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

IPR2024-00965
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Molecular Loop's Exhibit 2002
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1 APPEARANCES:

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PAUL SPELLMAN, PH.D.

Wednesday, April 9, 2025

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PAUL SPELLMAN, PH.D.

Wednesday, April 9, 2025

Tammy Moon CSR No. 13184, RPR, CRR

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Exhibit 1004	Article " A pyrosequencing-tailored nucleotide barcode design unveils opportunities for large-scale sample multiplexing"	65
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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

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

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

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

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

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

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

1 **A. Yes.** 09:19:11
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
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
10 **A. Those present.** 09:19:57
11 Q. Anyone else? 09:19:58
12 **A. No.** 09:19:59
13 Q. How long did you meet? 09:20:00
14 **A. Over the past three days.** 09:20:02
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
20 **A. Just the attorneys present.** 09:20:17
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

In preparing for your deposition today, did 09:20:33
you review any documents that you hadn't reviewed 09:20:36
before you submitted your declarations in this case? 09:20:39
A. I don't believe so, but I'm not certain. 09:20:43
Q. Have you reviewed the petitions that 09:20:45
Illumina submitted in these cases? 09:20:48
A. I don't believe I've reviewed them myself, 09:20:51
no. 09:20:54
Q. Have you reviewed the preliminary responses 09:20:54
that Molecular Loop filed in these cases? 09:20:58
A. I don't believe I've seen them. 09:21:00
Q. Have you reviewed the board's institution 09:21:01
decisions in these cases? 09:21:04
A. I don't believe I've seen institution 09:21:05
decisions. 09:21:07
Q. In your work on these matters, have you 09:21:08
reviewed any documents other than the exhibits that 09:21:12
are listed as materials considered in your 09:21:17
declaration? 09:21:20
A. I don't believe so. 09:21:20
Q. All right. I want to go through just a 09:21:21
couple general concepts that I think are relevant to 09:21:33
the opinions here. You are familiar with 09:21:37
pyrosequencing, true? 09:21:40
A. Yes. 09:21:41

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

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

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

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

was amplified in emulsion PCR? 09:27:26

A. Correct. It is possible to see more than one DNA molecule per bead, and then you get a complex mixture or perhaps even a chimera. 09:27:28 09:27:31 09:27:35

Q. And when this sequencing is happening, what else is in that well with that DNA bead? 09:27:38 09:27:43

A. My understanding, there are some reagents that are -- I'm not -- how it works exactly, that -- I cannot tell you what else is in there. Things to facilitate the sequencing process -- these are commercial platforms. 09:27:46 09:27:48 09:27:51 09:27:55 09:27:57

Q. Okay. But within each well on the flow cell in pyrosequencing, there is a bead of DNA that's sort of free floating and then other reagents for the reaction that ultimately emit light when bases are added one by one. Is that a fair summary? 09:27:58 09:28:01 09:28:06 09:28:10 09:28:16

A. I don't think the beads are free floating in the sense that they -- you know, if they diffused out, that would be extremely bad. So, no, they're spatially constrained in a way that locks them in. 09:28:20 09:28:23 09:28:26 09:28:30

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

A. Yes. 09:28:34

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

A. Yeah. The physics of a ball pit and the physics of these microsurfaces are not equivalent. 09:28:36 09:28:39

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

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

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

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

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

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

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

A. So in the context of the work with Tim Butler and later Chris Boniface, our lab did that extensively. And there are a variety of different tricks that one might utilize to do that. 09:38:49 09:38:56 09:39:00 09:39:03

But some of the things that one might wish to do with Illumina might require the cooperation of Illumina to do. So if one wanted to change the P5 and P7s, those are -- those are -- it's a commercial product. 09:39:06 09:39:10 09:39:13 09:39:16 09:39:19

One cannot -- one cannot just change it without help. And getting Illumina to do something like that, I think, has been done, but I've never asked. And I think it would require a minor miracle. 09:39:20 09:39:23 09:39:25 09:39:28 09:39:33

Q. So the Illumina sequencer expects, I'll say, P5 and P7 on the template DNA in order to make the sequencing work, true? 09:39:36 09:39:39 09:39:43

A. From a commercial point of view, using commercial reagents, your sequences would have to have P5 and P7 generally, yes. 09:39:46 09:39:48 09:39:53

Q. Are you familiar with the concept of index hopping? 09:39:54 09:39:57

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

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

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

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

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

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

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

1 **A. No.** 09:49:21
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
5 **A. No.** 09:49:32
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
10 **A. No.** 09:49:42
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 Q. At the time of the invention of the '200 09:50:20

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

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

1 **A. Correct.** 09:52:23
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

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

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

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

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

matter, were you aware of the '200 and the '852 10:09:51
patents? 10:09:58
A. Very unlikely. 10:09:58
Q. Before you were engaged by Illumina in this 10:09:59
matter, were you aware of any of the -- any of the 10:10:02
inventors on the Molecular Loop patents? 10:10:03
A. I have known George Church for most of my 10:10:12
career. 10:10:15
Q. How about any of the other two inventors? 10:10:16
A. The other two named inventors is Gregory 10:10:19
Porreca and Mark Umbarger. I am not -- I don't 10:10:24
believe I'm familiar with. 10:10:27
Q. What generally is your relationship with 10:10:28
George Church? 10:10:31
A. I'm not sure he would know who I am, but 10:10:33
we've -- I've interacted with a postdoc in his 10:10:36
group -- I believe his name was John Ock -- circa 10:10:39
late '90s. And we have had some interactions -- 10:10:45
maybe early 2000s -- for several years. So John, I 10:10:49
believe, was a postdoc for George at the time. 10:10:51
Q. And are you aware of Dr. Church's lab at 10:10:53
Harvard generally from your work in the field? 10:10:57
A. Absolutely. 10:10:59
Q. Dr. Church's lab at Harvard is a fairly 10:11:02
well-known research lab in the genetics industry. 10:11:06

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

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

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

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

in this case, a number of them are cited in your 10:16:32
declarations, true? 10:16:37
A. Yes. 10:16:37
Q. Is it fair to assume that if you cited a 10:16:37
document or paper in your report, you thought that 10:16:42
that was a trustworthy source? 10:16:44
**A. "Trustworthy" has a lot of connotations to 10:16:48
it, but -- but I thought it was a relevant document 10:16:51
that -- that added relevant information to the case.** 10:16:55
Q. Okay. Are there any documents that you 10:16:58
relied on in the citations in your report that you 10:17:02
would not consider to be trustworthy sources? 10:17:05
A. No. 10:17:08
Q. In your declaration -- I believe it's 10:17:08
paragraph 2 -- you state that you are being 10:17:13
compensated your standard hourly rate of $500 an 10:17:17
hour, true? 10:17:21
**A. Yes. I also receive a differential for 10:17:22
travel and a differential for deposition time.** 10:17:26
Q. What do you mean by a "differential"? 10:17:28
**A. Half time for travel and one and a half 10:17:30
times during these proceedings.** 10:17:35
Q. Got it. So for travel, you charge 250 an 10:17:37
hour. For depositions, you charge 750 an hour. For 10:17:40
all other work in this case, you charge 500 an hour. 10:17:45

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

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
11 **A. Counsel?** 10:19:42
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

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

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

of Parameswaran and Gloor, do you have an opinion on 10:29:03
whether the person of ordinary skill would choose 10:29:05
one round of PCR or two? 10:29:11
A. It would be my firm position that a POSA 10:29:14
would examine the art and decide on what made the 10:29:18
most sense for their purposes, given the 10:29:22
configuration of their assays. 10:29:25
The -- the scope of Parameswaran and Gloor 10:29:28
are specific examples in the art, and a POSA would 10:29:32
take that teaching and utilize it to solve the 10:29:39
problem that they were trying to solve. 10:29:45
Q. Okay. And in your combination here where 10:29:47
you're taking Parameswaran's experiment and running 10:29:52
it on the Illumina machine in Gloor, do you have an 10:29:53
opinion on whether the person of ordinary skill 10:29:57
would choose one round of PCR or two for that 10:29:58
application? 10:30:02
A. I think they would choose whichever they 10:30:03
thought made the most sense. 10:30:07
Q. Okay. And do you have an opinion on which 10:30:08
one makes the most sense? 10:30:09
A. I think they're probably equivalent, but I 10:30:10
reserve the right to look at a specific 10:30:14
counterfactual example. 10:30:16
Q. Okay. Now, Parameswaran and Gloor also 10:30:18

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

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

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

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

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

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

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

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

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

level of ordinary skill in this case, did you check 11:02:18
to see how the inventors on the Molecular Loop 11:02:20
patents measured up to your definition? 11:02:22
A. No, I did not. 11:02:26
Q. Can you go to paragraph 15 of your 11:02:26
declaration, please. 11:03:12
A. Yes. 11:03:13
Q. You state there that you have been well 11:03:13
aware of, and your lab routinely uses, unique and 11:03:18
nonunique dual index sequencing methods. Do you see 11:03:22
that? 11:03:26
A. I do. 11:03:26
Q. What unique dual index sequencing methods 11:03:26
do you use in your laboratory? 11:03:33
**A. I would have to go back and check. I mean, 11:03:35
it is what it says. You are asking a specific paper 11:03:39
that's used? Did I have to -- I'd have to read the 11:03:41
methods to tell you which papers did and did not use 11:03:44
each of those schemes.** 11:03:47
Q. So when you referred to unique and 11:03:49
nonunique dual index sequencing methods in your 11:03:53
paragraph No. 15, are those commercially available 11:03:56
kits or methods, or are those methods that your lab 11:04:01
designed specifically for the experiments that you 11:04:04
do? 11:04:09

1 **A. It -- it should be both.** 11:04:09
2 Q. Okay. What commercially available kits or 11:04:11
3 methods does your lab use for unique dual indexing 11:04:16
4 sequencing methods? 11:04:21
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
7 Q. Are you aware of any commercially available 11:04:26
8 kits or methods that your lab uses for unique dual 11:04:30
9 index sequencing methods? 11:04:35
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
14 Q. Okay. Are you aware of any unique dual 11:04:44
15 index sequencing kits or methods that are 11:04:49
16 commercially offered by Illumina? 11:04:52
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
20 Q. Which ones are you thinking of? 11:05:01
21 MR. RAICH: I'm going to object to scope. 11:05:03
22 THE WITNESS: I believe we have used the 11:05:10
23 TruSeq in variation configurations, but the exact 11:05:11
24 time and place, I'm not certain. 11:05:15
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-adapter 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

1 **A. Yes.** 11:23:46
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

look a lot like or be exactly equivalent to a template crossing-over error. Distinguishing them can be extremely difficult. 11:26:26 11:26:29 11:26:32

But -- and it was well -- even in a single sample, not multiplex sample, where you are just sequencing DNA from a single source, one can get template crossing-over errors. That kind of error would be not very easy to detect using the unique barcode -- unique dual indexing approaches. 11:26:36 11:26:42 11:26:45 11:26:50 11:26:53 11:27:01

Q. And the chimeric molecules that are discussed in the '200 and '852 patent -- you understand those chimeric molecules in the examples are all formed during amplification of nucleic acids, true? 11:27:06 11:27:09 11:27:12 11:27:15 11:27:25

MR. RAICH: Object to form. 11:27:25

THE WITNESS: Can you please repeat the question. We're looking at the '852 claims? 11:27:27 11:27:28

MR. MATTY: 11:27:31

Q. I'm referring to the description, the specification, which is generally the same for both patents. And my question is the chimeric molecules that are described in the Molecular Loop patents -- you understand those chimeric molecules are all formed during amplification of nucleic acids, true? 11:27:32 11:27:35 11:27:37 11:27:39 11:27:41 11:27:44

A. The figures in this specification show 11:27:53

that. I'm not sure that it's technically correct to 11:27:58
say that all of the -- all of the ways that one can 11:28:02
get the template crossover errors happened in the 11:28:05
way this described. 11:28:11
So I think it's very important to recognize 11:28:12
the specification describes a likely mode of 11:28:14
template crossover error, but it's very clear that 11:28:20
it doesn't limit it to that. 11:28:22
The specification is -- it says "for" -- 11:28:24
something like "for the sake of assumption" or "we 11:28:29
assume" or something like that, but it does not 11:28:31
actually prove that these template crossover errors 11:28:34
are the only mechanism or limited to them -- to 11:28:38
those. 11:28:42
Q. In all your review of the '200 and '852 11:28:42
patents, did you see any discussion or examples of 11:28:47
chimeric molecules that were formed some other way 11:28:49
than during amplification of nucleic acid? 11:28:53
A. I'm going to have to read because the exact 11:29:07
columns and sources, I don't have notated. 11:29:11
Q. If you want me to repeat the question after 11:29:14
you read, just let me know. 11:29:16
A. Yes. Specification's longer than I 11:29:17
remember. Apologies. I thought it was much 11:32:06
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

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

can you explain to me again how you arrived at the claim construction that you are providing in paragraph 122. 11:40:13 11:40:16 11:40:18

A. I read the specification. I considered the use of terms in the art. In my opinion, template crossover error is not a very common phrase, and so I considered the specification and the requirements for multiplex and the -- the ability -- ability to describe being limited to detect crossover events between samples rather than within samples. 11:40:22 11:40:24 11:40:33 11:40:35 11:40:41 11:40:46 11:40:51

And we have had a lengthy conversation about internal chimeras within samples as being quite common. And there are a whole set of methods in the literature prior to this that would have been used for detecting in-sample chimeras. 11:40:53 11:40:56 11:40:59 11:41:02 11:41:05

But specifically, the chimeras in this are limited to between sample chimeras. And so I interpreted template crossover to be limited to between sample chimeras. 11:41:08 11:41:14 11:41:18 11:41:22

Q. And in your work in forming your opinions here, I understand that you applied the legal standards that were described to you as, you know, the appropriate way to do -- anticipation, obviousness, claim construction, things like that, true? 11:41:23 11:41:30 11:41:37 11:41:39 11:41:44 11:41:48

1 **A. Yes.** 11:41:48
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
2 Q. Is there any literature that -- let me 11:43:14
3 start over. 11:43:24
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

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

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

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

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

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

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

1 **A. Very unlikely.** 12:06:48
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
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
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

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

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

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

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

in Exhibit 1019 that talks about chimeras being 12:14:13
formed between nucleic acids from different samples? 12:14:16
A. Well, I will read this sentence for you: 12:14:28
"Consequently, amplification products from damaged 12:14:34
templates, such as archaeological DNA, are made up 12:14:38
of a high proportion of chimeric molecules." 12:14:42
So intrinsic to archaeological DNA is the 12:14:45
fact that that is a mixture of material. Paabo 12:14:49
might get bone or tooth or hair from an ancient 12:14:52
individual. They have been doing this for 35 years. 12:14:57
And unfortunately, there is a mixture of 12:15:02
stuff that is not human in those samples. There's 12:15:05
bacteria. There's fungus. There's God-knows-what 12:15:07
in there. So depending on how you view "sample" -- 12:15:11
if you mean "sample" as this sample from this tooth, 12:15:16
no, I don't think so. 12:15:19
If you mean it as a mixture of complicated 12:15:20
mixtures of organisms, then absolutely. And I think 12:15:24
from his perspective, he would be very concerned 12:15:27
about the sequences that bridge between individual 12:15:32
organisms. 12:15:35
Q. In your review of Exhibit 1019, did you see 12:15:36
any discussion of chimeras being formed on the 12:15:39
surface of the flow cell? 12:15:43
A. That would be impossible. 12:15:44

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

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

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

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

is an example of chimeric combination, true? 13:16:45

A. Yes. 13:16:48

Q. And in the sequences in Figure 6, they have two barcodes. They're different barcodes, right? 13:16:49 13:16:51

A. Yes. 13:16:54

Q. And those are meant to show barcodes tagging nucleic acids from two different samples, true? 13:16:54 13:16:56 13:17:00

A. I believe that's correct, yes. 13:17:00

Q. And then at the bottom of your Figure 6, you are depicting what would be a chimera that's being formed from nucleic acids from different samples, true? 13:17:02 13:17:04 13:17:08 13:17:10

A. Let me correct you. The previous line, I think -- I think the picture is a little more generic than you described. The barcodes are attached to two different sequences. I don't know that they -- that they have to be from different samples. 13:17:12 13:17:15 13:17:18 13:17:21 13:17:24 13:17:27

Q. Okay. So your intent in what you were portraying was two different sequences being combined, not necessarily sequences from different samples, true? 13:17:28 13:17:31 13:17:34 13:17:38

A. It would represent any of those things. 13:17:38

Q. All right. Let's go to paragraph 62 of 13:17:40

your declaration. 13:17:43

A. Yes. 13:17:52

Q. In paragraph 62, you have some discussion 13:17:53
of read lengths, and you state that Illumina 13:17:59
sequencing -- let me start that over. 13:18:02

In paragraph 62, you have some discussion 13:18:05
of read lengths, and you state that: "As of 13:18:08
July 2010, Illumina sequencing generated reads of 13:18:10
about 150 nucleotides in length." Do you see that? 13:18:13

**A. I do. I should note it's paired-in 150s, 13:18:18
if I understand it correctly.** 13:18:23

Q. Right. And the support that you cite for 13:18:24
that is an Illumina press release, right? 13:18:26

A. Correct. 13:18:28

Q. Was that Illumina press release that you 13:18:29
cited something that you found, or was that provided 13:18:32
to you? 13:18:34

**A. I suspect I was aware of it when it came 13:18:36
out. I play close attention to Illumina press 13:18:41
releases, whether -- I doubt that I brought it in 13:18:44
litigation.** 13:18:46

**But I was -- I'm nearly certain I was aware 13:18:48
of it. Whether or not I -- certainly aware of the 13:18:50
consequences of it. Whether or not I could trace it 13:18:54
back to that exact press release, I don't know.** 13:18:56

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Q. Okay. So the sequence and primer 13:46:24
requirements in Gloor say that a read has to have 13:46:31
two valid sequence tags. And it has to have two 13:46:35
primer sequences, but there can be up to three 13:46:39
mismatches in each primer, true? 13:46:43
A. Correct. 13:46:46
Q. Okay. And you understand those to be the 13:46:46
sequence tag and primer requirements that Gloor 13:46:54
talks about in the part that you quoted in your 13:46:58
declaration, true? 13:47:00
A. Yeah. It's possible there's additional 13:47:01
criteria in here, but I believe it's covered here. 13:47:02
Q. Okay. So if a given read has two valid 13:47:04
sequence tags, it's going to pass the sequence tag 13:47:12
requirement, right? 13:47:14
A. Yes, I believe that's correct. 13:47:16
Q. And then if that read has two primer 13:47:16
sequences, allowing up to three mismatches per 13:47:19
primer, it's going to pass the primer requirements, 13:47:22
right? 13:47:26
A. I believe that's correct. 13:47:26
Q. Now, the valid sequence tags, those refer 13:47:27
to tags that were actually added to the nucleic acid 13:47:36
at the beginning, before PCR. And those are shown 13:47:41
in Table 2, right? 13:47:43

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
15 **A. That is correct, yes.** 13:48:44
16 Q. 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

index sequence. 13:49:54
MR. MATTY: 13:49:54
Q. Right. And in the index hopping -- let me 13:49:54
start that over. 13:49:59
In your understanding of index hopping, 13:49:59
valid sequences -- let me try that again. 13:50:06
In your understanding of index hopping, 13:50:12
sample tags can jump from one nucleic acid to the 13:50:18
other while still being a valid sample tag, true? 13:50:21
A. Yes, it is possible in -- it is possible 13:50:31
for both tags to switch in index hopping. 13:50:36
Q. And after the index hop, they would still 13:50:39
be valid sequence tags because they match the tags 13:50:42
that were added to nucleic acid at the beginning, 13:50:45
right? 13:50:48
A. Yes. Formally speaking, if you had Tag A 13:50:48
and Tag -- A1 and A2 and B1 and B2, it is formally 13:50:50
possible to switch from A1 to A2 to B1/B2. 13:50:56
Q. Let's go to the abstract of Gloor. 13:51:00
A. Yes. 13:51:12
Q. Gloor notes in the third sentence there 13:51:22
that: 13:51:27
"Combinatorial sequence tagging can 13:51:27
be used to examine hundreds of samples 13:51:29
with far fewer primers than is required 13:51:32

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

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

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

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

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

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

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

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

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

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

Q. That sentence in Parameswaran that talks 14:07:17
about N forward and N reverse barcodes being used 14:07:23
for N squared libraries, that's not referring to 14:07:27
unique dual indexing, true? 14:07:31
A. That's correct. 14:07:34
Q. That part of Parameswaran is referring to 14:07:34
what you would call nonunique dual indexing, true? 14:07:39
A. Correct. 14:07:42
Q. Did you consider in your analysis of 14:07:43
Parameswaran why their abstract was highlighting 14:07:46
that one could sequence more libraries using 14:07:51
nonunique dual indexing? 14:07:54
MR. RAICH: Objection to form. 14:07:56
THE WITNESS: Yeah. I felt it was pretty 14:07:57
obvious I did consider it. 14:08:00
MR. MATTY: 14:08:02
Q. What do you mean by "it's pretty obvious"? 14:08:05
A. Well, I understood why they talked about 14:08:07
it. 14:08:11
Q. And in your view, why were they talking 14:08:11
about it? 14:08:14
A. The Parameswaran paper was interested in 14:08:15
thinking about how they might move toward very large 14:08:19
numbers of samples and coming up with a scheme to 14:08:24
handle that. 14:08:29

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

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

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

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 POSA 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

base pairs of DNA on a short-read sequencer, I'm just going to have to stop and wait until that's possible, because I can't do it. 14:14:20 14:14:23 14:14:27

Other protocols could be trivial. And so it's entirely up to the POSA to evaluate whether or not using some sequencing technology is possible. But that's well -- that's what POSAs do. 14:14:29 14:14:32 14:14:34 14:14:37

Q. On page two of Parameswaran -- we saw this earlier -- it has a blueprint for the barcodes you used. Do you see that? 14:14:39 14:15:07 14:15:10

A. Yes. 14:15:12

Q. Do you have an understanding for how Parameswaran came up with the particular blueprint for their barcodes? 14:15:13 14:15:16 14:15:19

A. It's not very accurately described in the methods on why it's done this way. I have some suspicions. I'm not sure -- I have not opined as to whether or not a POSA would have my understanding as to why they are constructed the way they are because I don't think there's necessarily a ton of teaching in the manuscript. 14:15:23 14:15:26 14:15:29 14:15:32 14:15:34 14:15:37 14:15:39

But my -- my own opinion is that they have a very specific structure that is actually quite well suited to the way the 454 sequencer works. 14:15:40 14:15:44 14:15:47

Q. And over on page three, there's a Table 1 14:15:51

that describes what Parameswaran calls "positional 14:15:57
nucleotide restrictions in the barcodes." Do you 14:16:01
see that? 14:16:05
A. Yes. 14:16:05
Q. Can you explain why those restrictions were 14:16:05
needed in Parameswaran? 14:16:07
A. I think it's a little strong to say that 14:16:09
they were needed. I think this lab is very 14:16:13
sophisticated and very thoughtful, and this is the 14:16:17
kind of paper that you can kind of tell they spent a 14:16:21
long time thinking about in very detailed ways. 14:16:26
So it's an interesting question of 14:16:32
whether or not any of these restrictions are 14:16:34
actually necessary or not or just "If we're 14:16:37
designing the system, let's do everything we can to 14:16:40
put as many safety guards on it as possible." 14:16:43
And I suspect it's rather the latter than 14:16:46
they tried a bunch of stuff and it all failed and 14:16:50
this is finally what worked. I think it's the other 14:16:52
way around. 14:16:55
They planned this very carefully, coming up 14:16:56
with every criteria they could think of that might 14:16:58
get in the way, and executed them all. That's my 14:17:01
instinct. 14:17:04
Q. Let me ask it the other way: Can you 14:17:04

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

Q. There, Parameswaran describes its DNA 14:19:43
amplification and pooling methods, right? 14:19:52
A. Yes. 14:19:57
Q. And we talked about this earlier. 14:19:57
Parameswaran performed two different rounds of PCR, 14:19:59
true? 14:20:01
A. Yes. With a slight caveat, yes. 14:20:12
Q. What's the caveat? 14:20:15
A. The second round of amplification with 14:20:18
temperatures and cycle lengths identical to initial 14:20:20
but with variable number of total cycles -- so 14:20:23
technically, that second round is actually three 14:20:28
separate reactions. So they didn't -- they chose 14:20:30
one of those, which is a -- it's a picky detail. 14:20:36
Q. I understand. So just to make sure we're 14:20:38
on the same page, there was an initial round of 20 14:20:42
cycles of PCR in Parameswaran, right? 14:20:45
A. Yes. 14:20:47
Q. And then Parameswaran took -- what it says 14:20:47
is 1/25 of the PCR product from the first round, 14:20:53
right? 14:20:57
A. Yes. 14:20:57
Q. And then it performed -- what it says is a 14:20:57
second round of amplification, but it had a variable 14:21:03
number of cycles, right? 14:21:07

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

possible the exact amount of material that was going into the sequencer for each one. 14:22:38 14:22:42

And so they didn't want tenfold differences in amounts of DNA from each sample going onto the sequencer. So they have been very fastidious about how to do that. 14:22:45 14:22:52 14:22:54 14:22:58

And so, I mean, you know, it says: "An analytical nondenaturing 4 percent gel to determine the fewest number of cycles that yielded a visible signal from PCR products," right? 14:22:59 14:23:06 14:23:08 14:23:12

So they're trying to get the least amount of DNA amplification they can get that still gives them something they can quantify. So it's a good strategy for balancing if you are worried about having, you know, very large differences in the number of reads per sample. 14:23:14 14:23:17 14:23:20 14:23:23 14:23:27 14:23:30

Q. Okay. And then after it did the quantitation and sort of picked the sample that they were going to use -- after all that, Parameswaran pooled products from 25 different samples together in what it says roughly equal molar ratios, true? 14:23:32 14:23:35 14:23:40 14:23:43 14:23:48

(Reporter clarification.) 14:24:07

A. I believe that's correct, yes. 14:24:07

Q. In Parameswaran, all of the PCR that was performed -- both the first round and the second 14:24:09 14:24:12

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

and go to page seven of the reference, if you have 14:39:05
that in front of you. 14:39:08
A. Yes, page seven. 14:39:10
Q. At the bottom left, there's a section that 14:39:12
says "Analysis of Data." Do you see that? 14:39:13
A. Yes. 14:39:16
Q. And in maybe the third sentence of that 14:39:16
section, it says that six of the forward barcodes 14:39:21
are exact reverse complements of six reverse 14:39:27
barcodes in Parameswaran. Do you see that? 14:39:31
A. Yes. 14:39:35
Q. And what Parameswaran's talking about 14:39:36
there -- when it says "reverse complements," it's 14:39:39
saying that for six of the forward barcodes and 14:39:42
their corresponding reverse barcodes in the 14:39:46
experiment" -- well, let me just ask you. 14:39:51
Maybe this is easier. What's your 14:39:55
understanding of what it means when Parameswaran 14:39:58
says "six forward barcodes were exact reverse 14:40:01
complements of six reverse barcodes"? 14:40:04
A. I understood that to mean that they could 14:40:07
not distinguish them without the additional cloning 14:40:11
linker information. It's possible that -- I'd have 14:40:16
to look at them more closely to figure out which 14:40:23
ones they are. 14:40:26

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

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

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

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

number; 47, a modest number; 54, a small number. 14:46:25

So these would be unexpected perfect-match 14:46:27

co-occurrences where you don't expect 43 to happen 14:46:30

with 42 or 47 or 54 and they observe some small rate 14:46:33

of that event. There are lots of zeros where you 14:46:38

don't see anything and then, you know, a set of 14:46:41

these interactions for various different events. 14:46:44

Q. Okay. Let's make sure that we are on the 14:46:46

same understanding. You said there were on-diagonal 14:46:50

numbers. Those are the largest numbers in the graph 14:46:56

that run down on a diagonal line through the chart. 14:46:59

That's what you are referring to? 14:47:02

A. Correct. 14:47:03

Q. And then in some of the other boxes that 14:47:04

aren't on that line, there's a lot of zeros, but 14:47:07

then there's some that do have nonzero numbers. 14:47:11

That's what you are referring to as "off-diagonal 14:47:13

numbers." Is that fair? 14:47:16

A. And the ones shaded in gray is the one that 14:47:17

I'm specifically talking about, yes. 14:47:20

Q. Okay. And the diagonal cells, the ones -- 14:47:22

the on-diagonal cells, those are all counting 14:47:24

instances of perfect expected barcode motifs in 14:47:29

Parameswaran, right? 14:47:34

A. Correct. 14:47:35

Q. And in the off-diagonal nonzero numbers, 14:47:36
those are counting instances of perfect unexpected 14:47:40
barcode motifs that Parameswaran detected, true? 14:47:44
A. Correct. 14:47:48
Q. And as you noted, some of those 14:47:48
off-diagonal numbers are fairly small, like one, 14:47:52
seven, or ten, right? 14:47:56
A. Correct. 14:47:57
Q. Others are what you called modest, like 14:47:59
444, 450, and 405 in Supplementary Table 4A, right? 14:48:02
A. Correct. 14:48:11
Q. In forming your opinions in this case, did 14:48:11
you consider why the particular off-diagonal cells 14:48:14
that contain modest numbers in the four or five 14:48:16
hundreds -- why those particular cells resulted in a 14:48:20
lot of unexpected perfect barcode motifs? 14:48:25
MR. RAICH: Objection to form. 14:48:28
THE WITNESS: I did not attempt to make 14:48:29
a -- my own interpretation of the data in a detailed 14:48:32
way. I -- I also looked at the other series of 14:48:34
Table 4. 14:48:39
And when you look at 4B and 4C and 4D, I 14:48:41
observed that the number of off-diagonal 14:48:45
interactions collapsed enormously so that they were 14:48:48
using the cloning linker able to help themselves. 14:48:51

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

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

linker essentially solved the problem, true? 14:51:24
MR. RAICH: Object to the form. 14:51:27
THE WITNESS: We're looking at Run 1. I 14:51:28
think Run 2 was a little noisier. 14:51:30
MR. MATTY: 14:51:32
Q. All right. Let me ask for Run 1 first, 14:51:33
then: Your understanding of the supplementary 14:51:35
tables presented for Run 1 is that the large numbers 14:51:37
of perfect unexpected barcode motifs that were found 14:51:41
were the result of sequencing errors, not barcode 14:51:46
swapping.
And that's why adding nucleotides from the 14:51:51
cloning linkers essentially solved the problem, 14:51:56
true? 14:51:58
MR. RAICH: Objection. Form. Foundation. 14:51:59
THE WITNESS: I think that that is a likely 14:52:01
interpretation, yes. 14:52:03
MR. MATTY: 14:52:03
Q. Let's go to Supplementary Tables 5A to 5F. 14:52:06
A. What page does that start on? 14:52:13
Q. Page 26 is 5A. 14:52:15
A. Yes. Okay. There we go. Each individual 14:52:19
one isn't labeled, so I was trying to -- yes, I'm on 14:52:22
5A. 14:52:26
Q. So in the supplementary Tables 5A to 5F, 14:52:27

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

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

THE VIDEOGRAPHER: Going off the record, 14:55:02
time is 2:54 p.m. 14:55:03
(Break taken.) 15:05:31
THE VIDEOGRAPHER: Back on the record. The 15:05:37
time is 3:05 p.m. 15:05:38
MR. RAICH: We have no questions for 15:05:40
Dr. Spellman. 15:05:42
Thank you very much for your time today. 15:05:43
MR. MATTY: We're done. 15:05:46
THE VIDEOGRAPHER: This concludes today's 15:05:46
deposition of Dr. Paul Spellman. Master video of 15:05:47
today's deposition will remain in the custody of 15:05:52
Henderson Legal Services. Time is 3:05 p.m. We are 15:05:54
now off the record. 15:05:58
(The matter concluded, 3:05 p.m.)

DECLARATION UNDER PENALTY OF PERJURY

I, PAUL SPELLMAN, PH.D., do hereby certify under penalty of perjury that I have read the foregoing transcript of my deposition taken on April 9, 2025; that I have made such corrections as appear noted on the Deposition Errata Page, attached hereto, signed by me; that my testimony as contained herein, as corrected, is true and accurate.

Dated this day of 2025.

PAUL SPELLMAN, PH.D.

STATE OF CALIFORNIA)
)
COUNTY OF SACRAMENTO)

I, TAMMY MOON, CSR No. 13184, Certified Shorthand Reporter, do hereby certify:

That prior to being examined, the witness in the foregoing proceedings was by me duly sworn to testify to the truth, the whole truth, and nothing but the truth;

That said proceedings were taken by me in shorthand and thereafter transcribed into typewriting under my direction and supervision;

That I am neither counsel for, nor related to, any party to said proceedings, nor in any way interested in the outcome thereof.

I further certify that I am not a party to any stipulation, if made, that would waive my duties mandated by the Court Reporters Board of California.

In witness whereof, I have hereunto subscribed my name.

Dated: 11th of April, 2025

---Tammy Moon-------

Tammy Moon, CSR No. 13184, RDR, CRR

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