 09:29:57

4 his Ph.D. somewhere around 2016/2017. Is that who 09:30:00

5 you are referring to? 09:30:05

6 A. **Correct. 2017, I believe.** 09:30:06

7 Q. So in the work that Tim Butler did in your 09:30:07

8 laboratory, did you design pyrosequencing primers 09:30:13

9 for him? 09:30:17

10 A. **No, I don't believe so.** 09:30:18

11 Q. His work involved designing primers, but he 09:30:19

12 did that work on -- that was part of the work that 09:30:24

13 he did, true? 09:30:27

14 MR. RAICH: Objection to form. 09:30:27

15 THE WITNESS: I would have supervised him 09:30:28

16 and helped him with anything that he needed help 09:30:29

17 with. 09:30:32

18 MR. MATTY: 09:30:32

19 Q. Okay. Now, you are obviously familiar with 09:30:33

20 Illumina sequencing, true? 09:30:37

21 A. **As I said, it's been a backbone technology** 09:30:38

22 **for my research laboratory for the past -- close to** 09:30:41

23 **20 years.** 09:30:44

24 Q. And can you give me the high-level 09:30:44

25 explanation of how Illumina sequencing works. 09:30:48

25

1 A. So broadly speaking, it is very similar to 09:30:54
2 the overall process of 454, the key differences 09:30:59
3 being, first, the 2D spatial surface that captures 09:31:03
4 templates is flat rather than the surface of a bead. 09:31:08

5 The PCR step constraint, rather than being 09:31:15
6 facilitated by the emulsion, is facilitated by 09:31:21
7 spatial constraint on the molecules themselves so 09:31:25
8 that they cannot reach from one spot to another. So 09:31:29
9 the templates are captured on the surface and then 09:31:33
10 copied locally on the surface. 09:31:37

11 And then the third substantial difference 09:31:40
12 is that the detection chemistry is all four bases 09:31:43
13 simultaneously and originally using four different 09:31:51
14 fluorescent detector colors, versus Roche using each 09:31:54
15 base one at a time and -- and Illumina using 09:32:02
16 reversible terminator chemistry versus -- versus 09:32:05
17 Roche not using that, I believe. 09:32:09

18 Q. Okay. You mentioned earlier -- I don't 09:32:11
19 want to put words in your mouth -- but something 09:32:32
20 like there were quirks with pyrosequencing relative 09:32:34
21 to other types of sequencing or Illumina sequencing. 09:32:37
22 What were you referring to? 09:32:40

23 A. Well, every -- all of the parallel 09:32:41
24 sequencers are trying to solve a specific set of 09:32:45
25 problems in specific ways and often to avoid 09:32:48

1 intellectual property of others. 09:32:54

2 And so the -- the single molecule 09:32:58

3 sequencers that do not directly sequence true single 09:33:05

4 molecules -- there have been sequencers that 09:33:09

5 sequence true individual molecules. 09:33:11

6 But the ones that are not sufficiently 09:33:13

7 sensitive to do so have to make copies, and they 09:33:15

8 have to keep copies nearby in some way. And so the 09:33:19

9 quirks are how do you achieve that thing? How do 09:33:24

10 you -- how do you spatially restrict or keep the 09:33:27

11 copies in some local configuration? 09:33:30

12 Various solutions have been proposed and 09:33:32

13 implemented. The most successful has been Illumina 09:33:35

14 in the marketplace so far, but Roche had a good 09:33:38

15 position early on. SOLiD was okay at this. 09:33:44

16 It has a different -- I can't actually 09:33:48

17 describe the SOLiD technology in detail on how it 09:33:51

18 worked because it's been a long time since I looked 09:33:54

19 at it, but they're all trying to solve the template 09:33:56

20 problem. 09:33:59

21 And then they're all trying to solve the 09:33:59

22 detection problem. How do you detect small numbers 09:34:01

23 of events from thousands or perhaps tens of 09:34:05

24 thousands of individual molecules -- which is a big 09:34:12

25 step up from one molecule but still nothing like the 09:34:14

27

1 number of copies you might see on a Sanger 09:34:17
2 sequencer. 09:34:21

3 So -- so that sensitivity problem -- and 09:34:24
4 they're building technologies that allow you to 09:34:26
5 detect small numbers of photons or small numbers of 09:34:28
6 whatever it might be. 09:34:33

7 Q. And for pyrosequencing and Illumina 09:34:34
8 sequencing specifically, the error profiles between 09:34:37
9 the two are different, true? 09:34:40

10 A. Yes. In general, Illumina has a much 09:34:45
11 flatter, more robust, and cleaner error profile. It 09:34:47
12 makes a small number of substitution errors and a 09:34:53
13 very small number of insertion deletion errors. 09:34:58

14 But its length restrictions can be somewhat 09:35:03
15 shorter than other platforms. There's a tradeoff 09:35:06
16 when -- and particularly when it was first 09:35:14
17 developed. By 2010, they were up to, you know, say, 09:35:16
18 roughly, 150 base pairs -- paired and sequencing. 09:35:19

19 The Roche platform tends to do quite well 09:35:24
20 on individual bases and double bases. After two 09:35:30
21 bases in a row, it tends to fall apart and tends to 09:35:36
22 make -- have substantial trouble with -- if there 09:35:40
23 were four of one base in a row, it would have 09:35:42
24 trouble sequencing that accurately. 09:35:45

25 It would tell you the base was there. It 09:35:48

28

1 just might get the number of bases in a row 09:35:51
2 incorrect. But in general, the 454 may have 09:35:54
3 problems with -- with indels at a much higher rate 09:35:57
4 than the Illumina. So broadly speaking, the 09:36:05
5 Illumina is a much more accurate sequencer than the 09:36:08
6 454. 09:36:11

7 Q. You mentioned length restrictions for 09:36:12
8 Illumina. What -- what do you mean by "length 09:36:14
9 restrictions"? What are those? 09:36:18

10 A. Sequencing technologies are balancing many 09:36:19
11 different features, one of which is accuracy. The 09:36:26
12 other is -- which is the length of the sequences 09:36:30
13 that were generated. 09:36:32

14 Sanger sequencing, for example, not 09:36:36
15 uncommonly does a thousand base pairs of sequencing 09:36:38
16 by the most successful iterations late -- late in 09:36:41
17 the development. 09:36:45

18 454, when it first came out, could often 09:36:46
19 sequence, say, around 100 base pairs. There are 09:36:49
20 constraints on that. Because of its chemistry, 09:36:53
21 that's an average length, and it's not a known 09:36:56
22 number on any individual molecule. 09:36:59

23 Illumina, when it first came out, was, say, 09:37:03
24 25 or 36 base pairs. They rapidly improved their 09:37:07
25 chemistry to be able to sequence 150 base pairs in 09:37:11

29

1 the 2010 time frame. Again, paired-end, so almost 09:37:15
2 300 base pairs. So this is a period of rapid 09:37:18
3 development in technology between 2005 and 2010. 09:37:20

4 Q. The -- never mind. 09:37:25

5 For primers with Illumina sequencing -- you 09:37:48
6 are familiar with the primers that are used in 09:37:51
7 Illumina sequencing? 09:37:53

8 A. I couldn't give you their sequences, but 09:37:54
9 they're broadly referred to as P5 and P7 as the 09:37:58
10 canonical ones. There are other primers utilized at
11 various different times.

12 But circa 2010, I think those are the -- 09:38:05
13 the common ones that were utilized. There are a 09:38:06
14 number of, again, specific adaptations that were 09:38:10
15 implemented for Illumina sequencing that -- some of 09:38:13
16 which actually came from Roche sequencing first. 09:38:16

17 So -- so there's been a constant interplay 09:38:19
18 of primers and designs that have features that might 09:38:21
19 be well suited to one platform or another but can be 09:38:26
20 adapted quite easily between. 09:38:29

21 Q. Have you ever designed or adapted primers 09:38:31
22 for Illumina sequencing? 09:38:35

23 A. Can you be more specific? 09:38:38

24 Q. You said the adapters -- or the primers can 09:38:40
25 be adapted for different applications. My question 09:38:44

30

1 is have you ever done that? 09:38:47

2 A. So in the context of the work with Tim 09:38:49

3 Butler and later Chris Boniface, our lab did that 09:38:56

4 extensively. And there are a variety of different 09:39:00

5 tricks that one might utilize to do that. 09:39:03

6 But some of the things that one might wish 09:39:06

7 to do with Illumina might require the cooperation of 09:39:10

8 Illumina to do. So if one wanted to change the P5 09:39:13

9 and P7s, those are -- those are -- it's a commercial 09:39:16

10 product. 09:39:19

11 One cannot -- one cannot just change it 09:39:20

12 without help. And getting Illumina to do something 09:39:23

13 like that, I think, has been done, but I've never 09:39:25

14 asked. And I think it would require a minor 09:39:28

15 miracle. 09:39:33

16 Q. So the Illumina sequencer expects, I'll 09:39:36

17 say, P5 and P7 on the template DNA in order to make 09:39:39

18 the sequencing work, true? 09:39:43

19 A. From a commercial point of view, using 09:39:46

20 commercial reagents, your sequences would have to 09:39:48

21 have P5 and P7 generally, yes. 09:39:53

22 Q. Are you familiar with the concept of index 09:39:54

23 hopping? 09:39:57

24 A. Broadly speaking, yes. 09:40:01

25 Q. What is index hopping to you? 09:40:03

31

1 **A. It's related to the patents in suit. It's** 09:40:09
2 **the idea that partial extensions during multiplex** 09:40:14
3 **reactions can move between templates and change** 09:40:21
4 **the -- and create an error in what you think you've** 09:40:25
5 **indexed.** 09:40:28

6 **Q. And index hopping can occur during Illumina** 09:40:28
7 **sequencing, true?** 09:40:32

8 **A. I -- I believe index hopping could happen** 09:40:34
9 **in any multiplex PCR reaction for any sequencer that** 09:40:37
10 **does indexes and multiplex.** 09:40:43

11 **Q. Including Illumina sequencers, right?** 09:40:45

12 **A. Absolutely. Yes.** 09:40:47

13 **Q. And you mentioned that '852 and '200** 09:40:48
14 **patents -- they describe examples of index hopping** 09:40:52
15 **happening on flow cell sequencers like Illumina's,** 09:40:55
16 **true?** 09:40:58

17 **A. I'd be a little careful about that. Index** 09:40:59
18 **hopping as a concept, I think, might be broader than** 09:41:02
19 **what's in '852 and '200, and there might -- the** 09:41:05
20 **colloquial use of index hopping may have specific** 09:41:10
21 **descriptors in the literature that may not be** 09:41:14
22 **relevant at '852 and '200. I think it might be a** 09:41:18
23 **broader concept.** 09:41:22

24 **Q. Okay. So let me -- the '852 and '200** 09:41:23
25 **patent describe examples of index hopping that can** 09:41:25

32

1 happen on Illumina's flow cell, but there might be 09:41:29

2 other examples too. Is that what you are saying? 09:41:32

3 MR. RAICH: Object to the form of the 09:41:34

4 question. 09:41:38

5 THE WITNESS: I think that broadly 09:41:38

6 speaking, the idea that indexes are misassigned 09:41:39

7 during multiplex PCR can happen on Illumina flow 09:41:42

8 cell. I think it could happen on a Roche, a bead 09:41:45

9 array, bead emulsion, or on potentially -- and 09:41:51

10 during the emulsion PCR. 09:41:54

11 But, yes, I think that something consistent 09:41:56

12 with index hopping as it's described colloquially in 09:41:58

13 the literature -- I have not defined it, to my best 09:42:02

14 of my knowledge, in the specifications. 09:42:04

15 And I don't believe it's in the -- in my 09:42:06

16 declaration, and I don't believe it's in the 09:42:08

17 specifications. So I prefer not to use the term 09:42:09

18 because it has a lot of extra connotations, 09:42:11

19 potentially. 09:42:13

20 MR. MATTY: 09:42:13

21 Q. Well, let's look at the patent. Let's look 09:42:17

22 at Figure 2 in the patent. 09:42:22

23 A. Yeah.

24 Q. Figure 2 in the Molecular Loop patents 09:42:35

25 shows one example of index hopping happening on the 09:42:39

1 surface of a flow cell, true? 09:42:39

2 A. Again, I don't believe it refers to it as 09:42:44

3 "index hopping." I'm not sure that phrase was 09:42:46

4 common in the literature at the time of the patent. 09:42:49

5 But what's -- what's described in the specification 09:42:52

6 is not inconsistent with my understanding of index 09:42:57

7 hopping as a term. 09:43:01

8 Q. Okay. So I guess taking the double 09:43:03

9 negative out, the mechanism that is shown in Figure 09:43:05

10 2 in the Molecular Loop -- Molecular Loop patent is 09:43:14

11 consistent with index -- index hopping as you 09:43:15

12 understand it? 09:43:18

13 A. I have not thought about all of the uses of 09:43:21

14 the term "index hopping," so I will reserve my right 09:43:23

15 to fully answer that question. 09:43:27

16 But in that A1 and A2 are indexes and that 09:43:30

17 the ultimate product at the bottom of Step 4 has 09:43:36

18 changed the initial indexes -- again, the 09:43:43

19 specification -- I don't believe he's used indexes, 09:43:48

20 so I don't quite understand why we're using these 09:43:52

21 terms. But it's not -- it would be consistent with 09:43:56

22 my understanding. 09:44:05

23 (Reporter clarification.) 09:44:13

24 Q. Index hopping can cause errors in 09:44:13

25 sequencing on Illumina machines, true? 09:44:17

34

1 **A. I -- I don't think that -- I mean, I don't** 09:44:24
2 **understand how that's relevant to the specification.** 09:44:29

3 **Q. Okay. I'm just asking a yes-or-no** 09:44:30
4 **question. Or if you don't know, that's fine too.** 09:44:35
5 **So let me try again: Index hopping during** 09:44:41
6 **sequencing can cause errors when using Illumina** 09:44:45
7 **sequencer machines, true?** 09:44:49

8 **A. Any situation in which the indexes or** 09:44:55
9 **barcode -- you know, identifier barcodes have** 09:45:03
10 **changed, including by mispriming of partial** 09:45:08
11 **molecules, will create molecules later on that may** 09:45:15
12 **create errors downstream. There are -- you know,** 09:45:21
13 **may or may -- yeah, it may.** 09:45:27

14 **Q. And when you say "mispriming," that's** 09:45:29
15 **something that happens earlier on. That's not** 09:45:32
16 **something that happens during amplification or** 09:45:36
17 **sequencing, right?** 09:45:38

18 **A. Mispriming can happen anywhere in a** 09:45:44
19 **sequencing workflow in which a polymerase extension** 09:45:47
20 **occurs. So that can happen during PCR. It can** 09:45:52
21 **happen at any step involving a DNA polymerase.** 09:45:55

22 **Q. Okay. And during a sequencing reaction** 09:46:00
23 **with sample indexes, if indexing happens in an** 09:46:02
24 **Illumina machine, that can lead to errors, true?** 09:46:08

25 **A. I don't think your -- I think you misstated** 09:46:11

35

1 **the question. You said "if indexing happens."** 09:46:13

2 Q. Sorry. If sample indexes are being used 09:46:16

3 and index hopping occurs during sequencing on the 09:46:19

4 Illumina machine, that can lead to errors -- that 09:46:24

5 index hopping can lead to errors, true? 09:46:27

6 A. It really depends on what you mean by 09:46:31

7 "errors." 09:46:37

8 Q. Are you aware of any errors that can be 09:46:37

9 caused by index hopping on an Illumina machine? 09:46:39

10 A. Well, when one talks about an error, one 09:46:43

11 normally talks about at the end of this assessment, 09:46:48

12 is there some mistake? 09:46:54

13 And so if in some workflow one required a 09:46:59

14 certain number of events to have happened and an 09:47:05

15 event is very rare, then a sequencing workflow may 09:47:09

16 be robust against such an event and not detect an 09:47:14

17 error because it is -- you know, there's some 09:47:18

18 process in place. 09:47:21

19 So as an example, it is very common in 09:47:24

20 sequencing workflows to require three unique 09:47:30

21 examples of something. And you wouldn't make a 09:47:33

22 statement that something had or had not occurred or 09:47:38

23 something -- that had occurred unless you had three 09:47:41

24 unique examples of it. 09:47:44

25 What the cause of those two unique examples 09:47:46

36

1 that you ignored is -- is hard to -- you know, you 09:47:50
2 might not even assess. So there would be no error 09:47:54
3 detected in that case because one had filtered it 09:47:59
4 out. So the phrasing you are using is seemingly all 09:48:02
5 the way to the end, when I don't know that that's 09:48:06
6 necessarily the case. 09:48:09

7 Q. Let me give a specific example, then. 09:48:09
8 Index hopping during Illumina sequencing can lead to 09:48:13
9 sample misassignment, true? 09:48:17

10 A. I think a better way to ask the question 09:48:24
11 might be index hopping during multiplex sequencing 09:48:28
12 broadly can lead to a single read being misassigned. 09:48:35

13 Q. So that's helpful. Index hopping on 09:48:41
14 Illumina machines which are doing the multiplex 09:48:46
15 sequencing can lead to individual samples -- 09:48:49
16 individual reads being misassigned to the wrong 09:48:54
17 sample, true? 09:48:56

18 A. And, again, I would -- I would say that 09:48:58
19 that is a general principle in pretty much all 09:49:00
20 multiplex sequencers that use indexes. 09:49:05

21 Q. And it's true for Illumina machines, right? 09:49:08

22 A. Yes. 09:49:11

23 Q. Do you know when Illumina first became 09:49:11
24 aware of index hopping potentially happening on its 09:49:16
25 multiplex machines? 09:49:20

37

1 A. No.

2 Q. Did you try to determine in your work on 09:49:22

```
3  this case when Illumina first acknowledged index 09:49:25
```

4 hopping happening on its machines? 09:49:30

A.

6 Q. Did you try to determine in your work on 09:49:32

7 this case whether Illumina was aware of index 09:49:34

8 hopping on its machines at the time of the invention 09:49:37

9 of the '200 and '852 patents? 09:49:40

A. No.

11 Q. In your work on this case, did you ask 09:49:43

12 anyone at Illumina whether they had any evidence of 09:49:45

13 Illumina's awareness of index hopping on its 09:49:48

14 machines at the time of the invention of the '200 09:49:52

15 and '852 patents? 09:49:55

16 MR. RAICH: I'll object to scope. 09:49:59

17 THE WITNESS: Again, I think you are using 09:50:00

18 "index hopping" in a very specific way that's very 09:50:03

19 broad, and I'm not sure -- we haven't defined it in 09:50:05

20 this case. So I -- the answer is no, but I reserve 09:50:09

21 the right to understand what you actually mean by 09:50:12

```
22 "index hopping," because it has -- we haven't 09:50:16
```

```
23     defined it.                                09:50:19
```

24 MR. MATTY: 09:50:19

25 0. At the time of the invention of the '200 09:50:20

38

1 and '852 patents, do you know what types of sample 09:50:22
2 indexes Illumina was instructing its customers to 09:50:27
3 use with their sequencers? 09:50:30

4 **A. Off the top of my head, no.** 09:50:32

5 Q. In your work in this case, did you try to 09:50:32
6 determine that? 09:50:34

7 **A. No.** 09:50:35

8 Q. In your declaration, obviously, you discuss 09:50:38
9 a number of pieces of prior art, right? 09:50:41

10 **A. Yes.** 09:50:44

11 Q. Did you go out and search for prior art on 09:50:44
12 your own in this case, or was the prior art provided 09:50:48
13 to you? 09:50:51

14 **A. I think I may have done some searching, but** 09:50:51
15 **I don't recall.** 09:50:54

16 Q. Do you remember how long you spent 09:50:54
17 searching? 09:50:56

18 **A. No.** 09:50:56

19 Q. Do you have an approximation? 09:50:56

20 **A. No.** 09:50:58

21 Q. You have no idea how long you spent 09:50:59
22 searching for prior art in this case? 09:51:02

23 **A. Less than 20 hours, certainly.** 09:51:04

24 Q. Okay. Now, for some of the specific 09:51:06
25 references throughout your appearance -- let me 09:51:12

39

1 start that over. 09:51:14

2 Throughout your opinions, you refer to the 09:51:15

3 Parameswaran reference. You are familiar with that, 09:51:19

4 right? 09:51:22

5 A. Yes. 09:51:22

6 Q. How did Parameswaran come to your attention 09:51:22

7 in this matter? 09:51:25

8 A. I don't recall. I believe counsel brought 09:51:26

9 it up, but I won't -- I'm not certain. 09:51:29

10 Q. Okay. Before your work in this case, were 09:51:31

11 you aware of the Parameswaran reference? 09:51:34

12 A. Possibly. 09:51:37

13 Q. Do you have any specific instance or memory 09:51:38

14 of you being aware of Parameswaran before this case? 09:51:42

15 A. It does not have an indelible mark on my 09:51:47

16 memory, but it is from a very high-profile lab. And 09:51:51

17 it is likely that it showed up in my inbox and was 09:51:56

18 discussed in some context, particularly with the 09:52:00

19 work with Tim Butler. 09:52:03

20 But whether or not I could remember the day 09:52:04

21 and time I first saw it -- there are certain papers 09:52:07

22 where I can tell you that, but this is not one of 09:52:10

23 them. 09:52:19

24 Q. All right. You also referred to the Gloor 09:52:19

25 reference. You are familiar with that, right? 09:52:21

40

A. Correct.

2 Q. How did the Gloor reference come to your 09:52:24

3 attention? Did you discover that, or did counsel 09:52:26

```
4 provide it? 09:52:28
```

5 A. I believe that counsel provided it. 09:52:29

6 Q. Before your work in this case, were you 09:52:31

7 aware of the Gloor reference? 09:52:34

8 A. Probably not, though I'm not certain. 09:52:37

9 Q. You also referred to a reference called 09:52:39

10 Bentley. You are familiar with that, right? 09:52:43

11 A. Actually, I believe I was aware of Gloor 09:52:44

12 because I did have a postdoc working in my lab on

13 vaginal microbiome work. And I believe she probably 09:52:49

14 would have discussed it with me because they were 09:52:50

15 **deeply related fields.** 09:52:52

16 But -- but I was not intimately familiar 09:52:53

```
17 with Gloor -- the publication, rather, than the 09:52:56
```

18 archive reference. Bentley, I was aware of, 09:52:58

19 although I -- whether or not I read it in detail, I 09:53:02

20 can't be certain. 09:53:05

21 Q. Okay. And last, there's the Binladen 09:53:06

22 reference. You are familiar with that, right? 09:53:10

23 A. I have read Binladen, yes. 09:53:13

24 Q. And how did Binladen come to your attention 09:53:14

25 in this matter? Is that one you discovered, or did 09:53:17

41

1 counsel provide it? 09:53:20

2 **A. I believe counsel provided it.** 09:53:21

3 Q. Okay. Throughout your opinions, you have a 09:53:22

4 number of different invalidity grounds, either 09:53:25

5 anticipation or obviousness, based on the prior art 09:53:28

6 or combinations of the art, true? 09:53:31

7 **A. Correct.** 09:53:33

8 Q. And in all of your grounds, your opinions 09:53:34

9 are that the prior art taught all limitations of the 09:53:37

10 challenged claims, true? 09:53:40

11 **A. In my opinion, all of the claims of the** 09:53:43

12 **'852 and '200 patents are either obvious or** 09:53:46

13 **anticipated by prior art.** 09:53:50

14 Q. Right. And within those opinions, whether 09:53:51

15 it's one reference for anticipation or multiple 09:53:53

16 references for obviousness, your opinions are that 09:53:59

17 the prior art taught all limitations of the claims, 09:54:01

18 true? 09:54:04

19 **A. Correct.** 09:54:04

20 Q. And you are familiar with the concept of 09:54:05

21 inherency in patent law? 09:54:08

22 **A. Yes.** 09:54:09

23 Q. You have not offered any opinions in this 09:54:10

24 case that rely on inherency for any claim 09:54:13

25 limitations, true? 09:54:16

42

1 **A. I'm not sure that's quite correct. I don't** 09:54:17
2 **know if I labeled them as inherent, but some things** 09:54:20
3 **that I've discussed have -- have sort of a** 09:54:23
4 **requirement that if something is there, it would** 09:54:28
5 **have been detected.** 09:54:30

6 **Q. Do you have an understanding for what the** 09:54:31
7 **legal requirements for inherency are?** 09:54:34

8 **A. I would have to check with counsel, and I** 09:54:37
9 **don't believe I have a discussion in the document on** 09:54:41
10 **it.** 09:54:43

11 **Q. And when you were doing your analysis under** 09:54:47
12 **the proper legal standards in this case, you relied** 09:54:49
13 **on the legal standards as they're laid out in the** 09:54:51
14 **sections of your declaration, true?** 09:54:54

15 **A. That is correct.** 09:54:56

16 **MR. RAICH: Counsel, can I have a copy of** 09:54:59
17 **the declaration if you are going to be using it?** 09:55:01

18 **MR. MATTY: Sure. Why don't we take a** 09:55:02
19 **break.** 09:55:04

20 **THE VIDEOGRAPHER: Going off the record,** 09:55:04
21 **the time is 9:54 a.m.** 09:55:05

22 **(Break taken.)** 10:07:18

23 **THE VIDEOGRAPHER: Okay. We're back on the** 10:07:21
24 **record. The time is 10:06 a.m.** 10:07:22

25 **MR. MATTY:** 10:07:26

43

1 Q. We're here in April 2025 for your 10:07:26
2 deposition. How long have you been working on this 10:07:32
3 case? 10:07:35

4 A. Something like a year. I don't recall 10:07:35
5 exactly when I was first contacted. 10:07:37

6 Q. Who first contacted you about this case? 10:07:39

7 A. I actually don't remember. 10:07:45

8 Q. Was it someone from Illumina? 10:07:47

9 A. I don't remember. 10:07:50

10 Q. Was it a lawyer? 10:07:51

11 A. I don't remember. 10:07:53

12 Q. Could it have been someone other than an 10:07:53
13 Illumina employee or a lawyer from Finnegan? 10:08:08

14 A. I wasn't contracted by a finder, if that's 10:08:12
15 what you are asking. So -- because I'm not billing 10:08:16
16 through some intermediary. I'm billing directly. 10:08:22

17 Q. By a "finder," you mean, like, expert 10:08:26
18 services -- 10:08:29

19 A. Correct.

20 Q. -- that will connect you with lawyers? 10:08:29

21 A. Correct. 10:08:30

22 Q. Okay. But you don't remember who reached 10:08:31
23 out to you about this case or who they worked for or 10:08:34
24 where they were from? 10:08:39

25 A. I assume it was either someone from 10:08:40

44

1 **Illumina or from Finnegan, but I'm not certain.** 10:08:43

2 Q. Okay. And that was roughly about a year 10:08:46

3 ago? 10:08:49

4 A. Sometime in the last year. Again, these 10:08:49

5 are -- these cases come and go, and the times -- 10:08:51

6 there's gaps, and you don't really remember. 10:08:54

7 Q. Before you were engaged by Illumina in this 10:08:56

8 matter, were you aware of Molecular Loop? 10:08:59

9 A. Yes. 10:09:02

10 Q. How were you aware of Molecular Loop before 10:09:02

11 this matter? 10:09:06

12 A. I believe they sell products that even some 10:09:07

13 of my team members have used. That's my 10:09:11

14 recollection. I could be wrong. 10:09:13

15 Q. And are you thinking of any particular 10:09:15

16 products? 10:09:22

17 A. My recollection -- and, again, my -- in 10:09:23

18 this case, a graduate student was performing some 10:09:27

19 work. And maybe it wasn't Molecular Loop, but she 10:09:31

20 was interested in sort of keeping reads together. 10:09:36

21 That's my recollection. But, again, I've 10:09:39

22 certainly heard the name in the field. I -- as a 10:09:42

23 PI, I don't necessarily investigate everything 10:09:46

24 myself. 10:09:49

25 Q. Before you were engaged by Illumina in this 10:09:49

45

1 matter, were you aware of the '200 and the '852 10:09:51
2 patents? 10:09:58

3 **A. Very unlikely.** 10:09:58

4 Q. Before you were engaged by Illumina in this 10:09:59
5 matter, were you aware of any of the -- any of the 10:10:02
6 inventors on the Molecular Loop patents? 10:10:03

7 **A. I have known George Church for most of my 10:10:12
8 career.** 10:10:15

9 Q. How about any of the other two inventors? 10:10:16

10 **A. The other two named inventors is Gregory 10:10:19
11 Porreca and Mark Umbarger. I am not -- I don't 10:10:24
12 believe I'm familiar with.** 10:10:27

13 Q. What generally is your relationship with 10:10:28
14 George Church? 10:10:31

15 **A. I'm not sure he would know who I am, but 10:10:33
16 we've -- I've interacted with a postdoc in his 10:10:36
17 group -- I believe his name was John Ock -- circa 10:10:39
18 late '90s. And we have had some interactions -- 10:10:45
19 maybe early 2000s -- for several years. So John, I 10:10:49
20 believe, was a postdoc for George at the time.** 10:10:51

21 Q. And are you aware of Dr. Church's lab at 10:10:53
22 Harvard generally from your work in the field? 10:10:57

23 **A. Absolutely.** 10:10:59

24 Q. Dr. Church's lab at Harvard is a fairly 10:11:02
25 well-known research lab in the genetics industry. 10:11:06

46

1 Would you agree? 10:11:11

2 A. Dr. Church is very well known in the 10:11:11

3 genetics field, yes. 10:11:20

4 Q. Stepping back a bit, this is not the first 10:11:23

5 time you've offered expert opinions as part of a 10:11:25

6 lawsuit, true? 10:11:29

7 A. That is correct. 10:11:30

8 Q. Including patent infringement cases, true? 10:11:31

9 A. Correct. 10:11:36

10 Q. And, also, you have given a number of 10:11:36

11 opinions in these IPR validity proceedings in the 10:11:38

12 past, true? 10:11:41

13 A. Correct. 10:11:42

14 Q. Do you know how many? 10:11:42

15 A. I believe the answer is 8, but I -- it's 10:11:43

16 around that number. Somewhere between -- more than 10:11:47

17 5 and less than 20. I believe the answer is 8 to 10:11:49

18 10. 10:11:52

19 Q. Okay. And you have never supported the 10:11:52

20 patent owner in an invalidity proceeding, true? 10:11:54

21 A. I believe that is correct. 10:11:57

22 Q. You stand by the expert opinions that you 10:11:59

23 have given in your past cases? 10:12:01

24 A. Yes. 10:12:03

25 Q. Are you aware of any expert opinions you 10:12:03

1 have given in the past that were wrong? 10:12:06

2 **A. No.** 10:12:08

3 MR. RAICH: Objection to form. 10:12:09

4 MR. MATTY: 10:12:10

5 Q. And have you ever withdrawn any expert 10:12:10

6 opinions that you have given in the past? 10:12:12

7 **A. Like, formally withdrawn? No, I don't** 10:12:15

8 **believe so.** 10:12:23

9 Q. Going back to when you first started 10:12:23

10 working on this case, have you ever worked with the 10:12:25

11 Finnegan law firm before this matter? 10:12:28

12 **A. I don't believe so.** 10:12:29

13 Q. Have you ever worked for Illumina before 10:12:30

14 this matter? 10:12:32

15 **A. I don't know how to answer that.** 10:12:39

16 MR. RAICH: Are there some sort of 10:12:40

17 third-party confidentiality or -- some sort of 10:12:43

18 confidentiality obligations? I'm not -- 10:12:46

19 THE WITNESS: I have had discussions with 10:12:49

20 Illumina on various issues over the past decade. 10:12:50

21 MR. MATTY: 10:12:57

22 Q. Have you ever worked for Illumina as an 10:12:57

23 expert in a patent case before, either in district 10:12:59

24 court or at the PTAB? 10:13:02

25 **A. I would have to check with Illumina on that** 10:13:08

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1 **one.** 10:13:10

2 Q. I guess maybe just yes or no for now -- I 10:13:11

3 don't know that I need the details if there's 10:13:16

4 confidentiality concerns. Have you ever worked for 10:13:19

5 Illumina before as an expert either in a patent 10:13:21

6 infringement case in district court or in IPR at the 10:13:25

7 PTAB? 10:13:28

8 **A. Can I sidebar with Illumina counsel?** 10:13:31

9 Q. It's -- if you are not sure, you can say 10:13:33

10 you are not sure. If you have or haven't, just -- 10:13:35

11 **A. I don't know what the rules are on** 10:13:38

12 **disclosure.** 10:13:40

13 Q. Okay. So you may have; you are just not 10:13:40

14 sure -- 10:13:42

15 **A. I have consulted with Illumina on** 10:13:43

16 **infringement cases.** 10:13:46

17 Q. Okay.

18 **A. I don't know if they were district. I** 10:13:47

19 **don't know -- you know, so -- and I don't --** 10:13:49

20 Q. Okay.

21 **A. I'd have to go back and check with them.** 10:13:54

22 Q. And I won't ask you which cases. Do you 10:13:57

23 know roughly how many cases you have consulted with 10:14:00

24 Illumina on in the past? 10:14:02

25 **A. It's either one or two previous ones.** 10:14:03

49

1 Q. Okay. After you were first contacted about 10:14:06
2 this case, how long did it take you to decide that 10:14:18
3 you would work for Illumina in this matter? 10:14:21

4 A. I don't recall. 10:14:24

5 Q. Do you know roughly? 10:14:25

6 A. I'd have to -- I'd have to check the email 10:14:31
7 correspondence logs. 10:14:33

8 Q. Okay. Did you review any documents before 10:14:34
9 deciding you would sign up for this case? 10:14:39

10 A. Counsel, am I allowed to answer that? 10:14:45

11 MR. RAICH: You can answer, "Yes," "No," "I 10:14:47
12 don't know," "I don't recall." 10:14:50

13 THE WITNESS: I believe so. 10:14:50

14 MR. MATTY: 10:14:51

15 Q. Okay. Did you review the Molecular Loop 10:14:52
16 patents that are at issue in this case before 10:14:58
17 deciding that you would sign up? 10:15:00

18 A. Counsel? 10:15:02

19 MR. RAICH: You can answer, "Yes," "No," "I 10:15:03
20 don't know," "I don't recall." 10:15:05

21 THE WITNESS: My recollection is that I 10:15:06
22 did, but I'm not 100 percent certain. 10:15:07

23 MR. MATTY: 10:15:09

24 Q. Okay. Did you review the prior art that's 10:15:09
25 being asserted in this case before deciding that you 10:15:11

50

1 would sign up? 10:15:14

2 **A. I don't recall.** 10:15:15

3 Q. Since you were contacted about a year ago, 10:15:15

4 roughly, how much time would you estimate you have 10:15:29

5 spent working on this matter? 10:15:32

6 **A. More than 30 hours but less than 100 hours.** 10:15:36

7 Q. Now, as part of your work, you have 10:15:39

8 reviewed quite a few documents, true? 10:15:50

9 **A. Correct.** 10:15:52

10 Q. Do you have an estimate for the amount of 10:15:53

11 time you spent reviewing documents in your work on 10:15:55

12 this case? 10:16:00

13 **A. No. I'd have to go to the billing records.** 10:16:00

14 **I have it in the billing records, but I don't know** 10:16:02

15 **off the top of my head.** 10:16:06

16 Q. Okay. How much time did you spend on 10:16:06

17 preparing the declarations that you have signed in 10:16:08

18 these two cases? 10:16:10

19 **A. More than 20 hours but less than 100 hours.** 10:16:13

20 **I'm not certain. So maybe less than 80 hours.** 10:16:18

21 Q. Okay. And the documents that you reviewed, 10:16:21

22 a number of them, maybe all of them, are cited in 10:16:24

23 your declarations, true? 10:16:28

24 **A. Sorry. Can you repeat the question.** 10:16:29

25 Q. Yeah. The documents that you have reviewed 10:16:30

1 in this case, a number of them are cited in your 10:16:32
2 declarations, true? 10:16:37

3 **A. Yes.** 10:16:37

4 Q. Is it fair to assume that if you cited a 10:16:37
5 document or paper in your report, you thought that 10:16:42
6 that was a trustworthy source? 10:16:44

7 **A. "Trustworthy" has a lot of connotations to 10:16:48
8 it, but -- but I thought it was a relevant document 10:16:51
9 that -- that added relevant information to the case. 10:16:55**

10 Q. Okay. Are there any documents that you 10:16:58
11 relied on in the citations in your report that you 10:17:02
12 would not consider to be trustworthy sources? 10:17:05

13 **A. No.** 10:17:08

14 Q. In your declaration -- I believe it's 10:17:08
15 paragraph 2 -- you state that you are being 10:17:13
16 compensated your standard hourly rate of \$500 an 10:17:17
17 hour, true? 10:17:21

18 **A. Yes. I also receive a differential for 10:17:22
19 travel and a differential for deposition time. 10:17:26**

20 Q. What do you mean by a "differential"? 10:17:28

21 **A. Half time for travel and one and a half 10:17:30
22 times during these proceedings. 10:17:35**

23 Q. Got it. So for travel, you charge 250 an 10:17:37
24 hour. For depositions, you charge 750 an hour. For 10:17:40
25 all other work in this case, you charge 500 an hour. 10:17:45

52

1 Fair? 10:17:48

2 A. Correct. 10:17:48

3 Q. And this says that that is your standard 10:17:49

4 hourly consulting rate. How long has that been your 10:17:53

5 standard rate? 10:17:57

6 A. There were a couple cases I just completed 10:17:58

7 that I had a carryover rate that was a little lower, 10:18:01

8 like 400. There's a -- there's another case that I 10:18:04

9 just -- that's moving forward at 750. So it's -- it 10:18:09

10 depends on what my current salary is and my current 10:18:14

11 position, in some respect. 10:18:18

12 Q. The two declarations that you signed in 10:18:19

13 this case span a few hundred pages, true? 10:18:30

14 A. Yes, I believe that's correct. 10:18:33

15 Q. Did you draft all of those few hundred 10:18:34

16 pages in your reports? 10:18:38

17 A. I drafted some sections, and counsel 10:18:39

18 drafted sections. I read them in their entirety, 10:18:42

19 and I agree with every word written. 10:18:46

20 Q. What sections of your declarations did you 10:18:47

21 draft in the first instance? 10:18:50

22 A. I don't recall. 10:18:52

23 Q. What sections of your declaration did the 10:18:52

24 lawyers draft in the first instance? 10:18:55

25 A. The same: I don't recall exactly which 10:18:58

53

1 sections were drafted by me or by counsel. 10:19:01

2 Q. Did you personally decide which arguments 10:19:03

3 to include in your expert declarations? 10:19:11

4 A. I made suggestions of arguments. Counsel 10:19:19

5 made suggestions of arguments. I agreed with all 10:19:21

6 arguments made in this document, and I stand by the 10:19:27

```
7  declaration as it's -- as it's written.                                10:19:30
```

8 Q. Are there any arguments that were suggested 10:19:31

9 to you that you decided not to include in the 10:19:33

10 declaration? And I'm just looking for a yes or no. 10:19:35

A. Counsel?

12 MR. RAICH: I think I'm going to instruct 10:19:50

13 the witness to not answer that question on privilege 10:19:53

14 grounds. 10:19:56

15 MR. MATTY: 10:19:57

16 Q. Are you going to follow your counsel's 10:20:01

```
17      instruction?                                     10:20:03
```

18 A. Yes.

10:20:04

19 Q. Are there any arguments that you suggested 10:20:04

20 to the lawyers that they told you not to include in 10:20:18

```
21    your declaration?                                10:20:20
```

22 MR. RAICH: Same instruction. 10:20:23

23 THE WITNESS: I decline to answer on advice 10:20:25

24 of counsel. 10:20:28

25 ///

1 MR. MATTY: 10:20:28

2 Q. All right. And just to make sure I got it
3 right, you said you may have drafted some of the 10:21:18
4 sections of your declarations yourself, but you 10:21:19
5 don't recall any such sections, true? 10:21:26

6 A. I did draft sections of the document 10:21:29
7 myself. I don't recall which ones they were. 10:21:32

8 Q. And sitting here today, you can't identify 10:21:35
9 any sections of your declaration that you drafted in 10:21:37
10 the first instance, true? 10:21:39

11 A. True. 10:21:41

12 Q. Have you -- in your work on these cases, 10:21:47
13 have you spoken with any other experts who are 10:21:50
14 working with Illumina? 10:21:52

15 A. In regard to the '852 and '200 series 10:21:53
16 patents? 10:21:58

17 Q. In relation to these IPRs. 10:21:58

18 A. The '852 and '200 IPRs -- the IPRs in these 10:22:01
19 cases? 10:22:07

20 Q. That's correct. 10:22:07

21 A. No. 10:22:08

22 Q. Let me just make sure I got it right. Just 10:22:09
23 generally, in your work with Illumina, have you 10:22:20
24 spoken with any of the other experts that they have 10:22:22
25 retained? 10:22:26

1 **A. To the best of my knowledge, I have not** 10:22:27
2 **spoken with other experts that Illumina has** 10:22:29
3 **retained, although the field is relatively small.** 10:22:32
4 **And I routinely talk to lots of people about lots of** 10:22:36
5 **things.** 10:22:39

6 **So I have collaborators who I believe are** 10:22:40
7 **also experts for Illumina on other issues, either --** 10:22:43
8 **and so I talk to them but not about issues in this** 10:22:47
9 **case.** 10:22:51

10 **Q. Okay. Let's go to your declaration on the** 10:22:51
11 **'852 patent, which is the 964 IPR.** 10:22:59

12 **A. Yes.** 10:23:03

13 **Q. Do you have that in front of you?** 10:23:03

14 **A. I do.** 10:23:05

15 **Q. Let's look at paragraph 166 of that** 10:23:05
16 **declaration. If you can let me know when you are** 10:23:09
17 **there.** 10:23:10

18 **A. Yes.** 10:23:19

19 **Q. About four lines down -- well, let me just** 10:23:19
20 **ask you to read the first sentence of that paragraph** 10:23:59
21 **to yourself.** 10:24:01

22 **A. Yes.** 10:24:05

23 **Q. So you give the opinion that performing the** 10:24:05
24 **UDI method in Parameswaran on an Illumina sequencer** 10:24:08
25 **would require exchanging adapter sequences and what** 10:24:13

56

1 you call "other minor modifications," true? 10:24:18

2 A. Yes. 10:24:21

3 Q. What other minor modifications are you 10:24:21
4 referring to there? 10:24:25

5 A. In 168, I discuss some of them, describing 10:25:07
6 the work from Meyer. "Exchanging adapter sequences, 10:25:11
7 removing and shortening several reaction steps, 10:25:16
8 introducing an amplification scheme," as described 10:25:19
9 in Meyer, might be necessary. 10:25:22

10 Depending on, you know -- a POSA would 10:25:29
11 routinely -- practitioners of the art at the time 10:25:32
12 would routinely examine one molecular biology method 10:25:36
13 and import it to some other similar system. So this 10:25:43
14 is not a particularly complicated process. The 10:25:46
15 exact steps one might take might include those 10:25:48
16 described in 168 or others. 10:25:51

17 Q. Let me ask specifically: In your 10:25:53
18 combination of Parameswaran and Gloor, you talk 10:25:54
19 about taking the unique dual indexing method from 10:26:01
20 Parameswaran and running that on Illumina sequencer 10:26:06
21 like the one in Gloor, true? 10:26:10

22 A. Yes. 10:26:12

23 Q. What changes would the person of ordinary 10:26:12
24 skill have to make to Parameswaran's method to make 10:26:16
25 it work on Gloor's sequencer? 10:26:18

1 MR. RAICH: I'll object to form. 10:26:30

2 THE WITNESS: I think it would be 10:26:38

3 instructive to look at Maughan, which I believe is 10:26:39

4 Example 1038. And the process for doing so is 10:26:47

5 described in Maughan. 10:26:51

6 They explicitly utilize the same structure 10:26:53

7 on 454 and Illumina in a single reference using 10:26:57

8 basically identical processes. So the -- one could 10:27:02

9 look at a resource like Maughan to determine how to 10:27:06

10 do it. 10:27:09

11 MR. MATTY: 10:27:09

12 Q. So is it your opinion that one would have 10:27:09

13 to take Parameswaran and Gloor and then look to 10:27:12

14 Maughan to follow sort of the process for adapting 10:27:15

15 Parameswaran to run on Gloor? 10:27:19

16 A. No. 10:27:21

17 MR. RAICH: Objection to form. 10:27:21

18 THE WITNESS: I don't believe that's 10:27:25

19 correct. 10:27:25

20 MR. MATTY: 10:27:25

21 Q. Okay. One difference between Parameswaran 10:27:29

22 and Gloor is the number of rounds of PCR that are 10:27:30

23 used in their protocols. Are you aware of that? 10:27:35

24 A. It would be surprising if the PCR -- number 10:27:39

25 around PCR was identical. 10:27:42

58

1 Q. Well, in Parameswaran, it performs two 10:27:47
2 separate rounds of PCR, true? 10:27:53

3 A. **It's not uncommon.** 10:27:54

4 Q. And in Gloor, they only perform one round 10:27:55
5 of PCR, true? 10:27:59

6 A. **Not uncommon.** 10:28:00

7 Q. Okay. In your combination of Parameswaran 10:28:02
8 and Gloor, would there be one round of PCR or two? 10:28:03

9 A. **I suspect it could be done either way.** 10:28:08

10 Q. Okay. Have you formed any opinion on 10:28:11
11 whether the person of ordinary skill combining those 10:28:18
12 two references would use one round of PCR or two in 10:28:21
13 the combination? 10:28:28

14 A. **Again, I think they could probably do it 10:28:29**
15 **either way or with three rounds of PCR.** 10:28:30

16 Q. In your combination that you are relying on 10:28:33
17 for your invalidity opinions in this case, did you 10:28:35
18 consider whether there's one round of PCR or two or, 10:28:38
19 as you say now, three? 10:28:41

20 A. **From an obviousness perspective, a POSA 10:28:42**
21 **would look at what was required and choose the 10:28:45**
22 **appropriate amount of PCR to do and the exact 10:28:48**
23 **conditions under which to do it, all of which is 10:28:53**
24 **standard art circa 2007 to 2010.** 10:28:56

25 Q. And sitting here today, for the combination 10:29:00

1 of Parameswaran and Gloor, do you have an opinion on 10:29:03
2 whether the person of ordinary skill would choose 10:29:05
3 one round of PCR or two? 10:29:11

4 **A. It would be my firm position that a POSA 10:29:14**
5 **would examine the art and decide on what made the 10:29:18**
6 **most sense for their purposes, given the 10:29:22**
7 **configuration of their assays. 10:29:25**

8 **The -- the scope of Parameswaran and Gloor 10:29:28**
9 **are specific examples in the art, and a POSA would 10:29:32**
10 **take that teaching and utilize it to solve the 10:29:39**
11 **problem that they were trying to solve. 10:29:45**

12 **Q. Okay. And in your combination here where 10:29:47**
13 **you're taking Parameswaran's experiment and running 10:29:52**
14 **it on the Illumina machine in Gloor, do you have an 10:29:53**
15 **opinion on whether the person of ordinary skill 10:29:57**
16 **would choose one round of PCR or two for that 10:29:58**
17 **application? 10:30:02**

18 **A. I think they would choose whichever they 10:30:03**
19 **thought made the most sense. 10:30:07**

20 **Q. Okay. And do you have an opinion on which 10:30:08**
21 **one makes the most sense? 10:30:09**

22 **A. I think they're probably equivalent, but I 10:30:10**
23 **reserve the right to look at a specific 10:30:14**
24 **counterfactual example. 10:30:16**

25 **Q. Okay. Now, Parameswaran and Gloor also 10:30:18**

60

1 have different barcodes in their approaches, right? 10:30:22

2 A. Yes. 10:30:26

3 Q. And I take it in your combination, the 10:30:26

4 combination uses the barcodes from Parameswaran, 10:30:31

5 true? 10:30:34

6 A. I -- 10:30:35

7 MR. RAICH: Objection to form. 10:30:36

8 THE WITNESS: I believe that a POSA would 10:30:36

9 choose the barcodes that made sense given their 10:30:39

10 situation. The -- there's a lengthy discussion in 10:30:44

11 both Gloor and Parameswaran that would instruct POSA 10:30:49

12 to utilize barcodes and the relative strengths and 10:30:54

13 weaknesses of specific barcode configurations. 10:30:58

14 But in my opinion, a POSA would read those 10:31:01

15 and decide on barcodes that were informative and 10:31:06

16 useful in their configuration. Barcodes in 10:31:09

17 Parameswaran and Gloor are -- are instructed to use 10:31:13

18 specific rules, and those would be understood by a 10:31:22

19 POSA. 10:31:26

20 MR. MATTY: 10:31:27

21 Q. Okay. And in the combination that you are 10:31:27

22 proposing here, specifically taking Parameswaran's 10:31:29

23 experiment and running it on Gloor's sequencer, do 10:31:34

24 you have an opinion on which barcodes a person of 10:31:39

25 ordinary skill would choose for that combination? 10:31:43

1 MR. RAICH: Objection to form. 10:31:45

2 THE WITNESS: Again, I suspect that a POSA 10:31:45

3 could directly take the barcodes from Parameswaran 10:31:50

4 into Gloor or utilize the barcodes in Gloor instead 10:31:54

5 or utilize some different set of barcodes, given the 10:31:59

6 teachings of Parameswaran and Gloor. 10:32:04

7 But the exact sequences of barcodes as 10:32:06

8 shown in Parameswaran and Gloor are -- the exact 10:32:11

9 sequences themselves are not critical. 10:32:15

10 MR. MATTY: 10:32:18

11 Q. Okay. You have a lot of discussion in your 10:32:18

12 declarations about read length. You are familiar 10:32:32

13 with that, right? 10:32:37

14 A. Yes. 10:32:37

15 Q. In your combination of Parameswaran and 10:32:38

16 Gloor, what read length would that combined system 10:32:44

17 need to be able to provide for your combination to 10:32:47

18 work? 10:32:55

19 A. It would depend on what a POSA was trying 10:32:55

20 to achieve. 10:32:59

21 Q. And how would it depend on what a POSA was 10:33:00

22 trying to achieve? What do you mean by that? 10:33:02

23 A. The methods of Parameswaran are directed to 10:33:09

24 small RNA sequencing that have been turned into cDNA 10:33:11

25 and barcoding those. The methods of Gloor are 10:33:16

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1 directed toward multiplex -- sorry -- sequencing of 10:33:19
2 ribosomal RNA sequences. 10:33:26

3 And a practitioner of the art may choose to 10:33:32
4 sequence essentially anything in a targeted way. So 10:33:36
5 if they were sequencing a 10-base-pair fragment of 10:33:42
6 some region of the genome, that would have different 10:33:46
7 requirements than a thousand-base-pair region of the 10:33:49
8 genome. 10:33:57

9 They may or may not be capable of using a 10:33:58
10 specific platform to achieve the thousand-base-pair 10:34:01
11 process, but both Parameswaran -- or sorry -- both 10:34:04
12 the 454 and the Illumina sequencer could handle the 10:34:05
13 10-base-pair fragment in most configurations. So a 10:34:09
14 POSA would understand the limitations of each 10:34:15
15 sequencing system and adapt between the two. 10:34:17

16 Q. And so the length of the RNA or DNA that 10:34:23
17 the POSA is trying to read -- the length of that 10:34:29
18 template could change the read length that they need 10:34:32
19 in order to have a successful combination, true? 10:34:36

20 A. That is a limitation of all sequencers, not 10:34:40
21 just the 454 and the Illumina but also Sanger 10:34:44
22 sequencing beforehand, PacBio sequencing today, 10:34:50
23 Oxford Nanopore today, SOLiD sequencing. 10:34:55

24 A key component of each sequencing 10:35:00
25 technology for each read is the length of each read, 10:35:02

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1 and the methods when -- a POSA has available to them 10:35:07

2 are application dependent. 10:35:12

3 Q. Okay. And in your combination, there's 10:35:15

4 also barcodes on the template nucleic acids, right? 10:35:17

5 A. In this application, one would need to add 10:35:21

6 barcodes, potentially primers for PCRing if there 10:35:24

7 was a targeting step based on PCR. 10:35:29

8 Q. And the length of the barcodes could affect 10:35:32

9 the read length that the system needs to achieve in 10:35:35

10 order to work, true? 10:35:37

11 A. With barcodes in -- internal to the 10:35:41

12 products, yes. 10:35:44

13 Q. There's also linkers in the template of 10:35:50

14 nucleic acids and Parameswaran. You are familiar 10:35:55

15 with those, right? 10:35:57

16 A. Correct. 10:35:58

17 Q. The length of the cloning linkers that are 10:35:59

18 used in the template could also change the read 10:36:02

19 length the system would need to achieve in order to 10:36:07

20 work, true? 10:36:10

21 A. Using internal barcodes and cloning linkers 10:36:12

22 and the sequence that's being targeted and the other 10:36:19

23 side, cloning sequence and barcode, all add together 10:36:23

24 to give the needed sequence to achieve in a single 10:36:28

25 end. But one could achieve it with paired-end 10:36:32

1 **sequencing in another configuration, and a POSA** 10:36:35

2 **would understand this.** 10:36:39

3 Q. And how about primers? Do primers affect 10:36:40

4 the read length that the system needs to achieve to 10:36:43

5 work? 10:36:46

6 A. **The primers for locus targeting?** 10:36:46

7 Q. Yes. 10:36:51

8 A. **They would if they were included.** 10:36:51

9 Q. You are familiar with the concept of 10:36:53
10 homopolymers in DNA and sequencing, true? 10:37:42

11 A. **Yes.** 10:37:46

12 Q. What does a homopolymer mean to you in your 10:37:47
13 understanding? 10:37:51

14 A. **The conventional understanding of** 10:37:51
15 **homopolymer is a repeated DNA nucleotide of three or** 10:37:53
16 **more units.** 10:38:00

17 Q. Is that the understanding of homopolymer 10:38:02
18 that you used when you formed your opinions in this 10:38:08
19 case? 10:38:12

20 A. **The specification has a controlling** 10:38:12
21 **definition for homopolymer of two, so I would have** 10:38:14
22 **used that.** 10:38:18

23 Q. So you understand that a homopolymer 10:38:18
24 region, as it's used in the claims of Molecular 10:38:27
25 Loop's patents, refers to a sequence of two or more 10:38:37

1 nucleotides that are the same. Is that fair? 10:38:41

2 **A. It's an uncommon construction, but that is** 10:38:43

3 **what the specification says.** 10:38:46

4 Q. So when we see the term "homopolymer 10:38:47

5 region" in the claims of the patents, you understand 10:38:59

6 that to refer to a dinucleotide or a trinucleotide 10:39:03

7 or a tetranucleotide, et cetera? 10:39:09

8 **A. Correct.** 10:39:12

9 **(Reference to previously-marked Exhibit 1004)** 10:39:13

10 Q. Let's look at Parameswaran. I don't think 10:39:13

11 I've handed you that yet. I'll hand you what's been 10:40:40

12 marked as Exhibit 1004, which is the Parameswaran 10:40:47

13 reference. If you will go to page four of that 10:40:51

14 exhibit. Let me know when you are there. 10:41:18

15 **A. Yes, page four.** 10:41:20

16 Q. On Parameswaran at four, does -- that 10:41:21

17 describes generally the design of the barcoded 10:41:26

18 primers, right? 10:41:28

19 **A. Yes.** 10:41:31

20 Q. And it uses sort of placeholder letters, H 10:41:32

21 through O, and defines the sequence of each forward 10:41:38

22 and reverse barcode that Parameswaran used, right? 10:41:41

23 **A. That is correct.** 10:41:44

24 Q. And in the forward barcodes, there's a 10:41:45

25 section where there's a repeated J and a repeated L, 10:41:49

1 right? 10:41:54

2 A. Yes. 10:41:54

3 Q. And in the reverse barcodes, there's a 10:41:54
4 section where there's a repeated K and a repeated M, 10:41:57
5 right? 10:42:00

6 A. That is correct. 10:42:00

7 Q. And you understand that those signify 10:42:03
8 dinucleotide homopolymers, true? 10:42:07

9 A. That is what is included in the latter part 10:42:11
10 of the discussion. Later on in the document, the 10:42:13
11 authors of Parameswaran have a lengthy discussion on 10:42:16
12 how to avoid homopolymers, but they have chosen to 10:42:21
13 use dinucleotides in these -- in this context. 10:42:24

14 Q. And if you look at the end of that 10:42:27
15 paragraph, you said earlier that repeating two 10:42:29
16 nucleotides was commonly not known to be a 10:42:34
17 homopolymer. But Parameswaran refers to those as 10:42:38
18 "homopolymeric dinucleotides," true? 10:42:42

19 A. They do, and they also refer to avoiding 10:42:47
20 homopolymer runs. So they take both positions -- 10:42:54
21 and they also refer to avoiding homopolymeric
22 sequences.

23 (Reporter clarification.) 10:42:57

24 Q. What's a "homopolymer run," in your view? 10:42:57

25 A. I believe the phrase they use is 10:43:01

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1 **"homopolymeric sequences." I could look -- I could** 10:43:05

2 **find it for you if you'd like.** 10:43:10

3 Q. Okay. But Parameswaran says in each of 10:43:11

4 their barcodes, there are two homopolymeric 10:43:14

5 dinucleotides, true? 10:43:20

6 A. **They do.** 10:43:22

7 Q. And that matches the definition in the 10:43:22

8 Molecular Loop patents that you reference that says 10:43:28

9 a homopolymer can be two consecutive base pairs, 10:43:32

10 right? 10:43:35

11 A. **The controlling definition in the** 10:43:35

12 **specifications for these patents is two or -- is two** 10:43:37

13 **or more, yes.** 10:43:41

14 Q. Okay. So as it's referred to in the 10:43:41

15 Molecular Loop patents, for homopolymers, there are 10:43:44

16 two homopolymers in every barcode in Parameswaran, 10:43:47

17 true? 10:43:51

18 A. **That is correct.** 10:43:52

19 Q. I'm going to switch gears a little bit and 10:43:52

20 go back to some of your background. 10:43:59

21 A. **Yes.** 10:44:01

22 Q. I know you have a lengthy description in 10:44:01

23 your CV. I won't ask about all of it. But from 10:44:06

24 2003 to 2001 -- or I'm sorry -- 2003 to 2011, you 10:44:10

25 were a scientist and, I think, staff scientist at 10:44:13

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1 the Lawrence Berkeley Lab. Is that true? 10:44:18

2 A. That's correct. 10:44:20

3 Q. What is the Lawrence Berkeley Lab? 10:44:20

4 A. Lawrence Berkeley National Laboratory is 10:44:22

5 a -- is a part of the Department of Energy -- funded 10:44:27

6 by the Department of Energy and managed by the 10:44:29

7 University of California. 10:44:32

8 Q. What sort of work or research does -- let 10:44:33

9 me start that over. 10:44:39

10 What type of research did the Lawrence 10:44:39

11 Berkeley Laboratory do during your time there in 10:44:44

12 2003 to 2011? 10:44:46

13 A. I was recruited to Lawrence Berkeley Lab by 10:44:47

14 the division director for life sciences, Joe 10:44:51

15 W. Gray, to participate in the development of a 10:44:57

16 system biology program for the lab. 10:45:00

17 The lab had a biology interest that was 10:45:02

18 primarily driven by the low-dose energy program as 10:45:06

19 part of the Department of Energy, which primarily 10:45:13

20 focuses on nuclear risk and cancer development 10:45:14

21 through DNA damage as sort of a guiding principle. 10:45:18

22 But the life science division more broadly 10:45:23

23 had larger goals. Members of the life science 10:45:26

24 division included faculty or team -- staff 10:45:31

25 scientists like Eddy Rubin, who worked on mouse 10:45:36

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1 development; Len Pennacchio, who also worked on 10:45:40
2 life -- Jay Keasling, who worked on bioenergy; lots 10:45:43
3 of faculty at Berkeley who had appointments at 10:45:48
4 Berkeley Lab who worked on development or 10:45:52
5 high-throughput systems. Very broad. 10:45:55

6 I had been there partly as an adjunct 10:46:00
7 postdoc during my time in Gerry Rubin's lab working 10:46:04
8 on Drosophila genome sequencing and genome analysis 10:46:07
9 in the Drosophila. 10:46:09

10 So the -- although the Department of Energy 10:46:10
11 makes it sound like it might be highly restricted, 10:46:12
12 the life science division worked on many things and 10:46:16
13 was a key contributor to the genome project early on 10:46:21
14 as part of DOE team science efforts. So we were 10:46:24
15 broadly interested in genomics and systems biology 10:46:29
16 during my time at Lawrence Berkeley Lab. 10:46:33

17 Q. In your role as a scientist and staff 10:46:35
18 scientist there, what were -- what was your job? 10:46:38
19 What were you doing day-to-day? 10:46:41

20 A. I was a principal investigator and 10:46:43
21 coinvestigator on many grants that are listed during 10:46:48
22 that time. Supervised a team of scientists and 10:46:50
23 postdoctoral fellows as well as research associates 10:46:57
24 who didn't have advanced degrees performing genomic 10:47:02
25 research, primarily. 10:47:07

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1 Q. Were you using sequencers in your role as a 10:47:08
2 scientist and staff scientist at the Lawrence 10:47:11
3 Berkeley Lab? 10:47:15

4 A. Yes. We had substantial sequencing 10:47:15
5 capability projects that we did either in 10:47:17
6 collaboration with Eddy Rubin and Len Pennacchio or 10:47:22
7 Sue Celniker in the Drosophila program. 10:47:26

8 Q. Were you doing yourself any hands-on work 10:47:28
9 with sequencing machines during your time with the 10:47:30
10 Lawrence Berkeley Lab? 10:47:34

11 A. By the time I was a scientist and staff 10:47:35
12 scientist, I no longer did day-to-day research in 10:47:39
13 the bench. I supervised those who did and designed 10:47:44
14 experiments, directed them, coordinated the work. 10:47:49

15 Q. What sequencing platforms did you have in 10:47:54
16 your laboratory at the Lawrence Berkeley Lab? 10:47:56

17 A. I'm not sure all of the capabilities. In 10:48:01
18 addition to Berkeley Lab main campus, Berkeley Lab 10:48:05
19 had a joint genome institute in Walnut Creek that 10:48:10
20 was run by Dr. Rubin -- Eddy Rubin, not Gerry 10:48:13
21 Rubin -- and -- and Dr. Pennacchio and jointly 10:48:18
22 managed by UC Davis on their metagenomics programs. 10:48:23

23 They would have likely had all sequencers 10:48:28
24 that were commercially available during the time. 10:48:32
25 Dr. Celniker's team had an Illumina instrument, and 10:48:34

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1 we utilized that service. 10:48:38

2 We also used contract sequencing by the end 10:48:39
3 of my time at Berkeley Lab to -- you know, there 10:48:42
4 were commercial vendors whom you could submit 10:48:46
5 samples to. 10:48:49

6 Q. And I take it from your testimony earlier 10:48:49
7 you did not have any personal hands-on experience 10:48:52
8 with the Illumina instrument in that lab? 10:48:55

9 A. It was not uncommon. Indeed, it is quite 10:48:58
10 standard for Illumina instruments to be held in core 10:49:00
11 facilities where the exact mechanics are handled by 10:49:06
12 trained technicians. 10:49:09

13 But the large numbers of investigators used 10:49:11
14 the capabilities similar to the way that Gloor 10:49:14
15 itself handles the sequencing. Gloor -- Gloor sends 10:49:17
16 the sample to a core facility that provides the 10:49:21
17 sequencing. 10:49:23

18 So this is a standard process, given the 10:49:23
19 million-dollar price tag of instruments and the fact 10:49:26
20 that most labs don't run on a million dollars a 10:49:30
21 year, let alone -- and can't afford to maintain that 10:49:33
22 sort of equipment. 10:49:36

23 Q. Were you using any -- let me start that 10:49:37
24 over. 10:49:47

25 In your work at the Lawrence Berkeley Lab, 10:49:47

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1 were you running any experiments that used unique 10:49:54
2 dual indexing in sequencing? 10:49:57

3 A. I don't recall if by that time we were 10:50:03
4 using unique dual indexing. We would have -- at 10:50:06
5 Berkeley Lab directly, by the time I left, I had 10:50:15
6 become part of the Cancer Genome Atlas Project, 10:50:19
7 which is one of the -- one of the very large 10:50:23
8 consortium projects and one of 20 PIs in the 10:50:25
9 network. 10:50:30

10 I influenced the overall direction of 10:50:32
11 science projects within the network. A number of 10:50:39
12 those groups performed very large-scale sequencing, 10:50:44
13 including -- primarily done at the Broad Institute, 10:50:47
14 Washington University. 10:50:52

15 At the end, earlier Baylor University had 10:50:53
16 been involved. And then a substantial amount of 10:50:56
17 sequencing also happened at University of North 10:50:59
18 Carolina with my colleague Dr. Hoadley. 10:51:02

19 Right at the end of my time at Berkeley 10:51:07
20 Lab, I was asked to direct the program -- I was 10:51:10
21 asked to join NIH in a supervisory capacity 10:51:14
22 providing genomics oversight to projects like TCGA, 10:51:20
23 coordinating with the NHGRI. 10:51:25

24 Q. Let me go back. In the experiments you 10:51:35
25 were designing or supervising during your time at 10:51:37

1 the Lawrence Berkeley Lab, do you remember any of 10:51:40
2 those experiments using the unique dual indexing? 10:51:42

3 A. We did some level of exome sequencing at 10:51:50
4 the time, and that would often require multiplexing. 10:51:59
5 But I don't recall if it was dual-indexed, 10:52:00
6 single-indexed, unindexed, or unique and 10:52:04
7 double-indexed. 10:52:08

8 Q. For the experiments that you were designing 10:52:09
9 or supervising during your time at the Lawrence 10:52:12
10 Berkeley Lab, do you remember any of those 10:52:18
11 experiments using any particular type of sample 10:52:19
12 indexing? 10:52:23

13 A. I would have to -- the one that would be 10:52:25
14 most likely to -- to have information -- and I would 10:52:28
15 have to check -- would be this paper from Durinck et 10:52:32
16 al., 2011, Reference No. 45, published 2011. 10:52:42

17 But the original underlying data for that 10:53:02
18 would have been circa 2008/2009. That's whole exome 10:53:04
19 targeted sequencing of a series of samples. They 10:53:10
20 should have been done in multiplex, I believe, but I 10:53:13
21 would have to check the reference numbers on that. 10:53:20

22 Q. When you said the "Reference No. 45," 10:53:23
23 that's the reference that's listed at CV page 18 -- 10:53:26
24 in the CV in your declaration? 10:53:31

25 A. That's correct. Durinck, Steffen, et al. 10:53:33

1 **Co-corresponding author is myself with Dr. Cho from** 10:53:36

2 **UCSF.** 10:53:40

3 Q. Thank you. Let's go to paragraph 19 in 10:53:41

4 your declaration. It's the section about the level 10:56:37

5 of ordinary skill in the art. Can you let me know 10:56:42

6 when you are there. 10:56:47

7 A. **Sorry. Paragraph 19. Yes.** 10:56:50

8 Q. In that section, you give your 10:56:55

9 understanding of assessing the level of ordinary 10:56:58

10 skill in the art and then provide an opinion on what 10:57:05

11 that level of skill is in this case, true? 10:57:08

12 A. **I do.** 10:57:11

13 Q. And in paragraph 19, you list five 10:57:12

14 different factors that you say are -- that you say 10:57:15

15 you understand the level of ordinary skill are 10:57:20

16 determined from, true? 10:57:24

17 A. **That's what's written there, yes.** 10:57:25

18 Q. And the first factor is the type of 10:57:27

19 problems encountered in the art, right? 10:57:28

20 A. **That's what it says.** 10:57:31

21 Q. How did that factor -- or how did that -- 10:57:32

22 let me just ask: How did the types of problems 10:57:40

23 encountered in the art factor into your assessment 10:57:42

24 of what the level of ordinary skill is in this case? 10:57:44

25 A. **I evaluated it collectively. I don't know** 10:57:52

1 that I evaluated them individually to sort of build 10:57:54
2 a point system to come up with what a POSA might 10:57:57
3 look like. 10:58:01

4 But broadly speaking, the -- the -- a POSA 10:58:01
5 in the field at the time of the invention would have 10:58:09
6 to have significant experience and understanding of 10:58:17
7 high-throughput sequencers, their strengths and 10:58:21
8 limitations, and -- and how to utilize them. 10:58:26

9 Q. When your definition refers to -- I think 10:58:32
10 you just said "experience in high-throughput 10:58:34
11 sequencing technologies." What does that mean? 10:58:37

12 A. Well, you'll see in paragraph 20 the -- I 10:58:40
13 define them having a Ph.D. or, later, a master's 10:58:45
14 degree and at least two years or four years in 10:58:49
15 high-throughput sequencing technologies. 10:58:52

16 Q. Yeah. I'm just asking -- I'm trying to 10:58:54
17 understand what does "experience in high-throughput 10:58:56
18 sequencing technologies" mean? 10:59:00

19 A. High-throughput sequencing technologies 10:59:01
20 would include technologies like the 454, like the 10:59:05
21 Illumina sequencer, like the SOLiD sequencer, 10:59:09
22 potentially the transition from the very high-end 10:59:13
23 capillary sequencers of the early 2000s to the 10:59:16
24 multiplex sequencers. 10:59:19

25 But someone who has experience working with 10:59:22

1 not hundreds of sequence reads or necessarily even 10:59:26
2 thousands of sequencing reads but tens of thousands 10:59:30
3 to millions to hundreds of millions of sequence 10:59:33
4 reads, which is a different subset of skill than 10:59:36
5 might be required for handling Sanger sequencing. 10:59:39

6 Q. When you say "experience," does that 10:59:45
7 require hands-on experience with those sequencers? 10:59:48

8 A. No, I don't think so. 10:59:50

9 Q. Could it include academic experience, like 10:59:51
10 some of the research experience that you had? 10:59:54

11 A. What do you mean "academic"? 10:59:57

12 Q. I'll say research. Could it include 10:59:59
13 research experience, like some of the research 11:00:03
14 experience you have? 11:00:05

15 A. I don't understand the question. 11:00:05

16 Q. Could experience in high-throughput 11:00:06
17 sequencing technologies involve research experience 11:00:15
18 even if one wasn't using the sequencer hands-on? 11:00:16

19 A. I think that most of the practitioners of 11:00:20
20 the art who directed research programs at the time 11:00:24
21 of these inventions did not have hands-on 11:00:29
22 experience. 11:00:34

23 For example, it would be stunning to me if 11:00:34
24 Dr. Church had hands-on experience with a sequencer. 11:00:36
25 I am certain that Dr. Lander, who directed the Broad 11:00:40

1 Institute, did not have hands-on sequencing 11:00:45

2 experience. But no one would accuse him of not 11:00:48

3 having knowledge of how to perform the experiments. 11:00:51

4 Q. You have mentioned the Broad Institute a 11:00:53

5 couple times today. You are familiar with the Broad 11:00:58

6 Institute? 11:01:01

7 A. Yes. 11:01:01

8 Q. You are familiar with its researchers? 11:01:01

9 A. Oh, there's a lot of them, but I know many 11:01:03
10 of them. 11:01:05

11 Q. Do you have any opinions about the quality 11:01:05
12 of researchers at the Broad Institute? 11:01:08

13 A. The Broad Institute is a very 11:01:10
14 well-recognized institution with faculty that are 11:01:14
15 jointly recruited between Harvard, MDH, Dana-Farber, 11:01:20
16 MIT -- very well-respected institutions. 11:01:26

17 Q. When you were forming -- let me ask: For 11:01:29
18 the definition of person of ordinary skill that's 11:01:49
19 supplied in your declarations, did you come up with 11:01:51
20 that independently, or was that provided to you by 11:01:55
21 counsel? 11:01:58

22 A. I don't believe that I drafted that section 11:02:04
23 or came up with that definition on my own, if that's 11:02:07
24 the question. 11:02:10

25 Q. It was. When you were considering the 11:02:16

1 level of ordinary skill in this case, did you check 11:02:18
2 to see how the inventors on the Molecular Loop 11:02:20
3 patents measured up to your definition? 11:02:22

4 **A. No, I did not.** 11:02:26

5 Q. Can you go to paragraph 15 of your 11:02:26
6 declaration, please. 11:03:12

7 **A. Yes.** 11:03:13

8 Q. You state there that you have been well 11:03:13
9 aware of, and your lab routinely uses, unique and 11:03:18
10 nonunique dual index sequencing methods. Do you see 11:03:22
11 that? 11:03:26

12 **A. I do.** 11:03:26

13 Q. What unique dual index sequencing methods 11:03:26
14 do you use in your laboratory? 11:03:33

15 **A. I would have to go back and check. I mean,** 11:03:35
16 **it is what it says. You are asking a specific paper** 11:03:39
17 **that's used? Did I have to -- I'd have to read the** 11:03:41
18 **methods to tell you which papers did and did not use** 11:03:44
19 **each of those schemes.** 11:03:47

20 Q. So when you referred to unique and 11:03:49
21 nonunique dual index sequencing methods in your 11:03:53
22 paragraph No. 15, are those commercially available 11:03:56
23 kits or methods, or are those methods that your lab 11:04:01
24 designed specifically for the experiments that you 11:04:04
25 do? 11:04:09

1 A. It -- it should be both. 11:04:09

5 A. Again, I would have to go back to each 11:04:22
6 individual paper and read the methods to be sure. 11:04:25

10 A. Again, I would have to go back to the 11:04:36
11 methods of the papers and the laboratory -- you 11:04:38
12 know, work -- talk to all the colleagues I work with 11:04:40
13 to be sure which ones we have used. 11:04:42

17 A. I believe I've seen them, yes. I'm not 11:04:55
18 sure -- I believe we have ordered them, but I'm not 11:04:58
19 certain. 11:05:01

21 MR. RAICH: I'm going to object to scope. 11:05:03

25 ///

1 MR. MATTY: 11:05:16

2 Q. Okay. Any others other than TruSeq? 11:05:17

3 MR. RAICH: Same objection. 11:05:19

4 THE WITNESS: We -- we tend not to use 11:05:21

5 Illumina because their price margins are relatively 11:05:23

6 high. 11:05:26

7 MR. MATTY: 11:05:31

8 Q. Let me go to nonunique dual indexing 11:05:32

9 methods. Do you know if the nonunique dual indexing 11:05:37

10 sequencing methods that are used in your lab are 11:05:44

11 commercially available or specially designed 11:05:47

12 methods? 11:05:50

13 A. Again, if you go to Dr. Butler's work, his 11:05:51

14 dual-index/dual-adaptor approach would be one that 11:05:56

15 we -- he developed in my lab. So we have used a 11:06:00

16 number of schemes from Schmidt et al. and others in 11:06:05

17 a variety of these contexts. 11:06:09

18 Q. What commercially available kits or methods 11:06:13

19 does your lab use for nonunique dual indexing 11:06:21

20 sequencing methods? 11:06:26

21 MR. RAICH: Objection to scope. 11:06:27

22 THE WITNESS: I did not prepare that 11:06:31

23 assessment, so I can't tell you. 11:06:32

24 MR. MATTY: 11:06:33

25 Q. Okay. Are you aware of any nonunique dual 11:06:34

1 indexing sequencing kits or methods that are 11:06:37

2 commercially offered by Illumina? 11:06:39

3 MR. RAICH: Same objection. 11:06:41

4 THE WITNESS: Not with certainty, no. 11:06:42

5 MR. MATTY: I'm going to switch gears. Why 11:06:44

6 don't we take our break. 11:08:23

7 THE VIDEOGRAPHER: We're off the record. 11:08:24

8 The time is 11:07 a.m. 11:08:25

9 (Break taken.) 11:21:15

10 THE VIDEOGRAPHER: Okay. We're back on the 11:21:18

11 record. The time is 11:21 a.m. 11:21:19

12 MR. MATTY: 11:21:21

13 Q. I want to just close out our discussion of 11:21:35

14 Illumina sequencing. Illumina machines perform 11:21:40

15 sequencing by synthesis. That's your understanding, 11:21:42

16 right? 11:21:45

17 A. Correct. 11:21:45

18 Q. Illumina machines perform amplification on 11:21:46

19 a flow cell, true? 11:21:49

20 A. To the best of my knowledge, all the 11:21:51

21 commercial Illumina glass Solexa sequencers perform 11:21:54

22 PCR on -- in solid phase on the flow cell, yes. 11:21:59

23 Q. And Illumina machines perform sequencing on 11:22:03

24 a flow cell, true? 11:22:05

25 A. Yes. To the best of my knowledge, all 11:22:08

1 commercially available Illumina machines use flow 11:22:10

2 cells during the sequencing step itself. 11:22:13

3 Q. And Illumina machines perform multiplex 11:22:16

4 sequencing, true? 11:22:18

5 A. That one's a little more ambiguous. The 11:22:22

6 machines themselves, obviously, don't perform 11:22:25

7 multiplex sequencing. The users put DNA samples 11:22:27

8 into the sequencer, and they can choose to use 11:22:31

9 multiplex sequencing of various samples, but the 11:22:35

10 machines themselves don't do it. 11:22:39

11 Q. That makes sense. Illumina machines can be 11:22:41

12 used to perform multiplex sequencing. Fair? 11:22:43

13 A. To the best of my knowledge, every 11:22:46

14 sequencer that's commercially available in the last 11:22:48

15 30 years could do that. 11:22:51

16 Q. All right. Let's go to your declaration in 11:22:52

17 the 964 IPR, paragraph -- should be 122, which is 11:23:01

18 the beginning of the claim construction section. 11:23:06

19 Can you let me know when you are there. 11:23:08

20 A. Yes. Paragraph 122. 11:23:11

21 Q. You have a discussion in paragraph 122. 11:23:12

22 And at the end, you say you adopt the meaning of the 11:23:34

23 term "template crossover error" as used in the '852 11:23:37

24 patent, and then you specify what that meaning is. 11:23:41

25 Do you see you that? 11:23:44

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1 A. Yes.

2 Q. When you say you "adopted" that meaning, 11:23:46

3 what do you mean? 11:23:48

4 A. That I construed all the claims in the 11:23:49

5 context of that interpretation of the phrase 11:23:54

```
6  "template crossover error." 11:23:56
```

7 Q. So are you giving a claim construction 11:23:59

8 opinion here? 11:24:01

9 **A. Yes, I believe so.** 11:24:02

10 Q. How did you arrive at the construction that 11:24:02

11 you are proposing for template crossover error? 11:24:05

12 A. I evaluated the specification, discussed it 11:24:10

13 with counsel, and construed the term as defined at 11:24:14

14 **the bottom.** 11:24:18

15 Q. What legal framework did you use for 11:24:19

16 your -- to form your claim construction opinion? 11:24:23

17 **A. The specification, as well as the overall** 11:24:26

18 standard of a person of ordinary skill, and its 11:24:30

19 plain and ordinary meaning. But in this particular 11:24:33

20 case, I adopted a specific meaning because I felt 11:24:36

21 that the term might not have a plain and ordinary 11:24:38

22 meaning that was understood to everyone. 11:24:43

23 Q. So in the meaning that you adopted, it says 11:24:46

```
24     its: "Sequences of chimeric molecules made from" 11:24:53
```

```
25  template nucleic acids derived from different 11:24:57
```

1 samples," right? 11:25:01

2 **A. Correct.** 11:25:02

3 Q. And in your opinion, is that the plain and 11:25:02

4 ordinary meaning of "template crossover error," or 11:25:04

5 is that different than the plain and ordinary 11:25:10

6 meaning?

7 **A. Template crossover error does not have to** 11:25:14

8 **be from samples that are different. So -- so in** 11:25:16

9 **this case, I construed it just to mean within** 11:25:19

10 **different -- from different samples.** 11:25:23

11 Q. Okay. In your understanding, the crossover 11:25:25

12 error that's referred to in the '852 patent has to 11:25:28

13 result from crossover between nucleic acids from 11:25:32

14 different samples. Fair? 11:25:36

15 **A. That -- that is the one that they are well** 11:25:38

16 **suited to detect and correct based on their overall** 11:25:42

17 **specification.** 11:25:45

18 Q. I guess what do you mean by that as "the 11:25:54

19 one they are well suited to detect and correct"? 11:25:57

20 **A. So chimeric molecules are well known in the** 11:26:01

21 **art, and I discuss that in my declaration. But** 11:26:06

22 **broadly speaking, any -- a very large set of** 11:26:08

23 **biochemical processes can create chimeric molecules** 11:26:12

24 **in sequencing workflows or more broadly.** 11:26:16

25 **And the creation of a chimeric molecule can** 11:26:21

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1 look a lot like or be exactly equivalent to a 11:26:26
2 template crossing-over error. Distinguishing them 11:26:29
3 can be extremely difficult. 11:26:32

4 But -- and it was well -- even in a single 11:26:36
5 sample, not multiplex sample, where you are just 11:26:42
6 sequencing DNA from a single source, one can get 11:26:45
7 template crossing-over errors. That kind of error 11:26:50
8 would be not very easy to detect using the unique 11:26:53
9 barcode -- unique dual indexing approaches. 11:27:01

10 Q. And the chimeric molecules that are 11:27:06
11 discussed in the '200 and '852 patent -- you 11:27:09
12 understand those chimeric molecules in the examples 11:27:12
13 are all formed during amplification of nucleic 11:27:15
14 acids, true? 11:27:25

15 MR. RAICH: Object to form. 11:27:25

16 THE WITNESS: Can you please repeat the 11:27:27
17 question. We're looking at the '852 claims? 11:27:28

18 MR. MATTY: 11:27:31

19 Q. I'm referring to the description, the 11:27:32
20 specification, which is generally the same for both 11:27:35
21 patents. And my question is the chimeric molecules 11:27:37
22 that are described in the Molecular Loop patents -- 11:27:39
23 you understand those chimeric molecules are all 11:27:41
24 formed during amplification of nucleic acids, true? 11:27:44

25 A. The figures in this specification show 11:27:53

1 that. I'm not sure that it's technically correct to 11:27:58
2 say that all of the -- all of the ways that one can 11:28:02
3 get the template crossover errors happened in the 11:28:05
4 way this described. 11:28:11

5 So I think it's very important to recognize 11:28:12
6 the specification describes a likely mode of 11:28:14
7 template crossover error, but it's very clear that 11:28:20
8 it doesn't limit it to that. 11:28:22

9 The specification is -- it says "for" -- 11:28:24
10 something like "for the sake of assumption" or "we 11:28:29
11 assume" or something like that, but it does not 11:28:31
12 actually prove that these template crossover errors 11:28:34
13 are the only mechanism or limited to them -- to 11:28:38
14 those. 11:28:42

15 Q. In all your review of the '200 and '852 11:28:42
16 patents, did you see any discussion or examples of 11:28:47
17 chimeric molecules that were formed some other way 11:28:49
18 than during amplification of nucleic acid? 11:28:53

19 A. I'm going to have to read because the exact 11:29:07
20 columns and sources, I don't have notated. 11:29:11

21 Q. If you want me to repeat the question after 11:29:14
22 you read, just let me know. 11:29:16

23 A. Yes. Specification's longer than I 11:29:17
24 remember. Apologies. I thought it was much 11:32:06
25 shorter. 11:32:09

1 Q. Review whatever you need to. 11:32:10

2 A. Can you repeat the question. I'm not all 11:33:10

3 the way through, but I've already -- I'm starting to 11:33:12

4 forget it. 11:33:14

5 Q. Sure. In your review of the '200 and '852 11:33:14

6 patent, do you see any discussion of chimeric 11:33:18

7 molecules being formed any way other than during 11:33:22

8 amplification of nucleic acids? 11:33:25

9 A. There is a discussion of the formation and 11:33:37

10 an assumption about how it happens. I'm not finding 11:33:40

11 it reviewing it at the moment. I think I must have 11:33:43

12 passed it. So in Column 6, midway through the 11:34:53

13 second full paragraph: 11:35:15

14 "Without being limited by any 11:35:16

15 particular theory or mechanism of 11:35:19

16 action, the data in Figure 3 suggests 11:35:22

17 that the nucleic acid Sample A and the 11:35:24

18 nucleic acid from Sample B landed within 11:35:27

19 a cluster radius on the solid support." 11:35:31

20 So from that interpretation, a POSA would 11:35:35

21 understand that it doesn't matter what the actual 11:35:38

22 mechanism is. It only matters that what you observe 11:35:41

23 is this thing. 11:35:43

24 And the -- they basically say, "We think 11:35:46

25 it's this, but we're not sure. And we reserve the 11:35:49

1 **right to say it's something else later on. We** 11:35:52
2 **haven't conclusively determined it, and it doesn't** 11:35:56
3 **matter."** 11:35:58

4 Q. Right. And that's describing, with 11:35:59
5 relation to Figure 3, chimeric sequences being 11:36:11
6 formed during the amplification process, right? 11:36:16

7 MR. RAICH: Objection to form. 11:36:21

8 THE WITNESS: I think roughly that's 11:36:22
9 correct, but the point -- the point I'm making is 11:36:29
10 that they don't know the exact mechanism of chimeric 11:36:31
11 formation. They assume it's this. 11:36:34

12 But there are others, and they very 11:36:36
13 explicitly say it's suggested, but they are not 11:36:38
14 limited to: "Without being limited to by any 11:36:42
15 particular theory or mechanism of action." That's 11:36:44
16 explicit. 11:36:47

17 MR. MATTY: 11:36:48

18 Q. So there might be a different specific 11:36:48
19 mechanism that occurs during amplification. But the 11:36:50
20 chimeras that are resulting from this phenomenon, 11:36:57
21 whether it's, you know, the bridging phenomenon or a 11:37:01
22 different one, is still being formed during the 11:37:05
23 amplification process that's described in the 11:37:08
24 patent, true? 11:37:12

25 A. **No, I don't think that's quite correct. I** 11:37:12

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1 think that -- I think that the practitioners here 11:37:15
2 understand that during PCRs in general -- now, they 11:37:18
3 have done a situation where the only step where you 11:37:22
4 could have had this happen is on the flow cell. 11:37:26

5 But if one had combined the samples prior 11:37:30
6 to placing them on this flow cell and then amplified 11:37:34
7 them or did a preliminary extension reaction, even 11:37:36
8 without a PCR step, one could have created the step 11:37:40
9 prior. 11:37:43

10 And I think that's consistent with the 11:37:44
11 claim language in one of the two patents and how 11:37:46
12 it's constructed. So my interpretation is they are 11:37:50
13 suggesting to a POSA that this crossover -- template 11:37:55
14 crossover between samples can happen. 11:37:58

15 And it may -- and in their experimental 11:38:03
16 configuration, they think it happens here. 11:38:09
17 Parameswaran actually thinks it happens during the 11:38:11
18 second-round PCR rather than on the flow cell. 11:38:14

19 I think it's possible that Parameswaran is 11:38:17
20 incorrect and that it's also happening on the flow 11:38:18
21 cell in Parameswaran, but there -- Parameswaran 11:38:21
22 references believe that it's happening in the 11:38:24
23 second. It can technically happen at either place. 11:38:29

24 And in this particular case, they haven't 11:38:33
25 done the second-round PCR, necessarily, so there 11:38:34

1 might not be an opportunity for it to have happened 11:38:37

2 prior to the step. 11:38:41

3 And it may be limited here where -- where 11:38:42

4 they have much more certainty, given this 11:38:44

5 experimental configuration. But it's not limited to 11:38:46

6 this experimental configuration, and anything that 11:38:49

7 allows you to get template crossover would create 11:38:50

8 these molecules. 11:38:53

9 Q. Parameswaran does not amplify on a flow 11:38:55

10 cell, true? 11:38:58

11 A. Parameswaran uses an emulsion PCR to 11:39:02

12 perform the amplification analogous to cluster 11:39:07

13 formation on the flow cell. 11:39:10

14 Q. Not my question. Parameswaran does not 11:39:12

15 amplify on a flow cell, true? 11:39:14

16 A. As I've said, it amplifies an emulsion PCR. 11:39:16

17 Q. An emulsion PCR in Parameswaran is not 11:39:20

18 performed on a flow cell, true? 11:39:23

19 A. I believe it would not meet most users' 11:39:25

20 definition of a flow cell. I believe that's 11:39:29

21 correct. 11:39:31

22 Q. Okay. Can we go back to your claim 11:39:31

23 construction. 11:40:05

24 A. Yes. 11:40:05

25 Q. I know you might have said it briefly, but 11:40:06

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1 can you explain to me again how you arrived at the 11:40:13
2 claim construction that you are providing in 11:40:16
3 paragraph 122. 11:40:18

4 A. I read the specification. I considered the 11:40:22
5 use of terms in the art. In my opinion, template 11:40:24
6 crossover error is not a very common phrase, and so 11:40:33
7 I considered the specification and the requirements 11:40:35
8 for multiplex and the -- the ability -- ability to 11:40:41
9 describe being limited to detect crossover events 11:40:46
10 between samples rather than within samples. 11:40:51

11 And we have had a lengthy conversation 11:40:53
12 about internal chimeras within samples as being 11:40:56
13 quite common. And there are a whole set of methods 11:40:59
14 in the literature prior to this that would have been 11:41:02
15 used for detecting in-sample chimeras. 11:41:05

16 But specifically, the chimeras in this are 11:41:08
17 limited to between sample chimeras. And so I 11:41:14
18 interpreted template crossover to be limited to 11:41:18
19 between sample chimeras. 11:41:22

20 Q. And in your work in forming your opinions 11:41:23
21 here, I understand that you applied the legal 11:41:30
22 standards that were described to you as, you know, 11:41:37
23 the appropriate way to do -- anticipation, 11:41:39
24 obviousness, claim construction, things like that, 11:41:44
25 true? 11:41:48

A. Yes.

2 Q. What legal framework did you use for 11:41:48

3 performing your claim construction in this case? 11:41:51

4	A. As I understand it, claim construction is	11:41:58
5	normally the terms in the -- in use are given their	11:42:01
6	plain and ordinary meaning unless there's a	11:42:06
7	controlling definition in the specification, which	11:42:08
8	we have one example so far, or in which the	11:42:11
9	specification uses something in a way that is not in	11:42:14
10	the plain and ordinary manner.	11:42:18

11 So the template crossover errors detectable 11:42:21
12 with unique barcodes are limited to between samples. 11:42:25
13 And so if all of the template crossing-over errors 11:42:32
14 occurred within a sample, you could not reduce the 11:42:37
15 error. 11:42:40

16	And, therefore, in order to achieve it, it	11:42:41
17	must be between-sample crossing-over. So the	11:42:45
18	specification guided my interpretation of the	11:42:49
19	language that is relatively uncommon.	11:42:53

20	Q. Other than the specification, did you	11:42:58
21	review any other evidence for your claim	11:43:00
22	construction?	11:43:02

23 A. I mean, the literature as a whole, which 11:43:03
24 would help a POSA understand individual terms, 11:43:06
25 right? So my knowledge of the literature as a -- as 11:43:11

1 a practitioner of the art. 11:43:12

4	What literature did you review for forming	11:43:24
5	your claim construction opinion that you are	11:43:31
6	offering on the '852 patent?	11:43:33

7 A. I don't think that's the way it's -- as I 11:43:35
8 understand it, works. I think that the person of 11:43:38
9 ordinary skill in the art has an understanding 11:43:41
10 outside specific reference, right? 11:43:43

11	So the specification can control. The	11:43:46
12	specification can guide a POSA about the meaning of	11:43:48
13	individual terms, but the -- the phrase "PCR" is not	11:43:52
14	defined, necessarily, in this occasion. Perhaps it	11:43:56
15	is. But if it were not, a POSA wouldn't have to	11:44:00
16	look to some other reference to learn what PCR was.	11:44:03
17	A person of ordinary skill in the art reading the	11:44:08
18	specification would know what PCR was.	11:44:09

19	So many terms have plain and ordinary	11:44:11
20	meanings to persons of ordinary skill in the art	11:44:14
21	without a reference attached to them. In my	11:44:20
22	opinion, template crossover error needed to be	11:44:22
23	defined because it was -- the plain and ordinary	11:44:26
24	meaning is inconsistent with the specification.	11:44:28

25 Q. Can you identify any example of a crossover 11:44:29

1 error in the specification that was not caused by 11:44:47
2 amplification of nucleic acids? 11:44:52

3 **A. I don't think it's possible to determine 11:44:57**
4 **the cause of any template crossing-over error in the 11:45:00**
5 **work here. It is likely -- and I think most POSAs 11:45:05**
6 **would believe that certain things were more likely 11:45:10**
7 **than others, but I don't think there's definitive 11:45:13**
8 **proof. 11:45:16**

9 **And I would point back to the sentence I 11:45:16**
10 **pointed you to before, that: "Without being limited 11:45:19**
11 **by any particular theory or mechanism of action" -- 11:45:22**
12 **although the specification is guiding a POSA to 11:45:27**
13 **believe that it is template crossing-over during a 11:45:31**
14 **PCR step, it is not limited to that. 11:45:35**

15 **It is only limited to between-sample 11:45:39**
16 **barcode switching, as we have described. 11:45:42**

17 **Q. Now, you say in the '852, other than 11:45:51**
18 **crossover error, you read all claim terms as having 11:45:55**
19 **their ordinary meaning, as understood by a POSA, 11:45:59**
20 **right? 11:46:03**

21 **A. I believe that's correct. 11:46:03**

22 **Q. And in your analysis of the '200 patent, 11:46:04**
23 **you state -- you don't provide a claim construction 11:46:07**
24 **opinion. You say you've read all claim terms as 11:46:12**
25 **having their ordinary meaning, as understood by a 11:46:15**

1 POSA, true? 11:46:18

2 A. That's correct. 11:46:19

3 Q. And is that true for the term "homopolymer 11:46:19

4 region" in the claims? 11:46:25

5 A. The -- in the '200 series? 11:46:29

6 Q. In the '200 patent, yes. 11:46:32

7 A. So I did -- I will apply the controlling 11:46:40

8 definition in the specification for that one. And 11:46:42

9 in my opinion, it doesn't change my overall 11:46:44

10 opinions. 11:46:47

11 Q. Well, in your declaration that you provided 11:46:47

12 us in this case, you said you were using the 11:46:49

13 ordinary meaning for all terms. You didn't refer to 11:46:54

14 any controlling definition for "homopolymer region" 11:46:57

15 or any other term. Which did you do? 11:47:00

16 A. I agree with you. In the -- in the 11:47:02

17 specification -- in my declaration, it says that it 11:47:04

18 doesn't change my opinion to use the controlling 11:47:06

19 definition in the specification. I believe it is 11:47:08

20 still obvious to perform the work -- 11:47:14

21 Q. Okay. So --

22 A. -- using the controlling definition. 11:47:18

23 Q. So you in your declaration apply the 11:47:19

24 ordinary meaning of homopolymer region. And you 11:47:22

25 looked at Parameswaran, which has homopolymeric 11:47:27

1 dinucleotides, and you gave the opinion that those 11:47:33

2 barcodes do not contain homopolymer regions, true? 11:47:35

3 **A. That is incorrect. They do contain 11:47:40**

4 **homopolymer sequences, given the controlling 11:47:42**

5 **definition of the specification. 11:47:45**

6 Q. Okay. So on Parameswaran, for homopolymer 11:47:47

7 regions, you are changing your opinion for whether 11:47:49

8 or not that discloses the claim limitation, true? 11:47:52

9 **A. It is correct that there are homopolymer 11:47:55**

10 **sequences in Parameswaran. 11:47:59**

11 Q. Okay. And, actually, in any of the prior 11:48:00

12 art that discloses dinucleotide homopolymers, those 11:48:09

13 are homopolymer regions as they're claimed in the 11:48:14

14 '200 patent, true? 11:48:17

15 MR. RAICH: Object to the form of the 11:48:19

16 question. 11:48:20

17 THE WITNESS: Does -- the controlling 11:48:21

18 definition of homopolymer would apply to any 11:48:24

19 dinucleotide that -- in a -- in a barcode that is 11:48:29

20 the same, yes. 11:48:31

21 MR. MATTY: 11:48:32

22 Q. Okay. Did you analyze the controlling 11:48:32

23 definition, as you have termed it, of homopolymer in 11:48:34

24 the '200 before you formed your opinions in this 11:48:38

25 case? 11:48:43

1 MR. RAICH: Objection. Form. 11:48:43

2 THE WITNESS: I'm not sure how to answer 11:48:43

3 that question. 11:48:45

4 MR. MATTY: 11:48:46

5 Q. Let me ask this: When did you first become 11:48:46

6 aware of what you said is a controlling definition 11:48:49

7 of homopolymer in the '200 patent? 11:48:52

8 A. Counsel? 11:48:55

9 MR. RAICH: You can answer. 11:48:56

10 THE WITNESS: I believe I identified it 11:48:56

11 over the weekend. 11:48:59

12 MR. MATTY: 11:49:00

13 Q. Okay. Meaning just this past weekend, when 11:49:03

14 you were preparing for your deposition? 11:49:06

15 A. Correct. 11:49:07

16 Q. Okay. Other than the template crossover 11:49:08

17 error in the '852 patent and the homopolymer region 11:50:52

18 claimed in the '200 patent, are there any other 11:50:58

19 claim terms that you are interpreting now 11:51:01

20 differently than their plain and ordinary meaning? 11:51:05

21 A. I don't believe so. 11:51:10

22 Q. In your review of the '200 and '852 11:51:32

23 patents, you also saw a discussion of 11:51:37

24 heteroduplexes, true? 11:51:40

25 A. Can you point me to a page, or do you want 11:51:42

1 me to find it? 11:51:44

2 Q. I can give you at least an example. One 11:51:52

3 example is at Column 4. Around line 43, it refers 11:52:14

4 to a heteroduplex. 11:52:18

5 A. Column -- sorry. Which page? 11:52:20

6 Q. Sorry. I was looking at Column 4, line 43. 11:52:22

7 A. In the specification? 11:52:28

8 Q. In the specification. 11:52:29

9 A. Sorry. I thought you said my declaration. 11:52:36

10 I apologize. Column 4, line 43. 11:52:38

11 Q. In the '852 patent. 11:52:41

12 A. Yeah. Yes, I see that. 11:52:43

13 Q. Do you have an understanding of what a 11:52:51

14 heteroduplex is? 11:52:53

15 A. Generally, a heteroduplex is when 11:52:54

16 noncomplementary strands or -- or noncopies of one 11:52:57

17 another have interlinked and bound to one another. 11:53:02

18 Q. What do you mean by "noncomplementary or 11:53:07

19 noncopies of one another"? 11:53:10

20 A. I think it would be unusual to use 11:53:12

21 "heteroduplex" to refer to -- so if you have some 11:53:15

22 specific DNA sequence and you melt it and you 11:53:20

23 reanneal so that copies can be -- bind to each other 11:53:27

24 again -- if all of the DNA sequences in a mixture 11:53:32

25 are a strand and its reverse complement, then you 11:53:37

1 can melt, reanneal, and you'll have shuffled the 11:53:43
2 strands. 11:53:48

3 But they will all be identical to one 11:53:49
4 another in a duplex DNA molecule. And I think it 11:53:52
5 would be unusual to describe that as a heteroduplex, 11:53:56
6 whereas if there was a sequence difference between 11:53:59
7 the two strands such that you have now introduced a 11:54:01
8 bubble or gap or some difference between the two -- 11:54:05
9 that you would then have a heteroduplex. 11:54:12

10 In some specific instances, you might 11:54:14
11 describe a heteroduplex as being partial binding of 11:54:17
12 one sequence to another sequence. So it's a 11:54:22
13 relatively broad term, and it would be operationally 11:54:25
14 defined. 11:54:30

15 Q. Is "heteroduplex" a standard term in the 11:54:32
16 art, in your experience? 11:54:35

17 A. Yes. 11:54:36

18 Q. Is there a difference between a chimeric 11:54:37
19 sequence and a heteroduplex, in your view? 11:54:40

20 A. Yes. So -- so, I mean, what's described 11:54:56
21 here in Panel 3 is that the heteroduplex is one way 11:54:57
22 of biochemically getting to a chimeric sequence. 11:55:00
23 There are others. 11:55:07

24 You could do ligation, for example, where 11:55:07
25 you took Sequence 1 and Sequence 2 and ligated them 11:55:09

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1 to create a chimera. That would not involve a 11:55:13

2 heteroduplex intermediary. 11:55:19

3 Q. Which you say "ligating," you mean, like, 11:55:19

4 connect them end to end? 11:55:20

5 A. Correct. Or with some overlap or something 11:55:22

6 like that, yes. 11:55:24

7 Q. So a heteroduplex is one mechanism for 11:55:26

8 creating a chimeric sequence but not necessarily the 11:55:29

9 only mechanism, correct? 11:55:41

10 A. Correct. 11:55:46

11 (Reporter clarification.) 11:55:49

12 Q. Okay. I'm going to go to paragraph 67 in 11:55:49

13 your declaration in the 964 case. If you could go 11:56:31

14 there, please. 11:56:34

15 A. Paragraph 67. 11:56:35

16 Q. That's right. 11:56:36

17 A. Yes. 11:56:41

18 Q. In paragraph 67, you cite a number of 11:57:02

19 references that you characterize as discussing 11:57:05

20 problems with single indexes that could arise during 11:57:08

21 PCR amplification, true? 11:57:12

22 A. That's what the -- yes, that's what it 11:57:14

23 says. 11:57:16

24 (Reference to previously-marked Exhibit 1017.) 11:57:16

25 Q. All right. I'm going to look at some of 11:57:16

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1 those references. I'll hand you Exhibit 1017, which 11:57:20
2 is the Lahr reference. Do you have Exhibit 1017 in 11:57:26
3 front of you? 11:57:50

4 **A. I do.** 11:57:50

5 Q. Are you familiar with this reference? 11:57:50

6 **A. Yes. I have reviewed it.** 11:57:52

7 Q. All right. Now, Exhibit 1017 generally 11:57:53
8 describes what the title calls "PCR-mediated 11:58:04
9 recombination," true? 11:58:07

10 **A. Yes.** 11:58:09

11 Q. Exhibit 1017 doesn't have any discussion of 11:58:09
12 any next-generation sequencing techniques, true? 11:58:15

13 **A. I haven't read it in the context of 11:58:21
14 checking to make sure it doesn't, but I would be 11:58:23
15 prepared to stipulate it.** 11:58:26

16 Q. Okay. 11:58:28

17 **A. I mean, if you want me to state absolutely 11:58:29
18 for sure, I would have to read it very closely.** 11:58:31

19 Q. Well, in your review of Exhibit 1017, you 11:58:41
20 didn't see any discussion of Illumina flow cell 11:58:45
21 sequencing, true? 11:58:48

22 **A. I don't recall.** 11:58:52

23 Q. In your review of Exhibit 1017, did you 11:58:55
24 find any discussion of pyrosequencing? 11:59:00

25 **A. I don't recall.** 11:59:04

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1 Q. In your review of Exhibit 1017, did you 11:59:05
2 find any discussion of using indexes for nucleic 11:59:13
3 acids? 11:59:19

4 A. Again, I don't recall. 11:59:19

5 Q. In your review of Exhibit 1017, did you 11:59:21
6 find any discussion of using dual indexes for 11:59:27
7 nucleic acids? 11:59:31

8 A. Same answer. 11:59:32

9 Q. You don't recall? 11:59:32

10 A. I don't recall. 11:59:34

11 Q. In your review of Exhibit 1017, did you 11:59:35
12 find any discussion of unique dual indexing? 11:59:39

13 A. That would seem unlikely, given the title. 11:59:43
14 But, again, I -- I'd have to read it carefully to be 11:59:46
15 certain. 11:59:50

16 Q. What are you referring to in the title? 11:59:50

17 A. Oh, sorry. Given the line of questioning, 11:59:52
18 I just -- I think it's unlikely. 11:59:55

19 Q. In your review of Exhibit 1017, did you 11:59:57
20 find any discussion about pooling nucleic acid 12:00:04
21 samples together? 12:00:07

22 A. What do you mean by "pooling nucleic acid 12:00:13
23 samples together"? 12:00:17

24 Q. I mean combining nucleic acids from 12:00:17
25 different samples. So let me just use that 12:00:20

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1 phrasing, and I'll re-ask the question: In your 12:00:23
2 review of Exhibit 1017, did you find any discussion 12:00:26
3 about combining nucleic acids from different samples 12:00:29
4 together? 12:00:33

5 A. I think your phrasing is sufficiently 12:00:36
6 ambiguous. It's giving me pause. 12:00:40

7 Q. What can I clear up in my question? 12:00:41

8 A. So this is a very specific piece of work 12:00:46
9 on -- on a very technically interesting case. Actin 12:00:51
10 is one of the key components of eukaryotic cells, 12:01:03
11 and it is under tremendous selection and constraint. 12:01:10

12 And in this particular case, they're 12:01:14
13 looking at gene family evolution. So when you ask 12:01:23
14 about recombination samples, it's a little -- if you 12:01:27
15 are using the framework of the '852 and '200 series 12:01:32
16 patent specifications, then the answer would be no. 12:01:39

17 But other -- the phrasing -- since you are 12:01:43
18 not using exactly the same phrasing in the same way, 12:01:45
19 the take-home message of the Lahr reference is that 12:01:49
20 when you have similar sequences and PCR reactions, 12:01:55
21 you get lots of mispriming, lots of chimeric events, 12:01:58
22 and they're very easy to form. 12:02:02

23 And that is -- multiplex PCR, in general, 12:02:06
24 has this problem of mispriming or -- or chimeric 12:02:11
25 sequence creation that creates all sorts of weird 12:02:20

1 behaviors in multiplex PCR. 12:02:24

2 When the sequences get very, very similar 12:02:28

3 or have identical sequences in them, it facilitates 12:02:30

4 this even more. So the high-throughput sequencing 12:02:35

5 pipelines, where things are cloned with the same 12:02:40

6 linkers on the end it would multiplex, can lead to 12:02:43

7 this mispriming at much higher rates. 12:02:47

8 In this particular case, that happens 12:02:49

9 through these closely related actin sequences, as I 12:02:52

10 understand it, because of the evolutionary 12:02:56

11 constraints on actin. It's a guidepost to a POSA 12:02:58

12 about the hazards of similar sequences in complex 12:03:03

13 mixtures. 12:03:07

14 Q. In your review of Exhibit 1017, did you see 12:03:07

15 any discussion of multiplex sequencing? 12:03:10

16 A. Again, I -- I don't believe it's there. 12:03:12

17 Q. When you were working on this case, did you 12:03:14

18 find Exhibit 1017, or was it provided to you? 12:03:20

19 A. I would assume it was provided to me. 12:03:22

20 Q. Okay. In your review of Exhibit 1017, did 12:03:24

21 you see any discussion of chimeric sequences that 12:03:29

22 were formed from different samples? 12:03:31

23 A. Again, I think the sample part is a little 12:03:38

24 ambiguous. You might mean it from different 12:03:41

25 individuals. I have to read it very closely. It 12:03:46

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1 **could be from different strains. It could be from** 12:03:49
2 **different -- different samples, PCR'd from the same** 12:03:52
3 **sample. It's an ambiguous phrasing that you are** 12:03:56
4 **using.** 12:03:58

5 Q. Okay. In your review of Exhibit 1017, did 12:03:59
6 you see any discussion of chimeric sequences being 12:04:01
7 formed on the surface of a flow cell? 12:04:05

8 A. **I don't believe so.** 12:04:07

9 **(Reference to previously-marked Exhibit 1018.)** 12:04:08

10 Q. You can set that one aside. I'm going back 12:04:08
11 to your declaration at paragraph 67. It also cites 12:04:41
12 an Exhibit 1018, so I'll hand that one to you. Do 12:04:45
13 you have Exhibit 1018 in front of you? 12:04:57

14 A. **I do.** 12:04:59

15 Q. And you have reviewed Exhibit 1018 in your 12:05:00
16 work on this case? 12:05:02

17 A. **Yes, although I'm not sure the last time I** 12:05:03
18 **looked at it. It might have been a little longer.** 12:05:06

19 Q. Okay. And in your work on this case, did 12:05:08
20 you find Exhibit 1018, or was that one provided to 12:05:11
21 you? 12:05:16

22 A. **I would -- I would assume that it was** 12:05:16
23 **provided to me.** 12:05:18

24 Q. In your review of Exhibit 1018 in this 12:05:18
25 case, did you find any discussion of next-generation 12:05:24

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1 sequencing? 12:05:29

2 A. Given the date on the paper, it's almost 12:05:30

3 certainly impossible. 12:05:33

4 Q. And so in your review of Exhibit 1018, you 12:05:34

5 also did not find any discussion of Illumina flow 12:05:40

6 sequencing, true? 12:05:43

7 A. Given -- again, given the date, it's 12:05:43

8 essentially impossible. 12:05:47

9 Q. In your review of Exhibit 1018, you did not 12:05:47

10 find any discussion of pyrosequencing, true? 12:05:50

11 A. Again, I don't believe the pyrosequencing 12:05:54

12 had been invented in 1990. 12:05:57

13 Q. In your review of Exhibit 1018, did you 12:05:59

14 find any discussion of sample indexing? 12:06:02

15 A. I'd have to check, but I think it's 12:06:05

16 unlikely. Sample indexing, I believe, was invented 12:06:08

17 sometime after that, even on Sanger. 12:06:12

18 Q. Around when was sample indexing invented on 12:06:16

19 Sanger, to your recollection? 12:06:20

20 A. Varieties of sample indexing may have been 12:06:25

21 around in a -- in complicated ways, given cloning 12:06:29

22 vectors and other things. I have to think about it 12:06:33

23 more. I don't think I have an opinion on that. 12:06:37

24 Q. In your review of Exhibit 1018, did you 12:06:39

25 find any discussion of dual indexing? 12:06:43

A. Very unlikely.

2 Q. And I assume in your review of 12:06:49

3 Exhibit 1018, you did not find any discussion of 12:06:51

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4 unique dual indexing, true? 12:06:56
```

5 A. I think the point of the article is 12:06:56

6 completely oblique to the line of questioning, but 12:07:00

7 no. 12:07:02

8 Q. In your review of Exhibit 1018, did you 12:07:02

9 find any discussion of multiplex sequencing? 12:07:05

10 A. That's an interesting question. I would 12:07:08

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11 have to read it closely. It may very well -- not in 12:07:10
```

12 the terms of multiplex on a flow cell, for sure. 12:07:14

13 Q. Okay. Sitting here, from your review of 12:07:17

14 Exhibit 1018, do you remember any discussion of 12:07:21

15 multiplex sequencing? 12:07:22

16 A. Okay. How are we defining "multiplex" 12:07:29

```
17 sequencing"? 12:07:33
```

18 Q. Just given your general understanding of 12:07:33

19 multiplex sequencing. 12:07:35

20 A. I mean, the reason I'm balking is, like, 12:07:50

21 you know, I'm looking at page three. "A total of 37 12:07:52

22 **plaques" -- so 37 individual samples are being** 12:07:56

23 sequenced. 12:07:58

24 They're sequenced independently, rather 12:07:59

25 than in one pool, so -- but they're probably 12:08:03

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1 **sequenced on the same gel. So is that multiplex** 12:08:05

2 **sequencing or not? I'm not sure.** 12:08:09

3 Q. Let me ask this: In your review of 12:08:10

4 Exhibit 1018, did you see any discussion of pooling 12:08:12

5 nucleic acids from different samples together from 12:08:14

6 multiplex sequencing? 12:08:17

7 A. **No. That would not be present with this.** 12:08:17

8 Q. In your review of Exhibit 1018, did you 12:08:20

9 find any discussion of chimeras being formed from 12:08:22

10 different samples? 12:08:25

11 A. **I don't expect that that's likely.** 12:08:29

12 Q. And in your review of Exhibit 1018, did you 12:08:30

13 find any discussion of chimeras being formed on the 12:08:35

14 surface of a flow cell? 12:08:37

15 A. **No. That would be impossible.** 12:08:39

16 **(Reference to previously-marked Exhibit 1019.)** 12:08:40

17 Q. I'll hand you Exhibit 1019. 12:08:40

18 A. **Yes.** 12:09:16

19 Q. You are familiar with Exhibit 1019? 12:09:16

20 A. **I'm pretty sure. I haven't looked at it in** 12:09:19

21 **a while, but yes.** 12:09:22

22 Q. You have reviewed it as part of your work 12:09:23

23 in this case? 12:09:26

24 A. **In whole or in part, yes.** 12:09:27

25 Q. In your work on this case, did you find 12:09:28

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1 Exhibit 1019, or was it provided to you? 12:09:30

2 A. I would think that it was provided to me. 12:09:33

3 Q. In your review of Exhibit 1019, did you see 12:09:34
4 any discussion of next-generation sequencing? 12:09:38

5 A. Not possible, given the date. 12:09:41

6 Q. So in your review of Exhibit 1019, did you 12:09:42
7 find any discussion of Illumina flow cell 12:09:46
8 sequencing? 12:09:47

9 A. Not possible, given the date. 12:09:48

10 Q. In your review of Exhibit 1019, did you 12:09:49
11 find any discussion of pyrosequencing? 12:09:53

12 A. Very unlikely, given the date. 12:09:56

13 Q. In your review of Exhibit 1019, did you 12:09:58
14 find any discussion of sample indexing? 12:10:03

15 A. Using the definition of sample indexing as 12:10:11
16 a POSA would have understood it in 2010? That's a 12:10:15
17 question for you. 12:10:22

18 Q. Let's say yes. 12:10:23

19 A. No, that would not be present in this 12:10:25
20 document. 12:10:29

21 Q. Okay. Under any understanding of sample 12:10:29
22 indexing, did you see any discussion of sample 12:10:32
23 indexing in Exhibit 1019? 12:10:34

24 A. I mean, I think there's a very interesting 12:10:35
25 question. Like, when one loads a sample into a lane 12:10:37

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1 of a Sanger sequencing gel, one is effectively 12:10:40
2 indexing it, right? One is keeping track of it with 12:10:43
3 a location. It's a form of indexing. It's not a 12:10:46
4 DNA barcode index, necessarily, but it is a sequence 12:10:49
5 index. 12:10:53

6 Q. Did you see any discussion of nucleic acid 12:10:54
7 indexes being used in Exhibit 1019? 12:10:57

8 A. I don't believe so. 12:10:59

9 Q. When you reviewed Exhibit 1019, did you see 12:11:00
10 any discussion of dual indexing? 12:11:02

11 A. I -- no. 12:11:05

12 Q. And when you reviewed Exhibit 1019, did you 12:11:06
13 see any discussion of unique dual indexing? 12:11:09

14 A. No. 12:11:12

15 Q. When you reviewed Exhibit 1019, did you see 12:11:12
16 any discussion of pooling samples together from 12:11:24
17 multiplex sequencing? 12:11:28

18 A. Given the use of multiplex sequencing that 12:11:31
19 they were using, no, I don't believe it's present. 12:11:34

20 Q. When you reviewed Exhibit 1019, did you see 12:11:36
21 any discussion of chimeras being formed from 12:11:39
22 different samples? 12:11:42

23 A. I'd have to read it more closely to be sure 12:11:55
24 that it's not present. 12:11:58

25 Q. Can you identify for me any discussion of 12:11:59

111

1 chimeras being formed from different samples in 12:12:05

2 Exhibit 1019? 12:12:08

3 A. I'd have to read it closely. If you would 12:12:09

4 like me to, I can. 12:12:12

5 Q. If you need to review it, you can. 12:12:13

6 A. What do you refer to when you mean 12:12:49

7 "different samples"? 12:12:51

8 Q. I mean nucleic acids that are taken from 12:12:52

9 different samples. 12:13:05

10 A. So this is a little tricky because Paabo's 12:13:12

11 work is generally directed towards samples that are 12:13:20

12 composed of complicated mixtures, many of which 12:13:23

13 might be different individual organisms, for 12:13:26

14 example, or different people or things along that 12:13:31

15 line. 12:13:33

16 And so I think it's quite likely that Paabo 12:13:34

17 was concerned about chimeric sequences being 12:13:37

18 created, some of which might be between individuals. 12:13:42

19 I think that we have a very likely conclusion of -- 12:13:45

20 just in the abstract, right? 12:13:49

21 But the -- Paabo might have a sample, but 12:13:51

22 it's from not -- it can't control where it came 12:13:53

23 from, and it would be a mixture of things very 12:13:57

24 often. 12:13:59

25 Q. So can you identify for me any discussion 12:14:00

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1 in Exhibit 1019 that talks about chimeras being 12:14:13
2 formed between nucleic acids from different samples? 12:14:16

3 A. Well, I will read this sentence for you: 12:14:28

4 "Consequently, amplification products from damaged 12:14:34

5 templates, such as archaeological DNA, are made up 12:14:38

6 of a high proportion of chimeric molecules." 12:14:42

7 So intrinsic to archaeological DNA is the 12:14:45

8 fact that that is a mixture of material. Paabo 12:14:49

9 might get bone or tooth or hair from an ancient 12:14:52

10 individual. They have been doing this for 35 years. 12:14:57

11 And unfortunately, there is a mixture of 12:15:02

12 stuff that is not human in those samples. There's 12:15:05

13 bacteria. There's fungus. There's God-knows-what 12:15:07

14 in there. So depending on how you view "sample" -- 12:15:11

15 if you mean "sample" as this sample from this tooth, 12:15:16

16 no, I don't think so. 12:15:19

17 If you mean it as a mixture of complicated 12:15:20

18 mixtures of organisms, then absolutely. And I think 12:15:24

19 from his perspective, he would be very concerned 12:15:27

20 about the sequences that bridge between individual 12:15:32

21 organisms. 12:15:35

22 Q. In your review of Exhibit 1019, did you see 12:15:36

23 any discussion of chimeras being formed on the 12:15:39

24 surface of the flow cell? 12:15:43

25 A. That would be impossible. 12:15:44

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1 **(Reference to previously-marked Exhibit 1020.)** 12:17:47

2 Q. I'll hand you Exhibit 1020. 12:17:47

3 A. Yes. 12:17:53

4 Q. You are familiar with this exhibit? 12:17:53

5 A. I'm -- I've reviewed it in whole or in part 12:17:57

6 **but some time ago, yes.** 12:18:00

7 Q. In your work on this case, did you find 12:18:01

8 Exhibit 1020, or was it provided to you? 12:18:03

9 A. It was provided to me. I may have been 12:18:08

10 **familiar with it on my own.** 12:18:10

11 Q. In your review of Exhibit 1020, did you see 12:18:11

12 any discussion of next-generation sequencing? 12:18:14

13 A. Given the timestamp -- the date of the 12:18:19

14 **publication, no.** 12:18:21

15 Q. In your review of Exhibit 1020, did you 12:18:22

16 find any discussion of Illumina flow cell 12:18:25

17 sequencing? 12:18:27

18 A. Given the date of the publication, no. 12:18:27

19 Q. All right. In your review of Exhibit 1020, 12:18:29

20 did you find any discussion of pyrosequencing? 12:18:33

21 A. I would be surprised if they were present. 12:18:35

22 **I don't recall.** 12:18:38

23 Q. In your review of Exhibit 1020, did you 12:18:39

24 find any discussion of sample indexing? 12:18:44

25 A. I have to carefully read it to be sure, but 12:18:47

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1 I don't know. 12:18:50

2 Q. You can review if you need to. 12:18:54

3 A. At some level, there's something akin to 12:20:09

4 sample indexing, given the cloning linkers and the 12:20:12

5 PCR primers being utilized. But it's probably not 12:20:15

6 in the same context as we might describe as barcode 12:20:18

7 indexing. But there are related concepts present. 12:20:22

8 Q. Okay. In your review of Exhibit 1020, did 12:20:25

9 you see any discussion of dual indexing? 12:20:28

10 A. For the same reason, I think that the -- 12:20:32

11 these are ligated into vectors, and the vectors have 12:20:35

12 sequences that are defined and structured in the PCR 12:20:38

13 primers. And the primers used for sequencing, I 12:20:42

14 believe, are in both orientations. 12:20:45

15 So under some context, that is like a 12:20:47

16 barcode. Adding the wrong primers to a mixture 12:20:51

17 would not -- would not sequence it. So there are 12:20:55

18 some -- there are some relevant concepts that are 12:20:57

19 related to dual barcoding and single barcoding. 12:21:00

20 Q. And in Exhibit 1020, in your review, did 12:21:03

21 you see any discussion of pooling samples together 12:21:05

22 from multiplex sequencing? 12:21:08

23 A. No. I don't think that would be here. 12:21:11

24 Q. In your review of Exhibit 1020, did you see 12:21:13

25 any discussion of chimeras formed from different 12:21:15

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1 samples? 12:21:18

2 A. The reference is clearly about the 12:21:47

3 mechanism of the creation of these template 12:21:48

4 switching molecules and not about determining -- 12:21:51

5 identifying any real examples of them. 12:21:54

6 Q. So in your review of Exhibit 1020, did you 12:21:55

7 see any discussion of chimeras formed from different 12:22:09

8 samples? 12:22:12

9 A. It's a little -- I mean, a POSA reading 12:22:36

10 this discussion, first paragraph, for example -- 12:22:38

11 there's a discussion: "For several decades, 12:22:40

12 template switching has been postulated as a 12:22:42

13 mechanism for various recombinational events." 12:22:46

14 And it -- it concludes with: "These 12:22:48

15 results suggest that many of the recombinants 12:22:49

16 produced during the PCR probably arise via a 12:22:54

17 template-switching process." 12:22:57

18 So a POSA reading this would understand 12:22:59

19 that anytime one had done PCR with more than one 12:23:01

20 sample present in the PCR, this was a possibility 12:23:03

21 for something to occur. So I would say that would 12:23:05

22 be an indirect disclosure, but -- but a POSA 12:23:09

23 interested in multiplex PCR of a sample might very 12:23:12

24 well read this as relevant in part. 12:23:16

25 Q. Do you see anything in Exhibit 1020 that 12:23:20

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1 discusses chimeric sequences being formed on the 12:23:24
2 surface of a flow cell? 12:23:27

3 **A. No. That would not be possible, given the** 12:23:28
4 **date.** 12:23:31

5 MR. RAICH: Counsel, we have been going 12:23:39
6 about an hour. Do you -- 12:23:41

7 MR. MATTY: Let's take a break. We can go 12:23:43
8 off the record. 12:23:44

9 THE VIDEOGRAPHER: We're going off the 12:23:44
10 record. The time is 12:23 p.m. 12:23:45

11 (Lunch break taken.) 13:16:09

12 THE VIDEOGRAPHER: Okay. We're back on the 13:16:12
13 record. The time is 1:15 p.m. 13:16:12

14 MR. MATTY: 13:16:14

15 Q. I'm going to go back to your declaration in 13:16:15
16 the 964 IPR. And go to page 33. 13:16:18

17 **A. Yes.** 13:16:22

18 Q. At the top of page 33, you have a figure 13:16:23
19 that you labeled Figure 6, right? 13:16:28

20 **A. Yes.** 13:16:31

21 Q. And that's not a figure from any of the 13:16:32
22 references or anything like that; that's a figure 13:16:35
23 that was created for your declaration, true? 13:16:37

24 **A. I believe that's correct.** 13:16:41

25 Q. And what you are showing in your Figure 6 13:16:42

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1 is an example of chimeric combination, true? 13:16:45

2 A. Yes. 13:16:48

3 Q. And in the sequences in Figure 6, they have 13:16:49

4 two barcodes. They're different barcodes, right? 13:16:51

5 A. Yes. 13:16:54

6 Q. And those are meant to show barcodes 13:16:54

7 tagging nucleic acids from two different samples, 13:16:56

8 true? 13:17:00

9 A. I believe that's correct, yes. 13:17:00

10 Q. And then at the bottom of your Figure 6, 13:17:02

11 you are depicting what would be a chimera that's 13:17:04

12 being formed from nucleic acids from different 13:17:08

13 samples, true? 13:17:10

14 A. Let me correct you. The previous line, I 13:17:12

15 think -- I think the picture is a little more 13:17:15

16 generic than you described. The barcodes are 13:17:18

17 attached to two different sequences. I don't know 13:17:21

18 that they -- that they have to be from different 13:17:24

19 samples. 13:17:27

20 Q. Okay. So your intent in what you were 13:17:28

21 portraying was two different sequences being 13:17:31

22 combined, not necessarily sequences from different 13:17:34

23 samples, true? 13:17:38

24 A. It would represent any of those things. 13:17:38

25 Q. All right. Let's go to paragraph 62 of 13:17:40

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1 your declaration. 13:17:43

2 **A. Yes.** 13:17:52

3 Q. In paragraph 62, you have some discussion 13:17:53

4 of read lengths, and you state that Illumina 13:17:59

5 sequencing -- let me start that over. 13:18:02

6 In paragraph 62, you have some discussion 13:18:05

7 of read lengths, and you state that: "As of 13:18:08

8 July 2010, Illumina sequencing generated reads of 13:18:10

9 about 150 nucleotides in length." Do you see that? 13:18:13

10 **A. I do. I should note it's paired-in 150s,** 13:18:18

11 **if I understand it correctly.** 13:18:23

12 Q. Right. And the support that you cite for 13:18:24

13 that is an Illumina press release, right? 13:18:26

14 **A. Correct.** 13:18:28

15 Q. Was that Illumina press release that you 13:18:29

16 cited something that you found, or was that provided 13:18:32

17 to you? 13:18:34

18 **A. I suspect I was aware of it when it came** 13:18:36

19 **out. I play close attention to Illumina press** 13:18:41

20 **releases, whether -- I doubt that I brought it in** 13:18:44

21 **litigation.** 13:18:46

22 **But I was -- I'm nearly certain I was aware** 13:18:48

23 **of it. Whether or not I -- certainly aware of the** 13:18:50

24 **consequences of it. Whether or not I could trace it** 13:18:54

25 **back to that exact press release, I don't know.** 13:18:56

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1 Q. And you don't cite any studies or published 13:18:59
2 papers from 2010 demonstrating that Illumina 13:19:04
3 sequencing could actually generate reads of about 13:19:08
4 150 nucleotides, true? 13:19:11

5 A. I think the reason for that is very simple. 13:19:13
6 The publication history for papers lags commercial 13:19:16
7 availability of technology by between six months and 13:19:20
8 six years, depending on the application. So the 13:19:23
9 quickest one would expect to see a paper with that 13:19:28
10 would be, say, six months later. 13:19:32

11 Q. And you know in that Illumina press release 13:19:33
12 you cited it itself didn't refer to any studies or 13:19:36
13 any other publications that actually demonstrated 13:19:39
14 that Illumina sequencing could achieve reads of 150 13:19:43
15 nucleotides, true? 13:19:47

16 A. I would be very surprised if I had not 13:19:49
17 ordered -- or colleagues had not started using those 13:19:52
18 reagents and reporting them in consortium meetings 13:19:57
19 and conversations at that -- within months or weeks 13:20:01
20 of that happening. 13:20:06

21 The Broad Institute probably had access to 13:20:06
22 that ahead of time, and I had probably seen data 13:20:10
23 from Cancer Genome Atlas with those read lengths 13:20:12
24 prior to commercial launch or very close to 13:20:18
25 commercial launch. Those sequences and 13:20:20

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1 **presentations and others, I could probably find** 13:20:23
2 **evidence for.** 13:20:25

3 Q. Did you try to do that when you were 13:20:26
4 forming your opinions? 13:20:28

5 A. **No. I didn't think it was necessary. I** 13:20:29
6 **was -- I have the declaration -- I have the press** 13:20:31
7 **release from Illumina describing its technology.** 13:20:32
8 **I'm intimately familiar with its availability and** 13:20:36
9 **routinely utilize -- you know, companies, when they** 13:20:39
10 **make things commercially available, deliver them, in** 13:20:42
11 **my experience, like in this situation.** 13:20:46

12 Q. When you were forming your opinions in this 13:20:48
13 case, did you try to go find any reports or 13:21:00
14 consortium meetings or anything from the Broad 13:21:03
15 Institute from 2010 that actually demonstrated 13:21:05
16 Illumina sequencing achieving read lengths of 150 13:21:08
17 nucleotides? 13:21:14

18 A. **No, I did not.** 13:21:17

19 Q. Let's go to paragraph 171 in your 13:21:17
20 declaration that you have in front of you, and 13:21:22
21 that's the declaration in the 964 IPR. 13:21:23

22 A. **Yes, I have paragraph 171.** 13:21:26

23 Q. Here you provide your opinion that the read 13:21:35
24 lengths for Illumina sequencers in Gloor would have 13:21:38
25 been long enough to form dual indexing methods 13:21:41

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1 disclosed in Parameswaran, true? 13:21:43

2 **A. Yes, I state that.** 13:21:45

3 Q. And then there you cite back to that same 13:21:46

4 press release about 150-base-pair read lengths, 13:21:49

5 right? 13:21:54

6 **A. Yes.** 13:21:54

7 Q. And then you calculate the read lengths 13:23:48

8 that would have been required for sequencing each 13:23:51

9 template nucleic acid in Parameswaran, right? 13:23:53

10 **A. Yes.** 13:23:56

11 Q. And you calculate there the length of the 13:23:56

12 barcodes, the cloning linkers, and a small RNA-Seq 13:23:59

13 insert, true? 13:24:04

14 **A. Yes.** 13:24:05

15 Q. And you say in your footnote that: 13:24:05

16 "Adapter sequences are not included within the total 13:24:07

17 read length," true? 13:24:11

18 **A. Correct.** 13:24:12

19 Q. Can you explain to me why the adapter 13:24:13

20 sequences are not included in your calculation of 13:24:15

21 the read length that's needed for Parameswaran's 13:24:20

22 template nucleic acid? 13:24:23

23 **A. The things that are necessary for** 13:24:25

24 **sequencing to gain all the information are the** 13:24:26

25 **components described there: the barcodes, the** 13:24:33

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1 cloning linkers, and the RNA insert itself. 13:24:35

2 So 10 times 2 plus 16 or 17 times 2 plus 19 13:24:40

3 to 27. The additional information of sequencing the 13:24:44

4 adapter is unimportant. It actually creates 13:24:48

5 problems on Illumina sequencers to sequence 13:24:54

6 adapters, and there's a whole process for adapter 13:24:57

7 trimming. 13:25:00

8 Q. And in Parameswaran, you understand that 13:25:00

9 they sequenced the adapters, true? 13:25:03

10 A. I believe they sequenced the cloning 13:25:06

11 linkers. Which adapters did they sequence? If you 13:25:10

12 hand me Parameswaran, I'll look. 13:25:15

13 Q. I think you have it in front of you. 13:25:17

14 A. In looking at the design of Figure 1, I see 13:25:36

15 no reason to sequence either the -- either the 13:25:39

16 forward-sequencing or reverse-sequencing adapter. 13:25:42

17 Q. But you understand that what Parameswaran 13:25:45

18 is showing you that's Figure 1 is that it did 13:25:47

19 sequence those adapters, true? 13:25:50

20 A. Sorry. I'm looking for the methods. I 13:26:35

21 don't believe that's true. I'd have to work it out 13:27:04

22 carefully, but I don't believe -- I don't believe 13:27:14

23 that the forwarded and reversed -- the forward 13:27:15

24 adapter would be sequenced. 13:27:16

25 You might sequence the reverse adapter 13:27:17

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1 going the other direction and vice versa, but I 13:27:19
2 don't think they -- I don't think you get the 13:27:22
3 sequence of the entire insert -- entire fragment. 13:27:24

4 Q. You think they might have sequenced one 13:27:28
5 adapter in each read but not both? 13:27:30

6 A. Yes. I think that given the lengths of the 13:27:33
7 sequencing capabilities, that they might have -- 13:27:36
8 they might have -- they would likely have sequenced 13:27:39
9 on through -- in Figure 1, F code -- F barcode, F 13:27:41
10 cloning linker, small insert, R cloning linker, R 13:27:46
11 barcode, and then into the RC adapter when it was 13:27:51
12 going in the forward mode -- and the reverse mode, 13:27:55
13 the other way. 13:27:57

14 Q. In each of the forward adapter and the 13:27:58
15 reverse adapter in Parameswaran, those were each 19 13:28:01
16 nucleotides long, true? 13:28:05

17 A. So -- yes. Okay. So the F adapter is 13:28:12
18 19 -- 19. The forward sequence primer is 15, so 13:28:21
19 they would have collected four nucleotides of the F 13:28:25
20 adapter sequence, the way it's configured here. 13:28:29

21 And in the reverse direction, they would 13:28:31
22 have captured four nucleotide of the reverse, right? 13:28:33
23 So -- but formerly, those bases contained very 13:28:37
24 little or essentially zero information. And you 13:28:42
25 would have gotten rid of -- you would have ignored 13:28:44

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1 **them.** 13:28:46

2 Q. And in addition to those four nucleotides, 13:28:46
3 they also would have read the adapter on the other 13:28:50
4 end, right? 13:28:53

5 **A. Yes, and ignored it.** 13:28:54

6 Q. So in each read, the sequencing in 13:28:56
7 Parameswaran read: "Four nucleotides from one 13:28:59
8 adapter and 19 nucleotides from the other adapter," 13:29:02
9 true? 13:29:06

10 **A. It may have gone through completely. I** 13:29:06
11 **mean, they have -- the Roche method is not** 13:29:10
12 **deterministic, and I don't think they always** 13:29:12
13 **necessarily sequence to the end.** 13:29:15

14 Q. What do you mean by "not deterministic"? 13:29:18

15 **A. Because -- so in an Illumina sequencing,** 13:29:23
16 **each round of sequencing produces one base of** 13:29:28
17 **information. And if you sequence 75 cycles, you** 13:29:30
18 **will get 75 bases of information.** 13:29:35

19 **With Roche, because you flow the** 13:29:38
20 **nucleotides over the flow cell in order of some** 13:29:41
21 **prescribed order, the sequence you get out is** 13:29:45
22 **longer -- usually longer than one base for every** 13:29:50
23 **four bases you put over them.** 13:29:55

24 **So because all of the sequences in the F** 13:29:57
25 **barcode and R barcode as well as the insert are** 13:30:05

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1 different from one another, there is a possibility 13:30:10
2 that the total read length will vary, because when 13:30:14
3 you flow over the A, if the next base is a G but the 13:30:18
4 next base you flow over is a C, you won't get any 13:30:23
5 information for that molecule. 13:30:27

6 But for the ones where it was a G, you'll 13:30:30
7 get information. And so it's normally reported as 13:30:32
8 something like the number of bases for -- per 13:30:35
9 four-base cycle that you perform that you get 13:30:40
10 sequence. 13:30:43

11 And typically my recollection is that for 13:30:43
12 typical sequences on this platform, you'd get 13:30:48
13 somewhere between 1.9 to 2.2 bases per 4-base cycle. 13:30:51
14 You can do slightly better than that with 13:30:58
15 homopolymer runs, given the reduced accuracy. 13:31:03

16 But if you get three As, you get three As. 13:31:04
17 So you can get three bases per cycle or even more. 13:31:07
18 So that leads to read lengths that are not the same 13:31:12
19 in all situations, whereas Illumina read lengths are 13:31:15
20 essentially deterministic. 13:31:18

21 If you sequence 75 bases, you will get 75 13:31:19
22 bases of sequence. And so given the architecture of 13:31:24
23 Parameswaran, it is possible that some of their 13:31:30
24 molecules sequenced all the way to the end, past the 13:31:32
25 right adapter or left -- reverse adapter/forward 13:31:35

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1 **adapter, and some of them only made it through the** 13:31:40
2 **barcode.** 13:31:42

3 Q. Okay. When you were forming your opinions 13:31:43
4 for your combination of Parameswaran and Gloor, did 13:31:49
5 you make a determination of what minimum read length 13:31:55
6 would be needed for that combination to work? 13:31:58

7 A. Well, I will point out that the 13:32:03
8 **high-quality paired-end reads of 150 bases is 300** 13:32:05
9 **base pairs of sequence, which is much, much longer** 13:32:10
10 **than the products in Parameswaran. So I really -- I** 13:32:12
11 **didn't really have to.** 13:32:16

12 Q. I think that was a no, but let me ask 13:32:18
13 cleanly: When you were forming your opinions for 13:32:24
14 your combination of Parameswaran and Gloor, did you 13:32:28
15 make any determination of what minimum read length 13:32:30
16 would be needed for that combination to work? 13:32:33

17 A. It was -- it was a trivial yes because I 13:32:36
18 **looked at the length of Parameswaran, and I looked** 13:32:40
19 **at paired-end 150, which is 300. And I noted that** 13:32:44
20 **300 was much, much greater than the length of** 13:32:48
21 **Parameswaran.** 13:32:51

22 Q. And the 150 number, you got from the 13:32:52
23 Illumina press release, right? 13:33:04

24 A. Correct. 13:33:05

25 Q. Did you review that press release to see 13:33:06

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1 what it said about the read length people were 13:33:14

2 actually getting using the Illumina product? 13:33:18

3 **A. Even if -- even if people were not getting 13:33:20**

4 **150, which would be odd because, as I said, it's 13:33:23**

5 **deterministic -- it's 150 cycles -- I will also 13:33:26**

6 **point out that Gloor itself notes 76 and 100. 13:33:31**

7 **76 doubled is 152. 100 doubled is 200, 13:33:35**

8 **which, again, is longer than the total lengths of 13:33:42**

9 **the molecules in Parameswaran. So I was not 13:33:46**

10 **concerned about this, and it was not something I 13:33:48**

11 **spent more than a small amount of time on because, 13:33:53**

12 **to me, it was obvious. 13:33:55**

13 **Q. And Gloor also required overlap in its 13:33:56**

14 **paired-end reads of 10 to 15 nucleotides, true? 13:33:59**

15 **A. The Gloor methodology is completely 13:34:03**

16 **different. Are we switching to Gloor? 13:34:06**

17 **Q. I'm asking the question about Gloor. So 13:34:08**

18 **you mentioned Gloor's read length. My question is 13:34:10**

19 **Gloor also required what it calls "perfect overlap" 13:34:14**

20 **in its paired-end reads, and that overlap had to be 13:34:17**

21 **10 to 15 nucleotides. You know that, right? 13:34:22**

22 **A. Yes. Gloor has a good reason for doing 13:34:25**

23 **this. 13:34:28**

24 **Q. Okay. 13:34:28**

25 **A. But it's a completely different application 13:34:31**

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1 **than the one in Parameswaran. If we're porting** 13:34:33

2 **Parameswaran to Illumina using Gloor as a guide, the** 13:34:36

3 **overlap criteria of Gloor is irrelevant.** 13:34:39

4 Q. So in your combination of Parameswaran and 13:34:42

5 Gloor, does it use Gloor's overlap criteria? 13:34:45

6 A. **It doesn't have to, no.** 13:34:49

7 Q. Why is Gloor's overlap criteria irrelevant 13:34:50

8 to your combination of Parameswaran and Gloor? 13:34:53

9 A. **The overlap criteria in Gloor are about** 13:34:58

10 **detecting chimeras using the insert sequences** 13:35:02

11 **themselves, which is a different problem than is in** 13:35:07

12 **Parameswaran.** 13:35:12

13 Q. Look at Gloor. I placed it in front of 13:35:25

14 you. 13:35:29

15 A. **Yeah.** 13:35:29

16 **(Reference to previously-marked Exhibit 1005.)** 13:35:29

17 Q. It's -- it's been marked as Exhibit 1005. 13:35:29

18 Do you have that in front of you? 13:35:40

19 A. **I do.** 13:35:41

20 Q. A couple general concepts. First, you are 13:35:41

21 familiar with combinatorial dual indexing, true? 13:35:48

22 A. **Yes.** 13:35:51

23 Q. What's the difference between combinatorial 13:35:52

24 dual indexing and unique dual indexing, in your 13:35:56

25 view? 13:35:58

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1 **A. Combinatorial dual indexing would allow** 13:35:58
2 **reuse of an index or barcode in more than one** 13:36:05
3 **sample.** 13:36:07

4 **Q. And generally, combinatorial dual indexing** 13:36:08
5 **can be lower cost than unique dual indexing, true?** 13:36:13

6 **A. I'm not sure I'd agree with that. It's a** 13:36:27
7 **little more complicated than that.** 13:36:29

8 **Q. Would you agree that the number of distinct** 13:36:30
9 **primers that you have to design and create can** 13:36:33
10 **affect the cost of performing a sequencing reaction?** 13:36:44

11 **A. Yes. But the reason I'm balking at the** 13:36:47
12 **question is when one is engaged in relatively** 13:36:49
13 **high-throughput activities, the actual cost of the** 13:36:52
14 **massive primers becomes dominating.** 13:36:57

15 **And when one uses up the primer, one has to** 13:37:02
16 **use more. So they're -- the use -- in sequencing** 13:37:08
17 **technologies and cloning technologies, it was often** 13:37:12
18 **common that the minimum amount of primer you could** 13:37:15
19 **order from a company was a million times more than** 13:37:25
20 **you ever needed.** 13:37:28

21 **And as a consequence, the number of primers** 13:37:29
22 **you needed to buy was often wasteful because if you** 13:37:31
23 **wanted 50 primers, you had 50 million times more of** 13:37:35
24 **the stuff than you could ever use.** 13:37:40

25 **But by the time we get to Illumina** 13:37:42

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1 sequencing, the mass input necessary for cloning and 13:37:45
2 ligation very often in Illumina sequencing is no 13:37:49
3 longer bounded in quite the same way. 13:37:52

4 And it is possible that you do have -- you 13:37:56
5 are going to use up all your material. So, you 13:38:02
6 know, in many of the applications my lab has done, 13:38:05
7 we run out of a primer and have to reorder it. 13:38:09

8 And as a consequence, changing the primer 13:38:12
9 sequence at that point costs nothing because it's a 13:38:14
10 new -- you know, we're just ordering more primer, 13:38:16
11 and the costs are the same for more primer. 13:38:19

12 So it's not uniformly the case that more 13:38:22
13 primers cost more money. It's in -- when one are 13:38:25
14 doing PCR at small scale, that is true. But when 13:38:30
15 you get to full production mode, I don't agree with 13:38:34
16 you. 13:38:37

17 Q. Okay. So for a given experiment, let's 13:38:37
18 say, if you have 200 samples and you multiplex them 13:38:43
19 using combinatorial dual indexing, you could do that 13:38:50
20 using fewer primers than if you were to run those 13:38:55
21 same 200 samples with unique dual indexing, true? 13:38:59

22 A. That is true. 13:39:04

23 Q. Let's go to paragraph 149 in your 964 13:39:05
24 declaration. 13:39:12

25 A. Paragraph 149, yes. 13:39:19

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1 Q. There you reference sequence tag and primer 13:39:24
2 requirements from Gloor, right? 13:39:30

3 A. Yes. 13:39:32

4 Q. What does that refer to? What are the 13:39:33
5 sequence tag and primer requirements in Gloor? 13:39:36

6 A. Table 2 in Gloor on page six lists the 13:39:50
7 sequence tags, and then the primer sequences are 13:39:55
8 just denoted as L and R on this table. But these 13:40:01
9 are the various different sequences -- sequence tags 13:40:05
10 and primers present. 13:40:09

11 Q. In the part of Gloor that you quote in your 13:40:11
12 paragraph 149, it talks about read pairs that failed 13:40:16
13 to pass the sequence tag and primer requirements. 13:40:22
14 Do you see that? 13:40:25

15 A. I do. 13:40:26

16 Q. What does it mean for a read to fail to 13:40:26
17 pass the sequence tag and primer requirements in 13:40:30
18 Gloor? 13:40:33

19 A. Let me get that for you. So on page seven 13:40:33
20 of Gloor, there's a discussion of the processing of 13:41:48
21 the -- of the reads, and that continues on to page 13:41:51
22 eight, in which -- which gives them the output 13:41:58
23 sequences for each library -- or each sample. 13:42:04

24 Q. Let's look maybe at Gloor page 22 because I 13:42:07
25 think, according to your citation, that's the part 13:42:26

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1 that you were quoting in your declaration? 13:42:28

2 A. Yes, it is. Sorry. 13:42:30

3 Q. And it looks like at the bottom, maybe 13:43:20

4 about four lines up, it refers to "read pairs that 13:43:23

5 fail to overlap or that failed to pass the sequence 13:43:26

6 tag and primer requirements." Do you see that? 13:43:29

7 A. Yes. 13:43:31

8 Q. And that's the part that you quote, right? 13:43:32

9 A. It is, yes. 13:43:35

10 Q. So what does Gloor mean when it talks about 13:43:35

11 "read pairs that fail to pass the sequence tag and 13:43:39

12 primer requirements"? 13:43:42

13 A. Well, that's why I was on page six rather 13:43:43

14 than the discussion. The discussion summarizes it, 13:43:46

15 but the methods and the results would describe it. 13:43:49

16 So it would have been back there on page six, 13:43:54

17 roughly. 13:43:56

18 Q. Okay. Where does it describe on page six 13:43:57

19 what it means for a read pair to fail to pass the 13:43:59

20 sequence tag and the primer requirements? 13:44:05

21 A. So I guess I might even start a little 13:44:11

22 earlier, on page -- yeah. On page six and seven, 13:44:15

23 those two paragraphs describe the processing of the 13:44:17

24 data. 13:44:21

25 So starting at the very last line of six: 13:44:24

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1 "We received 18 million-something reads 76 13:44:27
2 nucleotides long from each end" -- so paired-end 13:44:32
3 152s. There were some number of reads containing 13:44:37
4 one or more low-quality positions. 13:44:40

5 And then they filter based on having Ns in 13:44:43
6 the sequence from extremely low quality, and then 13:44:47
7 they start trimming those things back to assemble 13:44:51
8 them into various strategies. So that's covered in 13:44:54
9 that section there. 13:44:57

10 Q. What part of that is showing a read length 13:44:57
11 that fails to pass sequence tag and primer 13:45:01
12 requirements? I'm not following where that is. 13:45:05

13 A. I think it's -- it's also a little above 13:45:36
14 that on page six. All programs to extract sequence 13:45:39
15 reads and index individual sequence units were 13:45:43
16 developed in house. Like, it's bridged in there. 13:45:45
17 It's very cryptic, I agree. 13:45:47

18 Q. Let me -- let me step back. What are the 13:45:49
19 sequence tag and primer requirements in Gloor? 13:45:56

20 A. So if you go to the middle of the second -- 13:46:05
21 second paragraph on page seven, we found that on -- 13:46:08
22 12 million sequences contain two valid sequence tags 13:46:12
23 and both primer sequences allowing up to three 13:46:17
24 mismatches per primer. So it's there in that 13:46:21
25 sentence. 13:46:24

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1 Q. Okay. So the sequence and primer 13:46:24
2 requirements in Gloor say that a read has to have 13:46:31
3 two valid sequence tags. And it has to have two 13:46:35
4 primer sequences, but there can be up to three 13:46:39
5 mismatches in each primer, true? 13:46:43

6 A. Correct. 13:46:46

7 Q. Okay. And you understand those to be the 13:46:46
8 sequence tag and primer requirements that Gloor 13:46:54
9 talks about in the part that you quoted in your 13:46:58
10 declaration, true? 13:47:00

11 A. Yeah. It's possible there's additional 13:47:01
12 criteria in here, but I believe it's covered here. 13:47:02

13 Q. Okay. So if a given read has two valid 13:47:04
14 sequence tags, it's going to pass the sequence tag 13:47:12
15 requirement, right? 13:47:14

16 A. Yes, I believe that's correct. 13:47:16

17 Q. And then if that read has two primer 13:47:16
18 sequences, allowing up to three mismatches per 13:47:19
19 primer, it's going to pass the primer requirements, 13:47:22
20 right? 13:47:26

21 A. I believe that's correct. 13:47:26

22 Q. Now, the valid sequence tags, those refer 13:47:27
23 to tags that were actually added to the nucleic acid 13:47:36
24 at the beginning, before PCR. And those are shown 13:47:41
25 in Table 2, right? 13:47:43

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1 A. Can you repeat your question. 13:47:55

2 Q. Yeah. Maybe I can ask it better. When it 13:47:56

```
3  says "valid sequence tags," "valid" means it matches 13:47:59
```

4 one of the sequence tags that was actually used in 13:48:05

5 the experiment. And those tags are shown in Table 13:48:08

6 2, correct? 13:48:10

⁷ A. Yes. 13:48:10

8 Q. Now, if you have a given nucleic acid that 13:48:13

9 has a left tag and a right tag on it and, during PCR 13:48:22

10 in Gloor, one of those tags switched with a 13:48:26

11 different nucleic acid, formed a chimeric molecule, 13:48:31

12 as long as that tag that jumped onto the nucleic 13:48:34

```
13 acid is valid, that read is still going to pass 13:48:37
```

```
14      Gloor's sequence tag requirement, true?                                13:48:41
```

A. That is correct, yes. 13:48:44

16 0. We talked about the concept of index 13:48:45

17 hopping earlier. Gloor's sequence tag requirements 13:49:13

18 were unable to detect index hops because in an index 13:49:20

19 hop, you still have two valid sequence tags, true? 13:49:27

20 MR. RAICH: Object to foundation. 13:49:31

21 THE WITNESS: I think that Gloor is not 13:49:34

22 quite completely saturated. I believe they have 13:49:37

23 more barcode pairs than samples. So there are -- 13:49:40

24 there are invalid barcode pairs, technically, I 13:49:46

25 believe, in Gloor that could detect a sequence -- an 13:49:49

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1 index sequence. 13:49:54

2 MR. MATTY: 13:49:54

3 Q. Right. And in the index hopping -- let me 13:49:54
4 start that over. 13:49:59

5 In your understanding of index hopping, 13:49:59
6 valid sequences -- let me try that again. 13:50:06

7 In your understanding of index hopping, 13:50:12
8 sample tags can jump from one nucleic acid to the 13:50:18
9 other while still being a valid sample tag, true? 13:50:21

10 A. Yes, it is possible in -- it is possible 13:50:31
11 for both tags to switch in index hopping. 13:50:36

12 Q. And after the index hop, they would still 13:50:39
13 be valid sequence tags because they match the tags 13:50:42
14 that were added to nucleic acid at the beginning, 13:50:45
15 right? 13:50:48

16 A. Yes. Formally speaking, if you had Tag A 13:50:48
17 and Tag -- A1 and A2 and B1 and B2, it is formally 13:50:50
18 possible to switch from A1 to A2 to B1/B2. 13:50:56

19 Q. Let's go to the abstract of Gloor. 13:51:00

20 A. Yes. 13:51:12

21 Q. Gloor notes in the third sentence there 13:51:22
22 that: 13:51:27

23 "Combinatorial sequence tagging can 13:51:27
24 be used to examine hundreds of samples 13:51:29
25 with far fewer primers than is required 13:51:32

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1 when sequence tags are incorporated at 13:51:35

2 only a single end." Do you see that? 13:51:37

3 **A. I do.** 13:51:39

4 **Q. Do you agree with that sentence?** 13:51:39

5 **A. Yes. And I should note, as I brought up** 13:51:45

6 **earlier, there are situations in which that is** 13:51:47

7 **economically favorable, and there are situations** 13:51:50

8 **in -- economically neutral.** 13:51:52

9 **Q. Are there situations in which it's** 13:51:55
10 **economically unfavorable?** 13:51:58

11 **A. There are situations in which it is** 13:52:05
12 **economically unfavorable because of potential** 13:52:08
13 **contamination. So there is a lengthy literature and** 13:52:17
14 **field of work. For example, my own work with** 13:52:25
15 **Dr. Faham at paired allele -- published in a series**
16 **of papers that I can point you to.** 13:52:33

17 **Making sure that you don't contaminate** 13:52:35
18 **things is really hard at scale. And one way to** 13:52:37
19 **avoid it is by altering the sequences from time to** 13:52:40
20 **time. So there are -- there are times when changing** 13:52:48
21 **sequences is advantageous.** 13:52:51

22 **Q. How can you contaminate sequence tags?** 13:52:54
23 **Like, how does that happen?** 13:52:58

24 **A. It can happen a lot of ways. Parameswaran,** 13:52:58
25 **for example, describes, like, you know, making** 13:53:02

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1 pipetting errors where small amounts of splashing 13:53:06

2 might happen or carryover in aerosols. 13:53:08

3 Once one has PCR products with all of the 13:53:11

4 sequences attached to them, it becomes a serious 13:53:15

5 problem. Especially, like, in the Illumina 13:53:19

6 platform, where you have P5, P7, everything has P5, 13:53:20

7 P7. Everything will amplify and carry through. 13:53:26

8 And so there is pretty good rationale from 13:53:28

9 time to time to incorporate new sequences that 13:53:34

10 should not exist previously. So there are -- there 13:53:37

11 can be real advantages to not maintaining sequences 13:53:38

12 uniformly forever. 13:53:44

13 Q. And the contamination that you are 13:53:44

14 describing is for things like pipette errors, and 13:53:47

15 that -- that's contamination that happens prior to 13:53:50

16 amplification in whatever sequencing method you are 13:53:56

17 using, true? 13:53:59

18 A. That would be where it would be most 13:54:01

19 problematic, right? Because if you have 13:54:03

20 contamination and no further rounds of 13:54:06

21 amplification, then you won't get a big explosion. 13:54:15

22 So the parts where it's really bad is where 13:54:19

23 you have a contamination of a sequence into 13:54:21

24 something that doesn't yet have the P5/P7 sequences 13:54:23

25 on it, for example. 13:54:26

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1 And if that's a moderate- or low-efficiency 13:54:27
2 step and you have even a small amount of 13:54:30
3 contamination, it can carry through and explode and 13:54:32
4 take over. 13:54:36

5 So that would be an uncommon use case, 13:54:37
6 but -- but, you know, in our work with paired 13:54:42
7 allele, for example, we routinely saw that, like, 13:54:47
8 the -- that you really have to pay attention to 13:54:50
9 these things. 13:54:51

10 Q. All right. Now, you have reviewed a lot of 13:56:12
11 patents in your work in this case and in other 13:56:16
12 patent disputes, true? 13:56:19

13 A. I'll have you define "a lot." 13:56:21

14 Q. Would you consider the number of patents 13:56:24
15 you have reviewed in your work to be a lot? 13:56:26

16 A. Not compared to the number you have 13:56:28
17 reviewed. 13:56:31

18 Q. Fair. You have a number of patents 13:56:31
19 yourself, true? 13:56:33

20 A. I think I have one. 13:56:33

21 Q. Okay. Are you familiar with the concept of 13:56:34
22 incorporation by reference in a patent? 13:56:37

23 A. Yes. I don't know if I can give a legal 13:56:40
24 definition. But the idea of it, I understand. 13:56:42

25 Q. And generally, regularly, patents will 13:56:44

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1 incorporate disclosures from prior publications that 13:56:46

2 they build upon, true? 13:56:50

3 MR. RAICH: Object to scope. 13:56:51

4 THE WITNESS: That's my understanding, yes. 13:56:53

5 MR. MATTY: 13:56:54

6 Q. Do you know if any of your own patents use 13:56:56

7 incorporation by reference? 13:56:59

8 A. It's a good question. I -- I'm not sure I 13:57:01

9 have read my own patent very closely, so it may very 13:57:03

10 well have. I did not write it, as you well know. 13:57:06

11 Q. When you read the Molecular Loop patents in 13:57:09

12 this case, you recognized that they referred to 13:57:12

13 existing scientific and patent publications in 13:57:15

14 discussing various general concepts related to 13:57:20

15 sequencing, true? 13:57:22

16 A. Yes. Looking at the face page, for 13:57:24

17 example, there are -- and it says "Continued" -- 13:57:27

18 there are whole lists of papers that I understand -- 13:57:30

19 I believe are either referenced or -- but they're -- 13:57:32

20 I don't think that's quite the same as included by 13:57:36

21 reference. 13:57:38

22 Q. In the description, the specification 13:57:39

23 itself, you also recognize that the Molecular Loop 13:57:42

24 patents refer to prior existing scientific and 13:57:45

25 patent publications in discussing various general 13:57:49

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1 concepts related to sequencing, true? 13:57:52

2 A. Yes. 13:57:54

3 Q. Let's go back to Parameswaran. 13:57:54

4 A. Yes. 13:58:08

5 Q. Parameswaran's title says that it's a 13:58:08

6 "pyrosequencing-tailored nucleotide barcode design." 13:58:11

7 Do you see that? 13:58:17

8 A. I do. 13:58:18

9 Q. What does "pyrosequencing-tailored" mean? 13:58:18

10 A. At the time of this work, the 454 was 13:58:21

11 the -- arguably the best multi- -- you know, 13:58:28

12 high-throughput sequencer available in terms of, 13:58:33

13 say, megabases of sequence per day or something -- 13:58:37

14 some criteria like that -- and would have provided 13:58:43

15 the lowest per-base cost. 13:58:45

16 And so a person of ordinary skill in the 13:58:48

17 art, when looking at something like a capillary 13:58:51

18 sequencer and then thinking about using a cheaper 13:58:54

19 higher-throughput instrument would say, "What can I 13:58:58

20 do with this instrument? What do I have to change 13:59:03

21 from a" -- "from a capillary sequencer? What" -- 13:59:05

22 you know, "What am I going to get out as an 13:59:09

23 advantage?" 13:59:12

24 And Parameswaran then took that statement 13:59:12

25 and executed a plan to come up with a way to use the 13:59:18

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1 pyrosequencer to achieve what they wanted. 13:59:23

2 Q. And in what way was Parameswaran's 13:59:25

3 nucleotide barcode design tailored for 13:59:36

4 pyrosequencing, in your view? 13:59:43

5 A. If you look at the list of barcodes -- I 13:59:44

6 have not gone into it, and it's not deeply discussed 13:59:47

7 in the -- in the methods about how they chose these 13:59:50

8 barcodes in the specific regime that we discussed 13:59:55

9 earlier, the HIJK regime. 13:59:58

10 But the principles under which 454 work -- 14:00:02

11 if these barcodes, for example, had -- had four or 14:00:07

12 five bases in a row, that would have been very bad 14:00:10

13 on a 454 instrument. They would have had a -- there 14:00:15

14 would have been a lot of indel errors in reading 14:00:18

15 that barcode. 14:00:21

16 My assumption is that they engineered these 14:00:22

17 barcodes to be ones that sequence very well on 454. 14:00:27

18 Having looked at lots of barcodes, there's nothing 14:00:34

19 about these barcodes that makes me think they 14:00:37

20 wouldn't sequence very well on some other platforms 14:00:41

21 as well. 14:00:44

22 Q. Okay. If there were a barcode that did 14:00:44

23 have four or five bases in a row that are the same 14:00:49

24 nucleotide, that could be a problem on 14:00:53

25 pyrosequencing, true? 14:00:56

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1 A. It's an interesting question. I was 14:00:57
2 thinking about it over the last couple days. One of 14:01:00
3 the problems with 454 is skipped bases, and I 14:01:04
4 haven't done a detailed examination of what would 14:01:14
5 happen. 14:01:17

6 But my impression is that one could 14:01:20
7 actually utilize some number of bases in 14:01:26
8 pyrosequencing -- say three -- to actually improve 14:01:30
9 the detection of that base. But you would just call 14:01:32
10 it an A instead of three As, right? So you would 14:01:35
11 improve your sensitivity. 14:01:39

12 So I think there are interesting behaviors 14:01:40
13 of the 454 that, in long sequence runs, could have 14:01:42
14 been utilized in even more sophisticated ways than 14:01:47
15 is present here to achieve really nice barcoding. 14:01:52
16 But I haven't tested those myself, and they 14:01:55
17 explicitly avoided such scenarios. 14:01:57

18 Q. Okay. And for Illumina sequencing at the 14:02:00
19 time of the invention of the Molecular Loop patents, 14:02:04
20 a person of ordinary skill would have known that a 14:02:09
21 barcode having a run of four or five bases in a row 14:02:12
22 would not create the same problem on Illumina 14:02:17
23 sequencing, true? 14:02:21

24 A. That's not quite correct. Illumina 14:02:22
25 sequencers were known to have problems sequencing 14:02:26

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1 several Gs in a row. I believe it's either three or 14:02:32
2 four. I believe it's a quad-G structure that 14:02:35
3 creates issues. 14:02:39

4 So there was a general bias around such 14:02:42
5 things, and there were a series of technical papers 14:02:44
6 on Illumina sequencing on how it actually functions. 14:02:49
7 And there is some disadvantage in having strings of 14:02:54
8 the same base over and over because Illumina 14:03:00
9 sequencers work by having all of the molecules in 14:03:03
10 the same base, because they do one base at a time. 14:03:10

11 And when you have lots of the same base all 14:03:13
12 in the same row, you have molecules that are one 14:03:16
13 base behind. And you can get some weird effects 14:03:20
14 when you do the deconvolution steps. So that's a 14:03:25
15 known problem. 14:03:29

16 Additionally, Illumina sequencers, 14:03:30
17 particularly these early sequencers, had a lot of 14:03:32
18 trouble when there wasn't very much sequence 14:03:36
19 diversity in the sequence. And so they're -- you 14:03:44
20 might not want to create lots of strings of the same 14:03:47
21 thing. 14:03:52

22 I think that's less of a problem in this 14:03:53
23 case. But in general, you know, I think the idea of 14:03:56
24 homopolymers -- they add relatively little 14:04:03
25 information that -- you know, if you just use 14:04:07

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1 homopolymers, you have to use a lot of sequence to 14:04:11
2 encode information. 14:04:14

3 So you -- rich sequences are more 14:04:15
4 information dense than homopolymer sequences in 14:04:19
5 general. But that being said, Illumina is certainly 14:04:23
6 more robust against homopolymers than -- than the 14:04:26
7 454 was. 14:04:32

8 Q. And you would agree that that was true at 14:04:32
9 the time of the invention: Illumina sequencing was 14:04:34
10 known to be more robust for sequencing homopolymers 14:04:38
11 than pyrosequencing, true? 14:04:41

12 A. Yes. You would certainly never put a run 14:04:43
13 of four bases in a pyrosequencer and expect to get 14:04:45
14 really good barcode sequencing out. You could 14:04:48
15 probably expect to do that often in Illumina. But 14:04:51
16 if there was no reason to, you would probably avoid 14:04:56
17 it. 14:04:58

18 Q. Okay. Going back to the abstract of 14:04:59
19 Parameswaran -- it's in the abstract, but it's 14:05:05
20 throughout the reference. It talks about 14:05:11
21 forward/reverse barcode pairs. Are you familiar 14:05:13
22 with that? 14:05:17

23 A. Yes. 14:05:17

24 Q. What is a forward/reverse barcode -- 14:05:17
25 forward and reverse barcode pair? 14:05:19

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1 **A.** In this experiment, because they had 14:05:23
2 uniquely labeled each sample with a forward and a 14:05:27
3 reverse barcode, they, just looking at Table 2, only 14:05:31
4 expect to see AGCCTAAGCT with its reverse, 14:05:36
5 AGCTTAGGCT. So -- so these barcode pairs are 14:05:45
6 expected to always go together. 14:05:48

7 **Q.** Meaning in Parameswaran, for a given 14:05:51
8 forward barcode, there was one set reverse barcode 14:05:55
9 that was expected to be on the same read, true? 14:06:00

10 **A.** Correct. Or -- yeah. Yes, on the same 14:06:03
11 read. 14:06:07

12 **Q.** Do you see in the abstract, about halfway 14:06:07
13 through, there's a sentence that starts: "With 14:06:44
14 improved read lengths"? 14:06:47

15 **A.** Yes. 14:06:54

16 **Q.** And I'll just read it. Parameswaran says: 14:06:54
17 "With improved read lengths of 14:06:57
18 pyrosequencers, combinations of forward 14:07:01
19 and reverse barcodes may be used to 14:07:02
20 sequence from as many as N squared 14:07:04
21 independent libraries for each set of N 14:07:07
22 forward and N reverse barcodes for each 14:07:11
23 defined set of cloning linkers." 14:07:14

24 Do you see that? 14:07:17

25 **A.** I do. 14:07:17

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1 Q. That sentence in Parameswaran that talks 14:07:17
2 about N forward and N reverse barcodes being used 14:07:23
3 for N squared libraries, that's not referring to 14:07:27
4 unique dual indexing, true? 14:07:31

5 A. That's correct. 14:07:34

6 Q. That part of Parameswaran is referring to 14:07:34
7 what you would call nonunique dual indexing, true? 14:07:39

8 A. Correct. 14:07:42

9 Q. Did you consider in your analysis of 14:07:43
10 Parameswaran why their abstract was highlighting 14:07:46
11 that one could sequence more libraries using 14:07:51
12 nonunique dual indexing? 14:07:54

13 MR. RAICH: Objection to form. 14:07:56

14 THE WITNESS: Yeah. I felt it was pretty 14:07:57
15 obvious I did consider it. 14:08:00

16 MR. MATTY: 14:08:02

17 Q. What do you mean by "it's pretty obvious"? 14:08:05

18 A. Well, I understood why they talked about 14:08:07
19 it. 14:08:11

20 Q. And in your view, why were they talking 14:08:11
21 about it? 14:08:14

22 A. The Parameswaran paper was interested in 14:08:15
23 thinking about how they might move toward very large 14:08:19
24 numbers of samples and coming up with a scheme to 14:08:24
25 handle that. 14:08:29

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1 Q. And the scheme that they suggested could be 14:08:29

2 used was nonunique dual indexing, true? 14:08:32

3 A. Yes, I believe that's correct. 14:08:35

4 Q. Let's go to Figure 1 in Parameswaran. 14:08:43

5 A. Yes. 14:08:50

6 Q. In the primers that we looked at earlier in 14:08:50

7 Parameswaran, they show the primers including an 14:09:05

8 adapter, a barcode, and a cloning linker, right? 14:09:08

9 A. Yes. 14:09:12

10 Q. Can you explain for me: What is the 14:09:12

11 adapter? What does that do? 14:09:17

12 A. That should help it bind to the bead in the 14:09:21

13 454 platform. 14:09:26

14 Q. And in the combinations that you are 14:09:27

15 proposing of Parameswaran with Gloor or Bentley in 14:09:29

16 their Illumina sequencing, would adapters be used in 14:09:37

17 that combination? 14:09:40

18 A. You would switch out the platform adapters. 14:09:41

19 Q. And there would be adapters there; they 14:09:45

20 would just be Illumina-style adapters, true? 14:09:47

21 A. Yes. 14:09:50

22 Q. And then for the barcodes, in your words, 14:09:50

23 what are the forward and reverse barcodes that are 14:10:00

24 in the primers in Parameswaran? 14:10:02

25 A. Sorry. The barcodes? I don't -- it 14:10:08

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1 **seems self -- feels self-evident, but --** 14:10:12

2 Q. Fair enough. And I take it the barcodes 14:10:14

3 that are in Parameswaran -- those would also be 14:10:16

4 included in the combinations that you are proposing 14:10:18

5 with Gloor or Bentley's Illumina sequencing, true? 14:10:21

6 MR. RAICH: Object to the form. 14:10:26

7 THE WITNESS: In my opinion, a POSA could 14:10:28

8 adapt those barcodes as appropriate, knowing the 14:10:31

9 sequence -- sequencing behaviors of Illumina versus 14:10:36

10 454, and simplify them, perhaps. So my instinct 14:10:42

11 would be they would shorten them and get rid of the 14:10:48

12 homopolymer runs because they're not adding value in 14:10:52

13 the Illumina platform. 14:10:55

14 MR. MATTY: 14:10:58

15 Q. All right. The next thing in the primer is 14:10:59

16 the cloning linker. Do you see that? 14:11:01

17 A. Yes. 14:11:03

18 Q. What are the cloning linkers that are used 14:11:04

19 in Parameswaran? 14:11:08

20 A. What are the sequences? 14:11:08

21 Q. Just generally, what are they? What do 14:11:10

22 they do? 14:11:13

23 A. They facilitate cloning these very small 14:11:13

24 RNA inserts that they are interested in collecting. 14:11:17

25 Q. And how do they facilitate cloning? 14:11:20

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1 A. Sorry. I'm looking for the methods. So 14:11:30
2 it's discussed in page two, beginning at the bottom 14:12:05
3 of materials and methods: 14:12:08

4 "cdna libraries were constructed 14:12:11
5 (using slight modifications of standard 14:12:15
6 procedures) as follows: RNA three prime 14:12:17
7 termini were coupled to adenylated DNA 14:12:20
8 linkers as described, and subsequent 14:12:22
9 ligation of the second linker was 14:12:25
10 performed" -- 14:12:25

11 So it's carried on in that. And there's -- 14:12:25
12 there's a slight modification of standard procedure, 14:12:27
13 so it's presumably referencing some earlier fire 14:12:30
14 paper. 14:12:34

15 Q. And in the combinations that you are 14:12:34
16 proposing that apply Parameswaran's methods on the 14:12:36
17 Illumina sequencers in Gloor or Bentley, does your 14:12:39
18 combination include the cloning linkers that are in 14:12:43
19 Parameswaran's primer? 14:12:45

20 A. This would be up to a POSA to determine 14:12:48
21 what they're trying to sequence, and a POSA would 14:12:50
22 have to understand where they -- if they were 14:12:54
23 sequencing -- intending to sequence small RNAs, 14:12:56
24 absolutely you would do it, more or less, exactly 14:13:00
25 this way. 14:13:01

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1 If you were sequencing whole human genome 14:13:02
2 DNA, you would do it some other way entirely, and 14:13:08
3 you would use a Bentley-like method. Or if you were 14:13:10
4 targeting something like RNA -- ribosomal RNA 14:13:13
5 sequences in Gloor, you would use a primer-based 14:13:19
6 method, like in Gloor -- something like that. 14:13:22

7 Q. So in the Parameswaran-based combinations 14:13:27
8 that you have analyzed, those combinations may or 14:13:31
9 may not include cloning linkers depending on the 14:13:33
10 particular application that's being performed? Is 14:13:36
11 that what you are saying? 14:13:39

12 A. Correct. When one -- when a POA thinks 14:13:40
13 about utilizing a platform, like massively parallel 14:13:43
14 sequencing, they have to decide what their 14:13:48
15 experiment is. 14:13:51

16 Are they doing, in the case of 14:13:52
17 Parameswaran, multiplex, short-read RNA sequencing? 14:13:53
18 Are they doing long-read RNA sequencing? Are they 14:13:59
19 doing DNA sequencing of targeted regions or the 14:14:03
20 whole genome? 14:14:06

21 And given that, they would then assess 14:14:08
22 whether or not some particular protocol could or 14:14:10
23 could not work. Some protocols might not work, 14:14:13
24 given some set of criteria. 14:14:15

25 If -- if I wanted to sequence a million 14:14:17

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1 base pairs of DNA on a short-read sequencer, I'm 14:14:20
2 just going to have to stop and wait until that's 14:14:23
3 possible, because I can't do it. 14:14:27

4 Other protocols could be trivial. And so 14:14:29
5 it's entirely up to the POSA to evaluate 14:14:32
6 whether or not using some sequencing technology is 14:14:34
7 possible. But that's well -- that's what POSAs do. 14:14:37

8 Q. On page two of Parameswaran -- we saw this 14:14:39
9 earlier -- it has a blueprint for the barcodes you 14:15:07
10 used. Do you see that? 14:15:10

11 A. Yes. 14:15:12

12 Q. Do you have an understanding for how 14:15:13
13 Parameswaran came up with the particular blueprint 14:15:16
14 for their barcodes? 14:15:19

15 A. It's not very accurately described in the 14:15:23
16 methods on why it's done this way. I have some 14:15:26
17 suspicions. I'm not sure -- I have not opined as to 14:15:29
18 whether or not a POSA would have my understanding as 14:15:32
19 to why they are constructed the way they are because 14:15:34
20 I don't think there's necessarily a ton of teaching 14:15:37
21 in the manuscript. 14:15:39

22 But my -- my own opinion is that they have 14:15:40
23 a very specific structure that is actually quite 14:15:44
24 well suited to the way the 454 sequencer works. 14:15:47

25 Q. And over on page three, there's a Table 1 14:15:51

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1 that describes what Parameswaran calls "positional 14:15:57
2 nucleotide restrictions in the barcodes." Do you 14:16:01
3 see that? 14:16:05

4 A. Yes. 14:16:05

5 Q. Can you explain why those restrictions were 14:16:05
6 needed in Parameswaran? 14:16:07

7 A. I think it's a little strong to say that 14:16:09
8 they were needed. I think this lab is very 14:16:13
9 sophisticated and very thoughtful, and this is the 14:16:17
10 kind of paper that you can kind of tell they spent a 14:16:21
11 long time thinking about in very detailed ways. 14:16:26

12 So it's an interesting question of 14:16:32
13 whether or not any of these restrictions are 14:16:34
14 actually necessary or not or just "If we're 14:16:37
15 designing the system, let's do everything we can to 14:16:40
16 put as many safety guards on it as possible." 14:16:43

17 And I suspect it's rather the latter than 14:16:46
18 they tried a bunch of stuff and it all failed and 14:16:50
19 this is finally what worked. I think it's the other 14:16:52
20 way around. 14:16:55

21 They planned this very carefully, coming up 14:16:56
22 with every criteria they could think of that might 14:16:58
23 get in the way, and executed them all. That's my 14:17:01
24 instinct. 14:17:04

25 Q. Let me ask it the other way: Can you 14:17:04

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1 explain why the restrictions in Table 1 were 14:17:06
2 included in Parameswaran? 14:17:08

3 A. So, like, H not equal to G -- they have 14:17:16
4 this note: "The terminal nucleotide of the F 14:17:20
5 adapter and the R adapter is a guanosine. H cannot 14:17:23
6 be part of a dinucleotide and, hence, cannot be a 14:17:26
7 guanosine," right? 14:17:29

8 So -- so they did not want to make their 14:17:31
9 barcode dependent on reading the doublet -- you 14:17:34
10 know, the homopolymer doublet of GG, so they 14:17:37
11 engineered around that. 14:17:40

12 I think it would have been fine, right? I 14:17:41
13 think the 454 actually does a pretty good job of 14:17:43
14 reading doublets. And if they put in a G there, it 14:17:47
15 probably would have worked 98 percent as well as if 14:17:51
16 they didn't. So would it have worked? Yes. 14:17:54

17 Would it have worked quite as well? 14:17:56
18 Probably not. And that's what I'm talking about. A 14:17:59
19 very fine scale -- let's just be brutally, you know, 14:18:01
20 detailed as we can. I mean, that's what this paper 14:18:04
21 kind of reads to me. Like, they're engineering 14:18:08
22 something they think is going to work great. 14:18:10

23 Q. Let's go to page three of Parameswaran. 14:19:36
24 Might be where you already are. 14:19:41

25 A. Yeah. 14:19:42

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1 Q. There, Parameswaran describes its DNA 14:19:43
2 amplification and pooling methods, right? 14:19:52

3 A. Yes. 14:19:57

4 Q. And we talked about this earlier. 14:19:57
5 Parameswaran performed two different rounds of PCR, 14:19:59
6 true? 14:20:01

7 A. Yes. With a slight caveat, yes. 14:20:12

8 Q. What's the caveat? 14:20:15

9 A. The second round of amplification with 14:20:18
10 temperatures and cycle lengths identical to initial 14:20:20
11 but with variable number of total cycles -- so 14:20:23
12 technically, that second round is actually three 14:20:28
13 separate reactions. So they didn't -- they chose 14:20:30
14 one of those, which is a -- it's a picky detail. 14:20:36

15 Q. I understand. So just to make sure we're 14:20:38
16 on the same page, there was an initial round of 20 14:20:42
17 cycles of PCR in Parameswaran, right? 14:20:45

18 A. Yes. 14:20:47

19 Q. And then Parameswaran took -- what it says 14:20:47
20 is 1/25 of the PCR product from the first round, 14:20:53
21 right? 14:20:57

22 A. Yes. 14:20:57

23 Q. And then it performed -- what it says is a 14:20:57
24 second round of amplification, but it had a variable 14:21:03
25 number of cycles, right? 14:21:07

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1 **A. That's why I'm -- no. They all had six,** 14:21:09
2 **eight, or ten. And then they chose one of those to** 14:21:13
3 **go forward with. So they actually did three** 14:21:16
4 **separate reactions, as I read it.** 14:21:19

5 Q. Got it. So I'm going to see if I'm 14:21:21
6 following this. The DNA pool all goes through the 14:21:28
7 first round of 20 cycles of PCR, right? 14:21:32

8 **A. Correct.** 14:21:34

9 Q. And then Parameswaran took 1/25 of that 14:21:35
10 first PCR product and put it through a second round 14:21:41
11 with six cycles. Another 1/25 -- put that through a 14:21:44
12 second round of eight cycles and a third 1/25 and 14:21:49
13 put that through a second round of PCR with ten 14:21:58
14 cycles. That's your understanding? 14:22:00

15 **A. That is my understanding.** 14:22:01

16 Q. And then of those three different -- I'll 14:22:02
17 call them aliquots -- but three different components 14:22:05
18 that went through the second PCR, Parameswaran chose 14:22:08
19 one of them and went forward with the experiment 14:22:11
20 using that one? 14:22:14

21 **A. Correct.** 14:22:15

22 Q. Why did Parameswaran do its PCR in that 14:22:15
23 slightly complicated two-round motif? 14:22:23

24 **A. Again, I think these folks are very detail** 14:22:28
25 **oriented, and they wanted to as carefully control as** 14:22:32

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1 possible the exact amount of material that was going 14:22:38
2 into the sequencer for each one. 14:22:42

3 And so they didn't want tenfold differences 14:22:45
4 in amounts of DNA from each sample going onto the 14:22:52
5 sequencer. So they have been very fastidious about 14:22:54
6 how to do that. 14:22:58

7 And so, I mean, you know, it says: "An 14:22:59
8 analytical nondenaturing 4 percent gel to determine 14:23:06
9 the fewest number of cycles that yielded a visible 14:23:08
10 signal from PCR products," right? 14:23:12

11 So they're trying to get the least amount 14:23:14
12 of DNA amplification they can get that still gives 14:23:17
13 them something they can quantify. So it's a good 14:23:20
14 strategy for balancing if you are worried about 14:23:23
15 having, you know, very large differences in the 14:23:27
16 number of reads per sample. 14:23:30

17 Q. Okay. And then after it did the 14:23:32
18 quantitation and sort of picked the sample that they 14:23:35
19 were going to use -- after all that, Parameswaran 14:23:40
20 pooled products from 25 different samples together 14:23:43
21 in what it says roughly equal molar ratios, true? 14:23:48

22 (Reporter clarification.) 14:24:07

23 A. I believe that's correct, yes. 14:24:07

24 Q. In Parameswaran, all of the PCR that was 14:24:09
25 performed -- both the first round and the second 14:24:12

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1 round was performed before any samples were pooled 14:24:15

2 together, true? 14:24:21

3 **A. No, that's not accurate. The -- right? So** 14:24:23

4 **remember: It's going to go into an emulsion PCR** 14:24:25

5 **that happens after pooling.** 14:24:29

6 MR. RAICH: Counsel, we have been going a 14:24:36

7 little over an hour. Is this a good time for a 14:24:38

8 break? 14:24:40

9 MR. MATTY: Yeah. Just a couple more on 14:24:41

10 this, and then we'll be there. 14:24:43

11 Q. In Parameswaran, the first and second 14:24:44

12 rounds of PCR that it describes -- both those rounds 14:24:46

13 were performed before any different samples were 14:24:52

14 pooled together, true? 14:24:54

15 **A. That is correct. And then it goes into the** 14:24:55

16 **emulsion PCR.** 14:24:59

17 MR. MATTY: All right. We can take that 14:25:01

18 break. 14:25:04

19 THE VIDEOGRAPHER: We're off the record. 14:25:04

20 Time is 2:24 p.m. 14:25:06

21 (Break taken.) 14:38:57

22 THE VIDEOGRAPHER: Okay. We're back on the 14:38:57

23 record. Time is 2:38 p.m. 14:39:01

24 MR. MATTY: 14:39:03

25 Q. All right. Let's go back to Parameswaran 14:39:04

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1 and go to page seven of the reference, if you have 14:39:05
2 that in front of you. 14:39:08

3 **A. Yes, page seven.** 14:39:10

4 Q. At the bottom left, there's a section that 14:39:12
5 says "Analysis of Data." Do you see that? 14:39:13

6 **A. Yes.** 14:39:16

7 Q. And in maybe the third sentence of that 14:39:16
8 section, it says that six of the forward barcodes 14:39:21
9 are exact reverse complements of six reverse 14:39:27
10 barcodes in Parameswaran. Do you see that? 14:39:31

11 **A. Yes.** 14:39:35

12 Q. And what Parameswaran's talking about 14:39:36
13 there -- when it says "reverse complements," it's 14:39:39
14 saying that for six of the forward barcodes and 14:39:42
15 their corresponding reverse barcodes in the 14:39:46
16 experiment" -- well, let me just ask you. 14:39:51

17 Maybe this is easier. What's your 14:39:55
18 understanding of what it means when Parameswaran 14:39:58
19 says "six forward barcodes were exact reverse 14:40:01
20 complements of six reverse barcodes"? 14:40:04

21 **A. I understood that to mean that they could 14:40:07
22 not distinguish them without the additional cloning 14:40:11
23 linker information. It's possible that -- I'd have 14:40:16
24 to look at them more closely to figure out which 14:40:23
25 ones they are. 14:40:26**

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1 **It's possible that if they -- if there was** 14:40:26
2 **a rearrangement event, they would switch hands and** 14:40:29
3 **then read out exactly the same. But either way, I** 14:40:32
4 **took it that the additional cloning linker** 14:40:34
5 **information helped reduce ambiguity on those.** 14:40:37

6 Q. What does it mean for one barcode to be a 14:40:39
7 reverse complement to the other? 14:40:44

8 A. If one barcode had sequenced ATG, the 14:40:46
9 reverse complement would be CAT. So they -- 14:40:50
10 they're -- they have -- they're in some ways like a 14:40:56
11 palindrome a little bit, right? They have -- they 14:41:00
12 have sequence -- they have a sequence characteristic 14:41:04
13 that, in DNA sequencing, can be difficult to 14:41:07
14 disambiguate. 14:41:10

15 Q. Do you have any understanding of why 14:41:11
16 Parameswaran used reverse complements for six of 14:41:17
17 their forward and reverse barcodes? 14:41:20

18 A. I did not spend any time trying to figure 14:41:24
19 it out. I would not have done it personally, but 14:41:26
20 there may have been a good reason. I didn't 14:41:30
21 identify it. 14:41:33

22 Q. Did you spend any time figuring out what 14:41:34
23 effect Parameswaran's use of reverse complement 14:41:36
24 barcodes had on the errors that it detected in some 14:41:36
25 of its sequence reads? 14:41:40

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1 **A. I did -- again, I did not break down all of** 14:41:44
2 **their reads and map them into the Table 3 version to** 14:41:46
3 **see where they were lying.** 14:41:51

4 **Q. Okay. At the end of Parameswaran, there's** 14:41:55
5 **a section of supplementary tables, supplemental** 14:41:57
6 **methods, and some supplemental data. Are you** 14:42:05
7 **familiar with those?** 14:42:09

8 **A. Yes. I have looked at those in some deck.** 14:42:10

9 **Q. Did you consider the supplemental** 14:42:12
10 **information in Parameswaran when you were forming** 14:42:15
11 **your opinions in this matter?** 14:42:16

12 **A. Yes, I have thought about them.** 14:42:18

13 **Q. All right. Can you turn to Supplemental** 14:42:20
14 **Table 1A.** 14:42:22

15 **A. Yes.** 14:42:27

16 **Q. What's your understanding of what** 14:42:27
17 **Supplementary Table 1A is showing in Parameswaran?** 14:42:30

18 **A. I interpret it to be the list of samples in** 14:42:35
19 **the left, 41, 42, 43 -- 454 just being the name of** 14:42:39
20 **the sequencer, as I interpret it. So Samples No. 41** 14:42:46
21 **to 65. And then it's listing a method, DL or 5P.** 14:42:52

22 **And then it's listing which reverse primer** 14:42:57
23 **and forward primer they used and then the sequence** 14:43:00
24 **of the reverse and forward primers. So it's just** 14:43:04
25 **providing an index for a user to see which -- which** 14:43:05

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1 sample went with which barcodes. 14:43:09

2 Q. All right. And for each primer that's 14:43:11

3 listed there, you see there's sequences of 14:43:46

4 nucleotides separated by dashes? 14:43:52

5 A. I do see that. 14:43:54

6 Q. Each of those starts with a 15-nucleotide 14:43:55

7 string; then, dash, a 4-nucleotide string; and then, 14:44:01

8 dash, a 10-nucleotide string. Do you see that? 14:44:07

9 A. I do. 14:44:09

10 Q. You understand those ten-nucleotide strings 14:44:09

11 are the barcodes that are referred to in 14:44:11

12 Parameswaran? 14:44:16

13 A. It looks consistent with that. I actually 14:44:17

14 had not mapped them all out. But, yes, it does look 14:44:19

15 like that they are. 14:44:23

16 Q. Okay. Did you review or consider the exact 14:44:23

17 barcodes that were used in these samples when you 14:44:36

18 were forming your opinions in this case? 14:44:38

19 MR. RAICH: Object to form. 14:44:42

20 THE WITNESS: I mean, I looked at the table 14:44:44

21 in Table 2. I did not do a deep, sophisticated 14:44:46

22 analysis of those barcodes to determine various 14:44:52

23 properties that they may or may not have. 14:44:55

24 MR. MATTY: 14:44:56

25 Q. Did you analyze how any of the specific 14:44:58

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1 barcodes that were used in Parameswaran could have 14:45:00
2 led to some of the errors that Parameswaran 14:45:03
3 observed? 14:45:06

4 **A. No.** 14:45:08

5 Q. Let's go to Supplemental Table 4A. And 14:45:10
6 there's a series of tables, 4A to 4F. 14:45:15

7 **A. Yes.** 14:45:19

8 Q. All right. Are you familiar with those 14:45:19
9 tables? 14:45:23

10 **A. Yes. I have looked at these.** 14:45:24

11 Q. Can you tell me what Supplementary Tables 14:45:25
12 4A to 4F are showing. 14:45:28

13 **A. As I understand, it's -- Supplementary** 14:45:30
14 **Table 4A is sort of the rawest version of the** 14:45:32
15 **barcode data, and it assesses each sample -- forward** 14:45:35
16 **and reverse barcode that's supposed to be unique and** 14:45:41
17 **whether or not when they saw -- I'll use barcode --** 14:45:45
18 **the third -- fourth column -- third column of data,** 14:45:49
19 **which is 454-43.** 14:45:54

20 **It's not labeled distinctly which one's the** 14:45:58
21 **forward and reverse, but it doesn't really matter.** 14:46:02
22 **You'll see that going down that cable -- table,** 14:46:04
23 **454-43 has an on-diagonal number with 454-43 that** 14:46:08
24 **has a very large number, 13,991, and then has** 14:46:16
25 **off-diagonal interactions with No. 42 with a small** 14:46:21

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1 **number; 47, a modest number; 54, a small number.** 14:46:25

2 **So these would be unexpected perfect-match** 14:46:27

3 **co-occurrences where you don't expect 43 to happen** 14:46:30

4 **with 42 or 47 or 54 and they observe some small rate** 14:46:33

5 **of that event. There are lots of zeros where you** 14:46:38

6 **don't see anything and then, you know, a set of** 14:46:41

7 **these interactions for various different events.** 14:46:44

8 Q. Okay. Let's make sure that we are on the 14:46:46

9 same understanding. You said there were on-diagonal 14:46:50

10 numbers. Those are the largest numbers in the graph 14:46:56

11 that run down on a diagonal line through the chart. 14:46:59

12 That's what you are referring to? 14:47:02

13 **A. Correct.** 14:47:03

14 Q. And then in some of the other boxes that 14:47:04

15 aren't on that line, there's a lot of zeros, but 14:47:07

16 then there's some that do have nonzero numbers. 14:47:11

17 That's what you are referring to as "off-diagonal 14:47:13

18 numbers." Is that fair? 14:47:16

19 **A. And the ones shaded in gray is the one that** 14:47:17

20 **I'm specifically talking about, yes.** 14:47:20

21 Q. Okay. And the diagonal cells, the ones -- 14:47:22

22 the on-diagonal cells, those are all counting 14:47:24

23 instances of perfect expected barcode motifs in 14:47:29

24 Parameswaran, right? 14:47:34

25 **A. Correct.** 14:47:35

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1 Q. And in the off-diagonal nonzero numbers, 14:47:36
2 those are counting instances of perfect unexpected 14:47:40
3 barcode motifs that Parameswaran detected, true? 14:47:44

4 A. Correct. 14:47:48

5 Q. And as you noted, some of those 14:47:48
6 off-diagonal numbers are fairly small, like one, 14:47:52
7 seven, or ten, right? 14:47:56

8 A. Correct. 14:47:57

9 Q. Others are what you called modest, like 14:47:59
10 444, 450, and 405 in Supplementary Table 4A, right? 14:48:02

11 A. Correct. 14:48:11

12 Q. In forming your opinions in this case, did 14:48:11
13 you consider why the particular off-diagonal cells 14:48:14
14 that contain modest numbers in the four or five 14:48:16
15 hundreds -- why those particular cells resulted in a 14:48:20
16 lot of unexpected perfect barcode motifs? 14:48:25

17 MR. RAICH: Objection to form. 14:48:28

18 THE WITNESS: I did not attempt to make 14:48:29
19 a -- my own interpretation of the data in a detailed 14:48:32
20 way. I -- I also looked at the other series of 14:48:34
21 Table 4. 14:48:39

22 And when you look at 4B and 4C and 4D, I 14:48:41
23 observed that the number of off-diagonal 14:48:45
24 interactions collapsed enormously so that they were 14:48:48
25 using the cloning linker able to help themselves. 14:48:51

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1 So either there are sequencing errors that 14:48:54
2 are converting one barcode into another in a way 14:48:58
3 that creates a misassignment, or there could be 14:49:04
4 barcode swapping. They have the whole discussion of 14:49:07
5 this in the manuscript. 14:49:10

6 But using the cloning linker helped a lot, 14:49:12
7 which implies that it's probably more like 14:49:15
8 sequencing, rather than barcode swapping, which 14:49:17
9 would not be fixed by using a cloning linker. 14:49:19

10 That's an interpretation that I think is 14:49:22
11 reasonable. And as they use more and more of the 14:49:25
12 cloning linker, their off-diagonal interactions got 14:49:31
13 progressively better. 14:49:31

14 MR. MATTY: 14:49:32

15 Q. What do you mean by "The errors for the 14:49:32
16 off-diagonal numbers are more likely sequencing, 14:49:35
17 rather than barcode swapping"? 14:49:41

18 A. If you look at Table D, there are -- 14:49:43
19 there's a two, and there's a one. And the rest is 14:49:45
20 zeros, and then there are lots of close matches and 14:49:48
21 no matches. 14:49:52

22 That suggests that these are -- that there 14:49:54
23 are some level of barcodes that are close to one of 14:49:57
24 the other barcodes but are not matching exactly, 14:50:01
25 which is consistent with sequencing errors as -- but 14:50:04

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1 I have not looked at those barcode data myself to 14:50:09
2 confirm that. 14:50:12

3 Q. And the -- the large numbers of 14:50:13
4 off-diagonal perfect unexpected motifs, those 14:50:17
5 generally drop off pretty sharply when one 14:50:23
6 nucleotide and then two nucleotides of the cloning 14:50:26
7 linkers are added to the motif, right? 14:50:30

8 MR. RAICH: Object to the form. 14:50:33

9 THE WITNESS: Correct. I believe they 14:50:33
10 chose three nucleotides as their dataset as the 14:50:35
11 cleanest is my recollection. And they didn't bother 14:50:38
12 going all the way to four because that created more 14:50:41
13 problems -- they were starting to lose data. That's 14:50:44
14 my understanding. 14:50:47

15 But I think they could have used one 14:50:47
16 nucleotide of the cloning linker. I think they 14:50:52
17 could have used no clone and just rejected the 14:50:55
18 off-diagonals as -- I think those are all reasonable 14:50:58
19 approaches. 14:51:01

20 MR. MATTY: 14:51:01

21 Q. And your understanding of the supplementary 14:51:01
22 tables is that the large numbers of perfect 14:51:04
23 unexpected barcode motifs that were found were the 14:51:09
24 result of sequencing errors, not barcode swapping. 14:51:14
25 And that's why adding nucleotides from the cloning 14:51:19

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1 linker essentially solved the problem, true? 14:51:24

2 MR. RAICH: Object to the form. 14:51:27

3 THE WITNESS: We're looking at Run 1. I 14:51:28

4 think Run 2 was a little noisier. 14:51:30

5 MR. MATTY: 14:51:32

6 Q. All right. Let me ask for Run 1 first, 14:51:33

7 then: Your understanding of the supplementary 14:51:35

8 tables presented for Run 1 is that the large numbers 14:51:37

9 of perfect unexpected barcode motifs that were found 14:51:41

10 were the result of sequencing errors, not barcode 14:51:46

11 swapping.

12 And that's why adding nucleotides from the 14:51:51

13 cloning linkers essentially solved the problem, 14:51:56

14 true? 14:51:58

15 MR. RAICH: Objection. Form. Foundation. 14:51:59

16 THE WITNESS: I think that that is a likely 14:52:01

17 interpretation, yes. 14:52:03

18 MR. MATTY: 14:52:03

19 Q. Let's go to Supplementary Tables 5A to 5F. 14:52:06

20 A. What page does that start on? 14:52:13

21 Q. Page 26 is 5A. 14:52:15

22 A. Yes. Okay. There we go. Each individual 14:52:19

23 one isn't labeled, so I was trying to -- yes, I'm on 14:52:22

24 5A. 14:52:26

25 Q. So in the supplementary Tables 5A to 5F, 14:52:27

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1 that shows a similar set of data for the second run 14:52:29

2 in Parameswaran, true? 14:52:32

3 **A. Correct.** 14:52:33

4 Q. And is your understanding the same for this 14:52:34

5 run -- for Run 2 in Parameswaran, for the data 14:52:37

6 that's presented in the supplementary table, it 14:52:47

7 shows that the large numbers of perfect unexpected 14:52:51

8 barcode motifs that were found were the result of 14:52:54

9 sequencing errors, not barcode swapping? 14:52:57

10 MR. RAICH: Objection to form. 14:53:00

11 THE WITNESS: It's less clear in these 14:53:01

12 tables. So I think that these are the underlying 14:53:03

13 data that are summarized in, I believe, Table 3 of 14:53:07

14 the main paper. 14:53:10

15 And it's sort of easier to look at it 14:53:11

16 there. If you look at the mismatched five prime and 14:53:17

17 three prime motif column, that is the summary of all 14:53:20

18 these data. 14:53:24

19 And you can see that adding one nucleotide 14:53:25

20 in Experiment 1 helped dramatically, and adding two 14:53:29

21 helped even more. It had a different behavior in 14:53:32

22 Experiment 2, right? Adding one base pair helped 14:53:35

23 enormously. And actually, adding two didn't help. 14:53:38

24 So although it's a very small number, that 14:53:42

25 would be consistent with some other mechanism other 14:53:46

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1 than sequencing error or accounting for the 14:53:50
2 mismatched five prime and three prime motifs for 14:53:52
3 solutions that are different than barcode plus 14:53:56
4 cloning linker, one nucleotide or more. 14:53:59

5 MR. MATTY: 14:54:01

6 Q. Let me ask -- I asked about Run 1. But for 14:54:01
7 Run 2, there's also a table of the exact barcodes 14:54:04
8 that were used. It's Supplementary Table 1B, right? 14:54:09

9 A. That sounds correct. I can go there. Yes, 14:54:13
10 I see that. 14:54:20

11 Q. It starts on page 16. 14:54:21

12 A. Yes. 14:54:22

13 Q. And similar to Table 1A, Table 1B shows the 14:54:23
14 exact ten-nucleotide barcodes that were used for 14:54:29
15 every sample in Run 2, true? 14:54:32

16 A. I believe that's correct, yes. 14:54:35

17 Q. In forming your opinions in this case, did 14:54:37
18 you consider the exact barcodes that were used in 14:54:39
19 this sample and how those barcodes might have 14:54:41
20 contributed to the errors that Parameswaran 14:54:44
21 detected? 14:54:46

22 A. I did not. 14:54:47

23 Q. All right. Those are all the questions I 14:54:56
24 have at the moment. 14:55:00

25 MR. RAICH: Let's go off the record. 14:55:01

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1 THE VIDEOGRAPHER: Going off the record, 14:55:02

2 time is 2:54 p.m. 14:55:03

3 (Break taken.) 15:05:31

4 THE VIDEOGRAPHER: Back on the record. The 15:05:37

5 time is 3:05 p.m. 15:05:38

6 MR. RAICH: We have no questions for 15:05:40

7 Dr. Spellman. 15:05:42

8 Thank you very much for your time today. 15:05:43

9 MR. MATTY: We're done. 15:05:46

10 THE VIDEOGRAPHER: This concludes today's 15:05:46

11 deposition of Dr. Paul Spellman. Master video of 15:05:47

12 today's deposition will remain in the custody of 15:05:52

13 Henderson Legal Services. Time is 3:05 p.m. We are 15:05:54

14 now off the record. 15:05:58

15 (The matter concluded, 3:05 p.m.)

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1 DECLARATION UNDER PENALTY OF PERJURY

2

3 I, PAUL SPELLMAN, PH.D., do hereby certify
4 under penalty of perjury that I have read the
5 foregoing transcript of my deposition taken on
6 April 9, 2025; that I have made such corrections as
7 appear noted on the Deposition Errata Page, attached
8 hereto, signed by me; that my testimony as contained
9 herein, as corrected, is true and accurate.

10

11 Dated this day of
12 2025.

13

14

15

16 PAUL SPELLMAN, PH.D.

17

18

19

20

21

22

23

24

25

1 STATE OF CALIFORNIA)
2)
3 COUNTY OF SACRAMENTO)

4 I, TAMMY MOON, CSR No. 13184, Certified
5 Shorthand Reporter, do hereby certify:

6 That prior to being examined, the witness
7 in the foregoing proceedings was by me duly sworn to
8 testify to the truth, the whole truth, and nothing
9 but the truth;

10 That said proceedings were taken by me in
11 shorthand and thereafter transcribed into
12 typewriting under my direction and supervision;

13 That I am neither counsel for, nor related
14 to, any party to said proceedings, nor in any way
15 interested in the outcome thereof.

16 I further certify that I am not a party to
17 any stipulation, if made, that would waive my duties
18 mandated by the Court Reporters Board of California.

19 In witness whereof, I have hereunto
20 subscribed my name.

21 Dated: 11th of April, 2025

22

23

24 *---Tammy Moon-----*

25 Tammy Moon, CSR No. 13184, RDR, CRR

A	119:14 142:1	123:17,20	advantages	amount 50:10
a.m 1:13 6:1,4	143:15	124:3,8,8	138:11	58:22 72:16
42:21,24	achieving	125:25 126:1	advice 53:23	127:11
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