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Transcript of Viktor Adalsteinsson, Ph.D.

Date: June 20, 2025

Case: Illumina Inc. -v- Molecular Loop Biosciences, Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA INC.,

Petitioner,

V.

MOLECULAR LOOP BIOSCIENCES, INC.,

Patent Owner.

Case Nos. IPR2024-00964 & IPR2024-00965

Patent Nos. 11,041,852 & 11,768,200

Videotaped Deposition of Viktor Adalsteinsson, Ph.D.

Boston, Massachusetts

June 20, 2025

9:09 a.m.

Job No.: 584956

Pages: 1 - 122

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13 Raechel Meyerowich, Videographer

14

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C O N T E N T S

EXAMINATION OF VIKTOR ADALSTEINSSON, PH.D.	PAGE
By Mr. Raich	6

E X H I B I T S

(Retained by Counsel.)

EXHIBITS		PAGE
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Exhibit 2010	Previously marked	114

1	June 20, 2025	9:09 a.m.	
2	P R O C E E D I N G S		
3	THE VIDEOGRAPHER:	Here begins Media No. 1	09:09:07
4	in the videotaped deposition of Dr. Viktor		09:09:10
5	Adalsteinsson, in the matter of Illumina Inc. v.		09:09:15
6	Molecular Loop Biosciences, Inc., in the United States		09:09:20
7	Patent and Trademark Office before the Patent Trial		09:09:23
8	and Appeal Board, Case Nos. IPR2024-0964 and		09:09:27
9	IPR2024-00965.		09:09:41
10	Today's date is June 20th, 2025. The time		09:09:44
11	on the video monitor is 9:09. The videographer today		09:09:47
12	is Raechel Meyerowich, representing Planet Depos. And		09:09:54
13	this video deposition is taking place at Finnegan,		09:09:58
14	Henderson, Farabow, Garrett & Dunner LLP, at Two		09:10:04
15	Seaport Lane, in Boston.		09:10:06
16	Would counsel please voice-identify		09:10:07
17	themselves and state whom they represent.		09:10:09
18	MR. RAICH: Bill Raich, of Finnegan, for		09:10:11
19	petitioner, Illumina Inc. With me today are my		09:10:14
20	colleagues from Finnegan, Yoonjin Lee and Li Zhang;		09:10:18
21	and also with me is Marcus Burch of Illumina.		09:10:23
22	MR. MATTY: Brian Matty, from Desmarais		09:10:25

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1	LLP, on behalf of Molecular Loop and the witness.	09:10:29
2	With me are my colleagues Kevin Goon and Cassandra	09:10:32
3	Mirarchi.	09:10:36
4	THE VIDEOGRAPHER: The court reporter	09:10:36
5	today is Alan Brock, representing Planet Depos.	09:10:38
6	The witness will now be sworn.	09:10:41
7	VIKTOR ADALSTEINSSON,	09:10:41
8	being first duly sworn or affirmed to testify to the	09:10:41
9	truth, the whole truth, and nothing but the truth, was	09:10:41
10	examined and testified as follows:	09:10:43
11	EXAMINATION	09:10:53
12	BY MR. RAICH:	09:10:53
13	Q. Good morning, Doctor. Could you please state	09:10:55
14	your full name and address for the record.	09:11:00
15	A. Viktor Adalsteinsson, 9 Carlton Drive, Acton,	09:11:01
16	Massachusetts 01720.	09:11:05
17	Q. Have you ever been deposed before?	09:11:07
18	A. No.	09:11:10
19	Q. Have you ever testified at trial before?	09:11:10
20	A. No.	09:11:12
21	Q. Have you ever testified at any other judicial	09:11:13
22	proceeding?	09:11:15

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1	A. No.	09:11:17
2	Q. You understand that you are testifying in two	09:11:19
3	proceedings before the United States Patent and	09:11:22
4	Trademark Office, IPR2024-00964 and IPR2024-00965?	09:11:25
5	A. Yes.	09:11:34
6	Q. Before we start, I'm going to go over a few	09:11:35
7	ground rules. You understand that you are under oath?	09:11:37
8	A. I do.	09:11:40
9	Q. Throughout the deposition your counsel may	09:11:41
10	object to some of my questions. Unless you're	09:11:44
11	instructed not to answer, you understand that you must	09:11:47
12	answer my questions?	09:11:49
13	A. I do.	09:11:50
14	Q. If you don't understand any of my questions	09:11:52
15	today, please let me know and I'll do my best to	09:11:55
16	rephrase them. If you answer my question, I'm going	09:11:57
17	to assume that you understood the question. Is that	09:11:59
18	fair?	09:12:02
19	A. Yes.	09:12:03
20	Q. We'll plan to take breaks about every hour or	09:12:04
21	so. If you need to take a break at any time, please	09:12:07
22	let me know. All I ask is, if there's a question	09:12:10

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1	pending, you provide an answer before we take a break.	09:12:13
2	Okay?	09:12:15
3	A. Yes.	09:12:15
4	Q. We have a court reporter who needs to	09:12:18
5	transcribe your answers, so you need to give a verbal	09:12:20
6	answer. Is that understood?	09:12:23
7	A. Yes.	09:12:24
8	Q. We can help the court reporter by not talking	09:12:26
9	over one another. So if you let me finish my	09:12:28
10	questions before giving your answers, I'll endeavor to	09:12:31
11	let you give complete answers before asking my next	09:12:34
12	question. Understood?	09:12:37
13	A. Yes.	09:12:38
14	Q. Is there any reason that you are unable to	09:12:39
15	answer any of my questions truthfully and accurately	09:12:41
16	today?	09:12:44
17	A. No.	09:12:44
18	Q. I see you have two documents in front of you.	09:12:46
19	What are those?	09:12:50
20	A. Those are my declarations.	09:12:51
21	Q. Could you hand them to me, please.	09:12:53
22	Now, you reviewed those declarations	09:13:15

1	before you signed them; correct?	09:13:59
2	A. Correct.	09:14:01
3	Q. And when you signed them, you believed that	09:14:03
4	they were complete and accurate?	09:14:05
5	A. Correct.	09:14:06
6	Q. Sitting here today, are there any changes	09:14:08
7	that you wish to make to either declaration?	09:14:10
8	A. No.	09:14:12
9	Q. Let's start with your declaration from the	09:14:18
10	964 proceeding. This is Exhibit 2001.	09:14:29
11	(Exhibit 2001 previously marked for	09:14:32
12	identification.)	09:14:34
13	Q. If you'd turn, please, to Paragraph 50. In	09:14:34
14	Paragraph 50 you stated, "I understand December 23,	09:14:49
15	2010, to be the effective priority date of the '852	09:14:52
16	Patent for purposes of the Petition." Correct?	09:14:55
17	A. Correct.	09:14:58
18	Q. And the same date, December 23rd, 2010,	09:15:00
19	applies for purposes of the '200 patent as well; is	09:15:03
20	that correct? If it's helpful, I'll direct you to	09:15:10
21	Paragraph 43 in your declaration in the 965 IPR.	09:15:12
22	A. Correct.	09:15:19

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1	Q. And what is your understanding of an	09:15:22
2	effective priority date?	09:15:23
3	A. That establishes a date of the invention.	09:15:25
4	Q. And how was the effective priority date	09:15:41
5	relevant to your obviousness analysis?	09:15:43
6	A. I considered what a person of ordinary skill	09:15:46
7	of the art would have known as of the priority date.	09:15:52
8	Q. Could you turn to Page 5 of your declaration.	09:16:00
9	And Section IV, entitled Education and Experience,	09:16:15
10	provides a summary of your education and experience.	09:16:19
11	Correct?	09:16:22
12	A. Correct.	09:16:22
13	Q. And in Paragraph 5 you stated, "I have earned	09:16:27
14	a Bachelor of Science in Chemical Engineering in 2010	09:16:31
15	from Schreyer Honors College at Pennsylvania State	09:16:34
16	University." Correct?	09:16:37
17	A. That's correct.	09:16:38
18	Q. As of December 23rd, 2010, you did not have a	09:16:39
19	Ph.D. degree; correct?	09:16:43
20	A. Correct.	09:16:47
21	Q. And as of December 23rd, 2010, you did not	09:16:48
22	have a master's degree; correct?	09:16:50

1	A. Correct.	09:16:53
2	Q. Now, in Paragraph 19 of your declaration, you	09:16:56
3	reproduced the definition of a person of ordinary	09:17:06
4	skill in the art proposed by Dr. Spellman for the 964	09:17:09
5	IPR; correct?	09:17:13
6	A. That's correct.	09:17:14
7	Q. And the same definition of a person of	09:17:15
8	ordinary skill in the art was proposed by Dr. Spellman	09:17:20
9	for the 965 IPR; correct?	09:17:22
10	A. I believe so.	09:17:26
11	Q. And you do not disagree with the definition	09:17:29
12	of a person of ordinary skill in the art proposed by	09:17:31
13	Dr. Spellman; correct?	09:17:35
14	A. Correct.	09:17:40
15	Q. And the definition proposed by Dr. Spellman	09:17:40
16	required either a Ph.D. degree or a master's degree;	09:17:43
17	correct?	09:17:49
18	A. Correct.	09:17:51
19	Q. As of December 23rd, 2010, you were not a	09:17:55
20	person of ordinary skill in the art as defined by	09:17:58
21	Dr. Spellman; correct?	09:18:02
22	A. Correct, but I believe I'm amply qualified to	09:18:03

1	opine on the case, as counsel has informed me. My	09:18:10
2	degrees are highly relevant to genetics, genetics	09:18:13
3	research. My dissertation at MIT was based on genome	09:18:17
4	sequencing, and I have been a principal investigator	09:18:25
5	at the Broad Institute for the past ten years, where	09:18:28
6	my lab develops novel genomic sequencing technologies.	09:18:31
7	So I understand it is not a requirement to	09:18:36
8	have had the qualifications of a person of ordinary	09:18:38
9	skill of the art at the time of the invention, but I	09:18:41
10	believe I am amply qualified to opine on this matter,	09:18:44
11	on this case.	09:18:48
12	Q. All right. So just again, Doctor: As of	09:18:49
13	December 23rd, 2010, you were not a person of skill in	09:18:53
14	the art as defined by Dr. Spellman; correct?	09:18:56
15	MR. MATTY: Objection to form, asked and	09:18:59
16	answered.	09:19:01
17	A. As I said, I believe I'm amply qualified to	09:19:03
18	opine on this case, for the reasons I provided.	09:19:07
19	MR. RAICH: Move to strike as	09:19:11
20	nonresponsive.	09:19:12
21	Q. You did not have the qualifications of a	09:19:13
22	person of skill in the art as defined by Dr. Spellman	09:19:15

1	as of December 23rd, 2010; correct?	09:19:17
2	MR. MATTY: Same objections.	09:19:20
3	A. As I said, I believe I'm amply qualified to	09:19:21
4	opine on the case due to my qualifications.	09:19:27
5	Q. Doctor, you understand you have to answer my	09:19:30
6	questions; right?	09:19:32
7	A. I do.	09:19:34
8	Q. My question isn't whether or not you believe	09:19:35
9	that you are amply qualified or not amply qualified.	09:19:38
10	My question is simply: You did not have the	09:19:40
11	qualifications of a person of skill in the art as	09:19:46
12	defined by Dr. Spellman as of December 23rd, 2010;	09:19:49
13	correct?	09:19:53
14	A. Correct, but I believe I'm amply qualified.	09:19:53
15	Q. Doctor, when were you first engaged on behalf	09:19:58
16	of Molecular Loop?	09:20:02
17	A. I don't recall the exact date. Approximately	09:20:05
18	a year or so ago.	09:20:08
19	Q. Was it for the purposes of these IPR	09:20:12
20	proceedings?	09:20:15
21	A. I was asked to consult on matters related to	09:20:22
22	the invention.	09:20:26

1	Q. So are you consulting for Molecular Loop on	09:20:30
2	matters other than the 964 and 965 IPR proceedings?	09:20:33
3	A. I am consulting on the matter of the	09:20:38
4	invention at hand in these IPR proceedings.	09:20:48
5	Q. Are you consulting for any pending	09:20:54
6	litigations between Molecular Loop and Illumina?	09:20:57
7	A. No.	09:21:02
8	Q. Are you doing any other consulting for	09:21:02
9	Molecular Loop other than providing your consulting	09:21:06
10	for the patents at issue in these IPRs?	09:21:11
11	A. No.	09:21:18
12	Q. Now, I asked you if you were consulting for	09:21:21
13	purposes of the IPR proceedings, and you answered you	09:21:28
14	were asked to consult on matters related to the	09:21:31
15	invention. But what was the distinction that you're	09:21:33
16	drawing there?	09:21:35
17	A. The IPR proceedings were initiated after my	09:21:36
18	engagement began.	09:21:44
19	Q. Who first approached you about consulting on	09:21:56
20	behalf of Molecular Loop?	09:22:16
21	A. Counsel, Brian Matty.	09:22:21
22	Q. Did you have a prior relationship with	09:22:25

1	Mr. Matty?	09:22:27
2	A. No.	09:22:28
3	Q. Or his law firm?	09:22:28
4	A. I have done other consulting for Brian Matty	09:22:39
5	and his law firm. When you defined "relation," I was	09:22:41
6	thinking this is outside of consulting. So yes, I've	09:22:47
7	done consulting for Brian Matty and Desmarais on other	09:22:51
8	matters.	09:22:55
9	Q. And did those matters relate to patents owned	09:22:59
10	by Illumina?	09:23:01
11	A. No.	09:23:06
12	Q. And what was the general subject matter of	09:23:10
13	your prior consulting with Mr. Matty?	09:23:14
14	MR. MATTY: Just one caution, because	09:23:22
15	there might be some confidentiality here. So you	09:23:23
16	can answer at a high level, and generally I think	09:23:26
17	that's probably enough.	09:23:28
18	A. Understanding genomic technologies.	09:23:32
19	Q. What's your consulting rate?	09:23:35
20	A. Typically 500 an hour.	09:23:40
21	Q. And for these proceedings?	09:23:42
22	A. 500 an hour.	09:23:48

1	Q. Since your engagement, how many hours have	09:23:52
2	you spent working on these proceedings on behalf of	09:23:56
3	Molecular Loop?	09:23:58
4	A. I don't know precisely. If I were to	09:23:59
5	estimate, on the IPR proceedings upwards of 80 hours.	09:24:05
6	I really would have to check my billing records to	09:24:18
7	know.	09:24:23
8	Q. Approximately how many hours did you spend	09:24:23
9	preparing your declarations?	09:24:26
10	A. Again, I don't know precisely. If I were to	09:24:28
11	give you an estimate, I would say more than 40 hours.	09:24:39
12	Q. Did you write the first draft of your	09:24:55
13	declarations?	09:24:57
14	A. For many of the sections, yes.	09:25:05
15	Q. Could you turn to the table of contents at	09:25:16
16	Pages 2 and 3 of your declaration in the 964 patent --	09:25:19
17	964 proceeding.	09:25:25
18	Could you identify which sections you	09:25:26
19	drafted in the first instance?	09:25:29
20	A. I could go through each of them if needed. I	09:25:31
21	believe I provided -- I can't recall for the	09:25:57
22	introduction. It's pretty basic information there.	09:26:02

1	Education and experience I believe I	09:26:06
2	provided. It's hard to recall for a lot of these	09:26:14
3	which -- it was a process.	09:26:31
4	Q. What was the process?	09:26:35
5	A. Well, typically, I would formulate my ideas,	09:26:39
6	discuss them with counsel, and often in many times put	09:26:42
7	together an initial write-up; and we would look at	09:26:52
8	that write-up together.	09:27:00
9	Would you like me to continue going	09:27:08
10	through all the sections?	09:27:09
11	Q. I'll ask you specific questions during the	09:27:11
12	course of the day.	09:27:13
13	A. Okay.	09:27:14
14	Q. Did you receive revisions from counsel on the	09:27:21
15	sections that you originally drafted of your	09:27:27
16	declaration?	09:27:29
17	A. Yes.	09:27:31
18	Q. Did you conduct any literature searches for	09:27:36
19	these proceedings?	09:27:40
20	A. I did.	09:27:44
21	Q. How many hours did you spend searching for	09:27:45
22	literature?	09:27:50

1	A. I don't recall. Some -- yeah, I really --	09:27:53
2	that would be hard to pinpoint. I mentioned north of	09:28:03
3	40 hours for the work on the declarations, but I can't	09:28:07
4	recall exactly how much of that was literature search	09:28:15
5	and, you know --	09:28:25
6	There are a limited number of exhibits,	09:28:29
7	and that focused -- you know, that was the core	09:28:34
8	material in the matter. And then I looked through a	09:28:42
9	fair amount of additional literature to formulate my	09:28:46
10	opinions and understand what a person of ordinary	09:28:50
11	skill of the art would or would not understand at the	09:28:54
12	time of the invention.	09:28:58
13	And it was as a result of that extensive	09:29:01
14	literature search that I formulated my opinions and	09:29:03
15	have formulated my drafts, which, while they have	09:29:08
16	undergone revision, I stand by everything that is in	09:29:12
17	my declaration.	09:29:17
18	Q. What keywords did you use for your literature	09:29:20
19	searching, to the extent you recall?	09:29:23
20	A. A lot of the key terms in the patents, unique	09:29:50
21	dual indexes, combinatorial dual indexes, barcoding,	09:29:55
22	PCR recombination, chimeras. And these are a lot of	09:30:09

1	the terms that are in the patents and in the IPR	09:30:16
2	petition and materials. But by no means was my search	09:30:25
3	limited to those terms.	09:30:32
4	As I mentioned, during my Ph.D. at MIT I	09:30:33
5	did extensive research on genome sequencing	09:30:36
6	technology. I was an affiliate at the Broad	09:30:41
7	Institute, a prominent genome center, among other	09:30:43
8	facets of biomedical research pursued there. And my	09:30:47
9	literature search was guided by my knowledge of	09:30:52
10	genomics and awareness of the literature and the	09:31:00
11	history and my own awareness of when various	09:31:03
12	discoveries, aha moments were made in the field of	09:31:16
13	genomics and how those relate to the subject matter at	09:31:20
14	hand.	09:31:24
15	Q. Are there articles that you identified in	09:31:31
16	your searching that you relied on but did not cite in	09:31:33
17	your declarations?	09:31:40
18	A. I provided citations in my declarations that	09:31:42
19	support all the key points that I am making. I don't	09:32:06
20	know that I can say that is inclusive of every paper I	09:32:12
21	found that would support each point. I would have to	09:32:21
22	think, but I included the key papers that I believed	09:32:31

1	show what would be understood at the time in the art	09:32:37
2	that a person of ordinary skill in the art would look	09:32:41
3	to for understanding the present state of genomic	09:32:46
4	research.	09:32:53
5	Q. You state that you provided citations in your	09:32:59
6	declarations that support the key points that you're	09:33:01
7	making. Did you omit articles that do not support	09:33:04
8	your position?	09:33:07
9	A. No. In my search -- and I searched	09:33:10
10	extensively -- I could not find articles that	09:33:17
11	contradicted the opinions I've provided, particularly	09:33:28
12	around the awareness of template cross-over, a core	09:33:33
13	issue at hand in this IPR proceeding.	09:33:38
14	Q. Have you reviewed any documents from the	09:33:43
15	litigation between Molecular Loop and Illumina?	09:33:45
16	A. No, just the IPR materials.	09:33:54
17	Q. Which database did you search in your	09:33:57
18	searching?	09:33:59
19	A. For what specifically?	09:34:00
20	Q. You mentioned you did extensive literature	09:34:05
21	searching. I wanted to know which database you used	09:34:07
22	to do your searching.	09:34:10

1	A. A combination of PubMed, Google Scholar --	09:34:12
2	standard ones.	09:34:24
3	Q. Did you search for patents as well as	09:34:25
4	articles?	09:34:28
5	A. I did.	09:34:29
6	Q. Did you search articles that cited	09:34:32
7	Parameswarm as part of your literature searching?	09:34:36
8	A. Yes, I looked both ways, at articles that	09:34:39
9	were cited in Parameswarm, among the other materials,	09:34:47
10	as well as articles that cited to it. Of course,	09:34:50
11	there's a large number of articles that cite to any	09:34:54
12	one paper. But I used my intuition to guide which	09:34:57
13	were the most relevant and reflective ones to examine,	09:35:03
14	and as I said, I looked extensively at what was known	09:35:08
15	at the time in the literature and used that to inform	09:35:14
16	my opinions.	09:35:17
17	Q. Could you turn to Paragraph 3 of your	09:35:18
18	declaration from the 964 IPR. And you listed	09:35:22
19	materials reviewed. Do you see that?	09:35:31
20	A. I see that.	09:35:33
21	Q. And they included your experience and	09:35:50
22	knowledge, the challenged patents, the prosecution	09:35:53

1	histories of the patents at issue, Illumina's	09:35:56
2	petitions and the materials cited therein,	09:35:59
3	Dr. Spellman's declarations, references cited therein,	09:36:02
4	and his deposition testimony, and the section entitled	09:36:05
5	All Other Materials Cited Herein. Correct?	09:36:09
6	A. Correct. And I believe the "all other	09:36:14
7	materials cited herein" include the manuscripts that	09:36:17
8	I've identified.	09:36:20
9	Q. What's a prosecution history?	09:36:23
10	A. That is a formal process -- the documentation	09:36:39
11	of the formal process of seeking patent protection for	09:36:42
12	an invention.	09:36:44
13	Q. Did you look at prosecution histories of any	09:36:46
14	patents other than the '852 and '200 patents?	09:36:49
15	A. No.	09:36:52
16	Q. What did you do to prepare for today's	09:37:05
17	deposition?	09:37:07
18	MR. MATTY: And just a general caution on	09:37:10
19	these kinds of questions: You can answer them	09:37:12
20	generally. Just don't get into the details of	09:37:14
21	communications you had with counsel.	09:37:16
22	THE WITNESS: Yes.	09:37:18

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1	A. I reviewed the IPR materials.	09:37:19
2	Q. Did you meet with anyone?	09:37:24
3	A. Aside from counsel, no.	09:37:30
4	Q. And which counsel did you meet with?	09:37:33
5	A. Brian Matty and his associate, Kevin Goon.	09:37:38
6	Q. How much time did you spend meeting with them	09:37:45
7	in Brian for today's deposition?	09:37:48
8	A. We met twice this week and a couple of times	09:37:58
9	in the weeks prior.	09:38:13
10	Q. Approximately how many hours in total?	09:38:16
11	A. I'd have to check precisely. I would say	09:38:21
12	maybe 20 hours, something like that.	09:38:31
13	Q. In preparing for today's deposition, did you	09:38:37
14	consider any materials not cited in your declarations?	09:38:41
15	A. No. As I mentioned, all my opinions are	09:38:45
16	cited to the exhibits that I have included.	09:38:54
17	Q. Could we turn to Paragraph 43 of your	09:39:00
18	declaration in the 964 IPR.	09:39:02
19	MR. MATTY: 43?	09:39:11
20	MR. RAICH: 43.	09:39:12
21	Q. In the first sentence of that paragraph you	09:39:19
22	stated, "At the time of the '852 Patent, the industry	09:39:22

1	did not appreciate the cross-over error caused by	09:39:25
2	chimeric molecules formed during cluster	09:39:28
3	amplification." Correct?	09:39:32
4	A. Correct.	09:39:36
5	Q. And what did you mean by "the industry"?	09:39:37
6	A. First, a person of ordinary skill in the art	09:39:44
7	at the time of the invention would not have	09:39:50
8	appreciated cross-over error, is what my analysis has	09:39:55
9	shown. Additionally, it's my firsthand experience,	09:39:59
10	having been a researcher at the time of the invention	09:40:04
11	in the field of genomics, using single-index barcode	09:40:09
12	kits from Illumina for many, many years after. I	09:40:14
13	remember vividly it wasn't until about 2017, 2018 when	09:40:23
14	this issue became appreciated. And I believe there's	09:40:28
15	a white paper referenced here, Exhibit 2003 in	09:40:33
16	particular, which really brought light to the issue of	09:40:39
17	template cross-over error.	09:40:45
18	Q. Did you -- other than counsel, did you speak	09:40:53
19	to anyone else about -- let me strike that.	09:40:57
20	Did you speak with anyone in the field	09:41:05
21	about their awareness or lack thereof of cross-over	09:41:09
22	error caused by chimeric molecules formed during	09:41:14

1	cluster amplification as of December 23, 2010, in	09:41:19
2	preparing your materials for this case?	09:41:22
3	A. If we could reference back to materials	09:41:26
4	reviewed on Page 5, you'll see no reference to that	09:41:32
5	effect.	09:41:36
6	Q. And if you turn to Paragraph 114 of your	09:41:50
7	declaration. And in the first sentence you state,	09:42:03
8	"The literature at the time of the invention explained	09:42:08
9	that cross-over error for flow-cell based NGS was not	09:42:10
10	thought to be a problem." Correct?	09:42:14
11	A. Correct.	09:42:17
12	Q. And then you discussed Exhibit 2005; correct?	09:42:20
13	A. Correct.	09:42:26
14	Q. And how did you identify that paper?	09:42:28
15	A. I believe it was from a literature search. I	09:42:42
16	can't recall precisely.	09:42:45
17	Q. Did counsel provide any references to you	09:42:48
18	that you relied on in your declaration?	09:42:51
19	A. I believe so. I don't recall which ones	09:42:53
20	specifically.	09:42:59
21	Q. And I guess besides -- well, strike that.	09:43:04
22	Beyond Exhibit 2005, what other literature	09:43:09

1	published before December 2010 did you consider for	09:43:16
2	your statement "The literature at the time of the	09:43:20
3	invention explained that cross-over error for	09:43:23
4	flow-cell based NGS was not thought to be a problem"?	09:43:26
5	A. So first I'd like to clarify: Exhibit 2005,	09:43:33
6	though it uses the term "cross-over error," I don't	09:43:38
7	believe it is even what the patent discloses, which is	09:43:42
8	template cross-over error that occurs during cluster	09:43:48
9	amplification on the surface of a flow-cell. I	09:43:51
10	believe this term in Exhibit 2005 is being used	09:43:54
11	broadly speaking to examine whether sequences from one	09:44:00
12	library could wind up in the analysis bin for another	09:44:07
13	library without specifying how, and their conclusion	09:44:17
14	was, no, that signal did not go from one library to	09:44:26
15	another.	09:44:33
16	Now, to get back to your question: The	09:44:35
17	literature at the time, the big thing people were	09:44:43
18	concerned about in terms of sequences being	09:44:45
19	misassigned to the wrong sample was that the sequencer	09:44:50
20	was reading the barcode wrong. And as a result, there	09:44:52
21	are many papers at the time of the invention and prior	09:45:00
22	to the time of the invention that describe how	09:45:02

1 barcodes need to be designed to be distinct from one 09:45:06
2 another, so that if a sequencer misreads bases in it, 09:45:12
3 that won't cause the barcode to be confused for 09:45:20
4 another. 09:45:23

5 So at the time of the invention, that is 09:45:24
6 the big -- that was the big concern. Cross-over error 09:45:31
7 and template cross-over error specifically is absent 09:45:36
8 from the literature, in my view. 09:45:40

9 Q. Okay, just turning back to my question. I 09:45:55
10 want to make sure that I understand your answer. 09:45:58

11 So the first sentence in your Paragraph 09:45:59
12 114 states, "The literature at the time of the 09:46:05
13 invention explained that cross-over error for 09:46:08
14 flow-cell based NGS was not thought to be a problem." 09:46:09
15 What specific references support that statement? 09:46:14

16 A. So, again, I've provided Exhibit 2005 as one 09:46:19
17 example. 09:46:23

18 Q. What other literature? 09:46:26

19 A. What other literature? We could look at 09:46:31
20 Parameswarm. We could look at Gloor. We could look 09:46:42
21 at all the other exhibits in this case. And what we 09:46:45
22 would see is that template cross-over error was not 09:46:50

1	thought to be a problem.	09:46:53
2	Q. Okay. So in addition to Exhibit 2005, it's	09:46:59
3	your position that other literature in the case	09:47:07
4	explained that cross-over error for flow-cell based	09:47:11
5	NGS was not thought to be a problem?	09:47:16
6	A. Yes. Isn't that why we're here today, to	09:47:18
7	understand whether template cross-over error was known	09:47:23
8	in the art at the time and is a key part of claim 1 of	09:47:25
9	the '852 invention? And so my analysis was directed	09:47:33
10	at whether or not that was known in the art at the	09:47:37
11	time.	09:47:40
12	Q. Okay. So in addition to Exhibit 2005, your	09:47:40
13	answer is Parameswarm and Gloor?	09:47:44
14	MR. MATTY: Objection to form.	09:47:48
15	A. I would say that's nonlimiting. This is,	09:47:50
16	again, why we're here today, is to understand in part	09:47:55
17	whether template cross-over error was known in the	09:48:01
18	field, and through my review of all the IPR materials,	09:48:04
19	I formed the opinion that it was not thought to be a	09:48:08
20	problem at the time of the invention.	09:48:12
21	Q. You referenced an Illumina white paper	09:48:17
22	earlier. Did you -- well, why don't we take a look at	09:48:20

1	Paragraph 128 of your declaration.	09:48:27
2	You stated that "Illumina itself provided	09:48:45
3	no indication that it was aware of cross-over error,	09:48:47
4	or that it was an issue on Illumina sequencers." And	09:48:51
5	then you cite some Illumina white papers. Correct?	09:48:55
6	A. Correct.	09:49:01
7	Q. Did you speak to anyone at Illumina to verify	09:49:03
8	whether or not Illumina itself was aware the issue of	09:49:06
9	cross-over error on Illumina sequencers?	09:49:15
10	A. I did not, but does that matter for an	09:49:18
11	obviousness analysis? My analysis is based on what is	09:49:21
12	known. The first two words of that sentence say, "A	09:49:24
13	POSA also would not have been motivated to identify	09:49:30
14	and discard cross-over error." And it's in part	09:49:32
15	because Illumina itself provided no indication that	09:49:36
16	template cross-over error was known at the time, but	09:49:42
17	also based on my overall analysis of the materials in	09:49:48
18	this case, it is very clear that template cross-over	09:49:52
19	error was not known at the time.	09:49:56
20	Q. Why don't we take a look at Paragraph 131 of	09:49:59
21	your declaration. And in the middle of that paragraph	09:50:07
22	you state, "By the time of the invention, the field	09:50:14

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1	had moved beyond Parameswarm's methods and already	09:50:18
2	enabled multiplexing in Illumina sequencers." Do you	09:50:23
3	see that?	09:50:26
4	A. I see that.	09:50:26
5	Q. And when you refer to the time of the	09:50:29
6	invention, what time are you referring to? What date	09:50:31
7	are you using?	09:50:35
8	A. The date we discussed at the very beginning,	09:50:35
9	on Page --	09:50:37
10	Is it December 23rd, I believe? If you	09:50:46
11	know where that is, you could help me save some time.	09:51:07
12	Q. I understand. December 23rd, 2010? Is that	09:51:09
13	the date you're referring to?	09:51:11
14	A. That's what I'm looking for, yeah.	09:51:12
15	Q. And I think I asked you this earlier, but let	09:51:17
16	me try to get a clear answer. What -- you searched	09:51:19
17	for references citing Parameswarm; correct?	09:51:28
18	A. Correct.	09:51:31
19	Q. And did you include any of those references	09:51:36
20	in your declarations in this case?	09:51:41
21	A. I don't recall offhand what every exhibit I	09:51:45
22	provided cites. I recall seeing a lot of similar	09:51:55

1	papers cited to one another. I don't recall which	09:52:03
2	specific ones cited Parameswarm, though.	09:52:10
3	Q. Could you turn to Paragraph 14 of your	09:52:24
4	declaration.	09:52:27
5	A. I'm there.	09:52:45
6	Q. And in the middle of that paragraph you	09:52:47
7	stated, "For example, if, at the time of the	09:52:49
8	invention, a person of skill in the art knew of the	09:52:53
9	problem and was instructed to make the patented	09:52:56
10	invention, they would almost always be able to make	09:52:58
11	the invention." Do you see that?	09:53:00
12	A. I see that. That's an example.	09:53:02
13	Q. I guess what did you mean by "instructed to	09:53:08
14	make the patented invention"?	09:53:12
15	A. Well, hindsight is 20/20, and part of an	09:53:15
16	invention involves discovering or seeing a problem in	09:53:20
17	a new way. And in this case, and in any case, it's	09:53:26
18	important to put oneself in the shoes of a person of	09:53:39
19	ordinary skill of the art at the time of the invention	09:53:45
20	and not let what we know now bias the judgment of what	09:53:49
21	a POSA would know at the time of the invention.	09:53:54
22	Q. Based on your understanding, if a person of	09:54:01

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1	skill in the art as of December 2010 knew of the	09:54:05
2	problem of cross-over error caused by chimeric	09:54:08
3	molecules formed during cluster amplification, would a	09:54:12
4	person of skill in the art have been motivated to	09:54:14
5	exclude those errors from the sequencing work flow?	09:54:17
6	A. That's a big hypothetical. I did not	09:54:22
7	consider that in my analysis because my analysis	09:54:24
8	showed a POSA was completely unaware of template	09:54:27
9	cross-over error at the time of the invention. So how	09:54:32
10	would they be motivated to reduce something they don't	09:54:37
11	know about?	09:54:39
12	Q. In the next sentence you stated, "In	09:54:49
13	performing my obviousness analysis, I have considered	09:54:52
14	whether the inventive contribution included defining	09:54:55
15	the problem in a new way or discovering that a problem	09:55:01
16	existed." Correct?	09:55:04
17	A. Correct.	09:55:06
18	Q. Based on your understanding, if a problem was	09:55:10
19	known to exist and the patent did not define the	09:55:13
20	problem in a new way, the patent would have been	09:55:17
21	obvious; correct?	09:55:20
22	MR. MATTY: Objection to the hypothetical.	09:55:21

1	A. I did not consider that because in this case	09:55:23
2	it was very clear that the invention was discovering	09:55:40
3	that a problem that nobody -- no POSA at the time of	09:55:45
4	the invention was aware of, and thus my opinions are	09:55:52
5	formed around that.	09:55:57
6	Q. And in the following sentence you stated,	09:55:59
7	"I'm aware that determining obviousness requires	09:56:03
8	showing, by a preponderance of the evidence, that a	09:56:05
9	person of skill in the art would have both recognized	09:56:09
10	the specific problem identified by the inventor and	09:56:11
11	found it obvious to use the inventor's methods as a	09:56:15
12	solution to the problem." Do you see that?	09:56:19
13	A. I see that.	09:56:21
14	Q. In opining on obviousness, did you limit your	09:56:25
15	analysis to the problem the patentee was trying to	09:56:28
16	solve?	09:56:31
17	A. No. I considered the state of the art at the	09:56:32
18	time of the invention and how the invention read on to	09:56:42
19	that.	09:56:48
20	So when we discussed in performing my	09:56:48
21	obviousness analysis considering whether the	09:56:52
22	contribution included defining the problem in a new	09:56:54

1 way or discovering that a problem existed, that was a 09:56:56
2 part of my overall obviousness analysis. 09:57:00

3 Q. Is it your understanding that a person of 09:57:10
4 skill in the art's motivation to arrive at the claimed 09:57:40
5 invention should focus on the specific problem that 09:57:43
6 the inventors tried to solve? 09:57:46

7 A. It's based on the claim in this case, in the 09:58:07
8 '852 patent, it's a method for reducing template 09:58:12
9 cross-over error. And the question is whether a 09:58:16
10 person of ordinary skill in the art at the time would 09:58:21
11 have, A, been aware of it. If they're not aware of 09:58:27
12 something, they can't solve a problem. And B, would 09:58:30
13 they take the steps in the claim to address it -- 09:58:33
14 among other things. 09:58:42

15 Q. In opining on obviousness, did you understand 09:58:45
16 that the motivation to modify the asserted references 09:58:47
17 to arrive at the claimed invention needs to be the 09:58:52
18 same motivation that the patentee had for the '852 and 09:58:55
19 '200 patents? 09:58:59

20 A. My analysis of motivation to combine 09:59:39
21 considered, again, whether a person of ordinary skill 09:59:48
22 of the art at the time knew of the problem -- again, 09:59:57

1 if they don't know a problem exists, they can't solve 10:00:01
2 it -- and whether they would take the steps that are 10:00:04
3 claimed in the invention to solve it. And there would 10:00:13
4 also have to be some reasonable expectation of success 10:00:19
5 in doing so. 10:00:22

6 So in the context of '852 there would have 10:00:28
7 to be awareness of template cross-over error and a 10:00:33
8 motivation to reduce it, and one would have to have 10:00:37
9 the reasonable expectation of success in putting the 10:00:41
10 prior art references together to achieve that. 10:00:45

11 Q. If you'd look in Paragraph 14, you see your 10:00:55
12 last sentence says, "I am aware that determining 10:01:15
13 obviousness requires showing, by a preponderance of 10:01:17
14 the evidence, that a person of skill in the art would 10:01:20
15 have both recognized the specific problem identified 10:01:24
16 by the inventor and found it obvious to use the 10:01:26
17 inventor's methods as a solution to that problem." Do 10:01:29
18 you see that? 10:01:33

19 A. I see that. 10:01:34

20 Q. And so it's your understanding that a person 10:01:35
21 of skill in the art needs to have recognized the 10:01:38
22 specific problem identified by the inventors; correct? 10:01:43

1	A. I believe one would have to be aware of a	10:01:48
2	problem to solve it.	10:02:24
3	Q. The specific problem identified by the	10:02:27
4	inventors; correct?	10:02:30
5	A. Yes, as I say in my declaration, I'm aware	10:02:35
6	that determining obviousness requires showing by a	10:02:47
7	preponderance of the evidence that a POSA would have	10:02:50
8	recognized -- both recognized a specific problem	10:02:52
9	identified by the inventor and found it obvious to use	10:02:54
10	the inventor's method as a solution to that problem.	10:02:57
11	Q. In opining on obviousness, you focused on	10:03:35
12	whether a person of ordinary skill in the art would	10:03:38
13	have been motivated to solve the specific problem	10:03:42
14	identified by the inventor?	10:03:44
15	A. That was part of it, but not all of it. I	10:03:47
16	can reread the line of my declaration, if you'd like.	10:04:00
17	Q. Sure.	10:04:02
18	A. "I'm aware that determining obviousness	10:04:04
19	requires showing, by a preponderance of evidence, that	10:04:07
20	a POSA would have both recognized a specific problem	10:04:10
21	identified by the inventor and found it obvious to use	10:04:12
22	the inventor's methods as a solution to the problem."	10:04:15

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1	But that's not the entirety of the	10:04:18
2	obviousness analysis. I describe in the prior	10:04:20
3	paragraphs leading up to that more completely the full	10:04:24
4	extent of the obviousness analysis.	10:04:27
5	Q. Could the motivation to modify a prior art	10:04:30
6	reference to arrive at the claimed invention be	10:04:33
7	different than the motivation that the patentee had?	10:04:40
8	Strike that.	10:04:47
9	You would agree that the motivation to	10:04:48
10	modify a prior art reference to arrive at the claimed	10:04:49
11	invention need not be the same motivation that the	10:04:54
12	patentee had?	10:04:59
13	A. Well, I'm aware that a POSA would have needed	10:05:12
14	a motivation to combine the references.	10:05:35
15	Q. And did that motivation need to be the same	10:05:50
16	motivation that the patentee had, or could it be a	10:05:53
17	different motivation?	10:05:55
18	A. If you're asking whether the motivation of	10:06:12
19	the inventor was to combine prior art references to	10:06:21
20	lead to the invention, the answer is resoundingly no.	10:06:25
21	This invention here discovered a new problem and	10:06:31
22	presented a solution to it that, when I look in the	10:06:39

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1 prior art, when I look at the past references, there's 10:06:42
2 no awareness of template cross-over error, and there's 10:06:47
3 no set of references one could put together that would 10:06:53
4 lead a person of ordinary skill in the art at the time 10:06:58
5 to arrive at this invention. 10:07:02

6 Q. So you would agree that the motivation to 10:07:09
7 modify a prior art reference to arrive at the claimed 10:07:11
8 invention need not be the same motivation that the 10:07:15
9 patentee had? 10:07:18

10 A. But if it doesn't achieve the claimed 10:07:20
11 invention, how is that relevant? People can combine 10:08:06
12 prior art references and come up with any number of 10:08:22
13 things. In this case there were no prior art 10:08:25
14 references that a POSA would have been motivated to 10:08:28
15 combine to arrive at the claimed invention. 10:08:32

16 Q. You would agree that in opining on 10:08:40
17 obviousness it would be error to look only at the 10:08:43
18 problem the patentee was trying to solve; correct? 10:08:46

19 A. It's always possible that a claimed invention 10:09:19
20 could solve more than the specific problem that an 10:09:27
21 inventor identified. But in this case it's very clear 10:09:31
22 what is the problem the inventor identified, and the 10:09:40

1	invention they arrived at in this case to reduce	10:09:48
2	template cross-over error.	10:10:03
3	MR. RAICH: Why don't we go ahead and take	10:10:09
4	a break.	10:10:10
5	THE VIDEOGRAPHER: We are going off the	10:10:11
6	record. The time is 10:10.	10:10:12
7	(Recess taken.)	10:10:15
8	THE VIDEOGRAPHER: We are back on the	10:24:28
9	record. The time is 10:24.	10:24:31
10	Q. Doctor, what is PCR?	10:24:37
11	A. Polymerase chain reaction.	10:24:40
12	Q. Could you turn to Paragraph 37 of your	10:24:43
13	declaration in the 964 IPR. And here you discuss	10:24:46
14	tagged nucleic acid molecules from each source being	10:25:04
15	pooled together for future amplification and	10:25:10
16	sequencing of the resulting amplicons. Right?	10:25:14
17	A. Correct.	10:25:19
18	Q. And then in Paragraph 38 you discuss	10:25:19
19	differences between amplification of Illumina	10:25:22
20	sequencers versus Roche/454 sequencers; correct?	10:25:28
21	A. That's correct.	10:25:41
22	Q. Now, in December 2010 Illumina sequencers	10:25:42

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1	amplified template nucleic acids attached to a solid	10:25:47
2	surface via an appended adapter; correct?	10:25:52
3	A. I'm sorry, could you repeat the question?	10:25:57
4	Q. In December 2010 Illumina sequencers	10:25:59
5	amplified template nucleic acids attached to a solid	10:26:03
6	surface via an appended adapter; correct?	10:26:07
7	A. Well, I would consider the adapter part of	10:26:13
8	the template nucleic acid once it's been incorporated.	10:26:17
9	Q. I understand the distinction you're drawing.	10:26:23
10	But you would agree that during Illumina sequencing	10:26:51
11	the template nucleic acid molecules are attached to a	10:26:55
12	solid surface via the appended adapters?	10:27:01
13	A. Well, they're attached to a flow-cell.	10:27:08
14	Q. Via the adapters; correct? If you could just	10:27:12
15	look in your first sentence of Paragraph 38. It says	10:27:17
16	it's attached to the solid surface via the appended	10:27:20
17	adapter. Do you see that?	10:27:23
18	A. Yes.	10:27:26
19	Q. And so would you agree that the template	10:27:32
20	nucleic acid molecules in Illumina sequencing are	10:27:38
21	attached via the appended adapter?	10:27:43
22	A. Again, as I said, I would still consider the	10:27:55

1	adapter part of the template nucleic acid once it's	10:27:58
2	been incorporated.	10:28:02
3	Q. The appended adapters are a portion of the	10:28:12
4	template nucleic acid molecules.	10:28:15
5	A. Yes, those anneal to the primers on the	10:28:24
6	surface of the flow-cell.	10:28:29
7	Q. The amplification process used for Illumina	10:28:34
8	sequencers was called bridge amplification; correct?	10:28:38
9	A. Correct.	10:28:42
10	Q. And in December 2010 bridge amplification was	10:28:44
11	also referred to as bridge PCR; correct?	10:28:47
12	A. I believe so, but it's somewhat of a misnomer	10:28:53
13	because bridge amplification is a very distinct sort	10:29:05
14	of reaction that takes place on the surface of a flow-	10:29:13
15	cell, and I would not -- if we're thinking of some of	10:29:17
16	the other exhibits in this case that refer to PCR in	10:29:27
17	general, I would think of the two as being very	10:29:30
18	distinct from one another.	10:29:33
19	Q. Bridge amplification -- the process of bridge	10:29:36
20	amplification uses the polymerase chain reaction;	10:29:41
21	correct?	10:29:48
22	A. Under very specialized conditions, including	10:29:48

1	I believe isothermal denaturation. So there are some	10:29:59
2	very distinct differences as compared to how	10:30:03
3	traditional PCR may be performed, for instance with	10:30:06
4	heat denaturation. So it's a very specialized	10:30:09
5	amplification approach.	10:30:13
6	Q. Now, in December 2010 Roche/454 sequencers	10:30:17
7	amplified template nucleic acids on microbeads;	10:30:25
8	correct?	10:30:31
9	A. Yes, with a different type of amplification	10:30:35
10	process.	10:30:48
11	Q. And the amplification process used for	10:30:48
12	Roche/454 sequencers was called emulsion PCR; correct?	10:30:51
13	A. Correct.	10:30:58
14	Q. Now, Doctor, as of December 2010 the Illumina	10:31:02
15	sequencing work flow included the addition of standard	10:31:06
16	adapter molecules, such as the P5 and P7 adapters, to	10:31:10
17	fragmented DNA; correct?	10:31:16
18	A. It wasn't always fragmented to begin with.	10:31:20
19	You could, for instance, start with unfragmented DNA	10:31:32
20	and through the process of PCR one could generate	10:31:38
21	amplicons that are of the size required for Illumina	10:31:48
22	sequencing with the P5 and P7 on either end.	10:31:53

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1	Q. As of December 2010 the Illumina sequencing	10:32:09
2	work flow included the addition of standard adapter	10:32:12
3	molecules such as the P5 and P7 adapters to nucleic	10:32:17
4	acids to be sequenced; correct?	10:32:24
5	A. P5 and P7 sequences were required to	10:32:32
6	facilitate sequencing.	10:32:37
7	Q. And as of December 2010 the Illumina	10:32:45
8	sequencing work flow included a PCR step to	10:32:49
9	selectively enrich DNA fragments having adapter	10:32:54
10	molecules on both ends; correct?	10:32:58
11	A. I believe there are exceptions, such as	10:33:03
12	PCR-free whole genome sequencing, where the adapters	10:33:36
13	are ligated to either end, and the amplification may	10:33:41
14	not need to be done -- or, rather, isn't done before	10:33:49
15	loading onto the sequencer.	10:33:53
16	Q. Okay. I do want to explore that. But let's	10:33:59
17	just maybe frame it this way: As of December 2010 the	10:34:02
18	standard Illumina sequencing work flow included a PCR	10:34:07
19	step to selectively enrich DNA fragments having	10:34:12
20	adapter molecules on both ends; correct?	10:34:15
21	A. Well, the purpose of the PCR was to generate	10:34:24
22	enough library to be sequenced.	10:34:28

1	Q. So do you have an understanding as to whether	10:34:37
2	or not in December 2010 the standard Illumina	10:34:39
3	sequencing work flow included a PCR step to	10:34:42
4	selectively enrich DNA fragments having adapter	10:34:47
5	molecules on both ends?	10:34:50
6	A. If the library's amplified before loading	10:34:57
7	onto the flow-cell, that will be done. There's, of	10:35:01
8	course --	10:35:29
9	But it doesn't mean that everything in the	10:35:29
10	sample will necessarily have a P5 and P7 when it's	10:35:33
11	loaded on the sequencer, if that's what you're getting	10:35:37
12	at.	10:35:39
13	Q. You mentioned an exception. You mentioned	10:35:42
14	the PCR-free whole genome sequencing method where the	10:35:44
15	adapters were ligated and no PCR enrichment step was	10:35:56
16	done before loading on the sequencer. Do you recall	10:36:02
17	that?	10:36:05
18	A. Yes.	10:36:06
19	Q. Was that available as of December 2010?	10:36:07
20	A. I did not investigate that as part of my	10:36:11
21	review for this case.	10:36:20
22	Q. Sitting here today, as of December 2010, are	10:36:28

1	you aware of any exceptions to the Illumina sequencing	10:36:41
2	work flow using a PCR step to selectively enrich DNA	10:36:43
3	fragments having adapter molecules on both ends?	10:36:50
4	A. It depends on the protocol. I'm thinking of,	10:37:24
5	if you do multiplex amplicon sequencing, or even just	10:37:31
6	a single sample, and you amplify it using primers that	10:37:37
7	are directed at the gene sequence but have the adapter	10:37:45
8	sequences at the 5' ends, it is possible that you will	10:37:49
9	generate PCR products that lack P5 and P7 on both	10:37:53
10	sides, and you don't necessarily need to further	10:38:00
11	amplify that, to my understanding, before loading it	10:38:03
12	onto the surface of a flow-cell.	10:38:06
13	Q. As of December 2010, if one did multiplex	10:38:15
14	amplicon sequencing and the primer sequences did not	10:38:20
15	have the adapter sequences at the 5' ends, a person of	10:38:28
16	skill in the art would have needed to include a PCR	10:38:41
17	step to selectively enrich DNA fragments having	10:38:46
18	adapter molecules on both ends; correct?	10:38:51
19	A. Again, I don't think one would need to. One	10:38:52
20	could also just ligate adapters and purify away the	10:38:58
21	unligated adapter.	10:39:05
22	Q. And are you aware of references disclosing	10:39:07

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1 this prior to December 2010 in the absence of the PCR 10:39:11
2 step? 10:39:16

3 A. Well, Gloor would come to mind, but I can't 10:39:17
4 recall the specifics. So if I were allowed to look at 10:39:48
5 the exhibit, I could let you know whether that's the 10:39:52
6 case, because I believe Gloor amplified -- I believe 10:39:54
7 the barcode is at the 5' end of the primer, but 10:40:15
8 there's not an adapter beyond that. And so Gloor must 10:40:18
9 add the adapter somehow after. 10:40:24

10 So in Gloor each sample is amplified on 10:40:28
11 its own to generate amplicons, and from my 10:40:30
12 recollection -- but I'd want to confirm it -- I don't 10:40:38
13 believe they are pooled and further amplified before 10:40:42
14 loading on the surface of a flow-cell. But if you'd 10:40:46
15 like, I could confirm that. 10:40:50

16 Q. We'll take a look at that -- okay? -- because 10:40:51
17 I do want to look at that. We'll circle back to it 10:40:55
18 within the next hour. Okay? 10:40:58

19 A. Okay. 10:41:00

20 Q. I'm going to hand you what's been marked as 10:41:04
21 Exhibit 1003 from the 964 IPR, and this is 10:41:06
22 Dr. Spellman's declaration. 10:41:14

1	(Exhibit 1003 previously marked for	10:41:15
2	identification.)	10:41:38
3	Q. And could you turn to Page 38, please.	10:41:38
4	A. I'm there.	10:41:47
5	Q. There's a Figure 8 on Page 38. Are you	10:41:53
6	there?	10:41:56
7	A. Yeah.	10:41:57
8	Q. And he has drawn a depiction of non-unique	10:41:57
9	dual-indexing there; correct?	10:42:00
10	A. That's correct.	10:42:06
11	Q. And in the setup of Figure 8, the 5' and 3'	10:42:09
12	identifier sequences are saturated, in that every	10:42:14
13	possible pair of identifier sequences is used;	10:42:19
14	correct?	10:42:27
15	A. In this case, yes.	10:42:34
16	Q. And so if one were to use this non-unique	10:42:44
17	dual-indexing setup, one could identify and exclude	10:42:48
18	sequences containing only one identifier sequence;	10:42:52
19	correct?	10:42:56
20	A. For non-unique dual-indexing, you need both	10:42:56
21	indices to be able to make sample assignment.	10:43:27
22	Q. So, for example, if the sequence analysis	10:43:40

1	identified a nucleic acid analyte containing 5' index	10:43:42
2	B but no 3' index, you could exclude that sequence	10:43:47
3	from the analysis; correct?	10:43:53
4	A. You want to know what sample it belongs to.	10:44:08
5	Q. And in this non-unique dual-indexing setup,	10:44:24
6	one could also identify and exclude sequences	10:44:28
7	containing an incorrect pair of identifier	10:44:31
8	sequences -- for example, a sequence that contained	10:44:35
9	identifier sequence A and then an erroneous barcode	10:44:38
10	not corresponding to any of the original identifier	10:44:43
11	sequences. Correct?	10:44:45
12	A. False. No. In non-unique dual-indexing	10:44:46
13	indices are repeated among samples, and therefore you	10:44:52
14	need --	10:45:00
15	Sorry, could you repeat your question?	10:45:06
16	Q. Sure. In this non-unique dual-indexing	10:45:08
17	setup, one could identify and exclude sequences	10:45:12
18	containing incorrect pairs of identifier sequences --	10:45:15
19	for example, a sequence containing identifier sequence	10:45:20
20	A and an erroneous identifier sequence not	10:45:23
21	corresponding to any of the original identifier	10:45:28
22	sequences.	10:45:31

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1	A. No. With non-unique dual-indexing, you would	10:45:37
2	not have the ability to do that.	10:45:39
3	Q. So, for example, if a sequence was obtained	10:45:44
4	that had identifier sequence A and an identifier	10:45:47
5	sequence that did not correspond to any of identifier	10:45:53
6	sequences 1 to 6, one could exclude that erroneous	10:46:02
7	sequence; correct?	10:46:08
8	A. Well, if it didn't contain another sequence,	10:46:54
9	another barcode 1 through 6, I wouldn't consider it	10:47:00
10	having a pair of identifier sequences. So no, I would	10:47:03
11	consider that just having a sequence with one barcode	10:47:08
12	on it.	10:47:11
13	Q. And so, for example, if the second barcode,	10:47:13
14	we'll call it in this case the 3' index, included	10:47:18
15	several additional bases that weren't in any of the	10:47:23
16	original 3' indexes but a correct barcode on the 5'	10:47:26
17	end, one could exclude that from the analysis;	10:47:33
18	correct?	10:47:36
19	A. But how is that possible? Because an index	10:47:37
20	read would be of a defined link, so you couldn't read	10:47:39
21	more bases beyond the index.	10:47:42
22	Q. And so if there -- if in the index there was	10:47:53

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1	a --	10:47:56
2	A. I'm sorry. Could I just clarify?	10:47:59
3	Q. Sure.	10:48:01
4	A. It depends on the type of library, if the	10:48:02
5	index read is a separate read, versus if the index is	10:48:04
6	in line with other nucleic acid. I'm sorry for	10:48:09
7	interrupting.	10:48:12
8	Q. Okay. And could you clarify your answer? I	10:48:13
9	want to make sure I understand it.	10:48:17
10	A. Could you repeat the original question?	10:48:20
11	Q. If the second barcode -- we'll call it in	10:48:24
12	this case the 3' index -- included several additional	10:48:28
13	bases that weren't in any of the original 3' indexes	10:48:32
14	but a correct barcode on the 5' end, one could exclude	10:48:35
15	that from the analysis; correct?	10:48:40
16	A. It depends on whether you're using that as	10:48:51
17	part of the search motif or not. You'd have to make a	10:48:53
18	conscious decision is that part of the index search	10:48:57
19	space or not. And so if you decided to include those	10:49:01
20	extra bases in your index search, it wouldn't match	10:49:11
21	the index you're looking for.	10:49:15
22	Q. Let's take a look at the setup of Figure 8	10:49:20

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1	again, but this time I want you to assume that no	10:49:23
2	sample is assigned to B-2. So, in other words, the	10:49:29
3	assigned pairs of identifier sequences are not	10:49:35
4	saturated. Correct? Do you understand?	10:49:39
5	A. I understand.	10:49:43
6	Q. Now, this would still be a non-unique dual-	10:49:44
7	indexing setup -- correct? -- in that individual	10:49:48
8	identifier sequences are being used for different	10:49:51
9	samples?	10:49:53
10	A. Yes, the tags are repeated among samples.	10:49:57
11	Q. Now, in this non-unique dual-indexing setup,	10:50:12
12	one could identify and exclude sequences containing an	10:50:15
13	incorrect pair of identifiers -- for example, B-2.	10:50:19
14	Correct?	10:50:25
15	A. Not quite, because if you're trying to figure	10:53:13
16	out what samples particular sequences belong to, in	10:53:18
17	non-unique dual-indexing you need the match -- you're	10:53:27
18	looking for a match to both of the barcodes that are	10:53:35
19	repeated -- both of the barcodes that, because the	10:53:41
20	barcodes are repeated among samples, it doesn't give	10:53:44
21	you the ability to say "this read doesn't belong with	10:53:47
22	sample B-1 because it has barcode B-2," for instance.	10:53:54

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1	Q. In my question we're just discussing whether	10:54:26
2	or not one could exclude sequences containing an	10:54:45
3	incorrect pair of barcodes that was not assigned to	10:54:51
4	any of the original samples in this non-unique	10:54:56
5	dual-indexing setup. Do you understand the question?	10:55:06
6	A. I do.	10:55:09
7	Q. So if one obtained sequences containing an	10:55:17
8	incorrect pair of identifiers -- for example, B-2 --	10:55:21
9	that was not assigned to any of the original samples,	10:55:26
10	one could identify and exclude those sequences;	10:55:32
11	correct?	10:55:38
12	A. I think in this case the problem is barcode 2	10:56:29
13	is repeated among other samples in the set, as is	10:58:23
14	barcode B, which makes it difficult to do exclusion.	10:58:33
15	Q. So if you received an index read that was B-2	10:58:42
16	in this non-unique dual-indexing setup we've been	10:58:47
17	discussing, would you assign it to, for example, C-2	10:58:50
18	or B-1?	10:58:57
19	A. For non-unique dual-indexing the challenge is	11:02:49
20	indexes are repeated among one another, and you need	11:02:52
21	both to be able to make the assignment. So in this	11:02:58
22	case, you wouldn't assign B-2 to B-1 or C-2.	11:03:44

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1	Q. So you could exclude the index read that was	11:03:55
2	B-2 in this non-unique dual-indexing setup because it	11:03:59
3	did not correspond to any of the original assigned	11:04:06
4	index reads for the samples; correct?	11:04:11
5	A. There wouldn't be a sample to assign it to.	11:05:19
6	Q. You agree that sequences with incorrect pairs	11:06:30
7	of identifiers can be identified and excluded in a	11:06:33
8	non-unique dual-indexing study provided that the	11:06:38
9	identifier sequence pairs as assigned are not	11:06:42
10	saturated?	11:06:45
11	A. Yeah, but that's very rare, isn't it? I	11:06:48
12	mean, folks are typically trying to figure out --	11:06:51
13	Q. That's not my question.	11:06:54
14	A. -- a minimum number of indices that can be	11:06:55
15	used.	11:06:57
16	MR. RAICH: Move to strike as	11:06:58
17	nonresponsive.	11:06:59
18	MR. MATTY: He's answering your question.	11:07:00
19	If you want to reask it.	11:07:01
20	Q. You agree that sequences with incorrect pairs	11:07:02
21	of identifiers can be identified and excluded in a	11:07:05
22	non-unique dual-indexing study provided that the	11:07:10

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1	identifier sequence pairs as assigned are not	11:07:14
2	saturated?	11:07:18
3	A. As I was saying, that would be an unlikely	11:07:23
4	scenario because researchers would typically be	11:07:33
5	considering the minimum number of indices that can be	11:07:39
6	used to sequence a given number of samples. If you	11:07:44
7	had 12 samples, for instance, I would use indices A-1	11:07:51
8	through 12.	11:07:58
9	If I had, in your example, 95 samples, I	11:07:58
10	probably wouldn't leave a hole in the middle. I would	11:08:03
11	actually go through the index schema.	11:08:07
12	So the kits that Illumina provided, I	11:08:13
13	recall vividly, used in my own research, may have	11:08:17
14	eight, let's say, indices for the eight rows of a 96	11:08:26
15	well plate and 12 columns for -- to make the	11:08:34
16	combinations here. It's only showing 6 by 6; right?	11:08:37
17	But imagine 8 by 12, just putting myself in the frame	11:08:42
18	of doing these experiments as a researcher.	11:08:45
19	I would never leave a gap. What you would	11:08:49
20	do is, you would go in order; right? If I had 96	11:08:52
21	indices but I only had 15 samples, I wouldn't just	11:08:57
22	leave a gap in the middle of the plate. I would use	11:09:02

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1	index A-1 through 12 -- right? -- and then I would go	11:09:05
2	on and do B-1, B-2, and B-3.	11:09:10
3	And in that configuration -- right? -- you	11:09:14
4	know, it -- or maybe I have it flipped.	11:09:20
5	But you get the idea. You would fill it	11:09:24
6	up in sequential order.	11:09:26
7	Q. And if in the setup you're describing you	11:09:30
8	obtained an index read of B-12, you could identify and	11:09:32
9	exclude that read; correct?	11:09:37
10	A. Maybe, but it wouldn't be a design choice.	11:09:48
11	It's not as though I would set up an experiment	11:10:17
12	intentionally to be able to do that. And the way I	11:10:20
13	described filling out -- there's different ways to	11:10:26
14	fill it out. What I was getting at is, I wouldn't	11:10:28
15	leave a hole right in the middle where you described	11:10:30
16	B-2. I would try to use the minimum number of indices	11:10:33
17	to sequence a given number of samples.	11:10:36
18	So let's say I had 48 samples. I might	11:10:38
19	use 6 times 8 to fill out a full matrix; right? If I	11:10:43
20	had 12 samples I might use 4 by 3.	11:10:50
21	Basically, with combinatorial indexing,	11:10:54
22	the whole idea of it is -- and this is what	11:10:57

1	Parameswarm taught -- is it allows you to sequence a	11:11:01
2	remarkable number of samples -- and what Gloor taught	11:11:04
3	as well -- with a minimum number of primers.	11:11:07
4	And so it's unlikely a design choice would	11:11:10
5	ever be to have a very sparse non-unique dual-indexing	11:11:15
6	matrix. The design choice of a researcher would be to	11:11:19
7	have a very compact matrix. And maybe there are edge	11:11:23
8	cases. Maybe there's an odd number of samples and you	11:11:29
9	wind up with a gap. But by and large, it's not as	11:11:32
10	though a POSA would do that by design -- leave a gap	11:11:35
11	so they can do some exclusion step -- but a POSA would	11:11:40
12	try to minimize the number of primers they need to use	11:11:44
13	to sequence a given set of samples. And generally,	11:11:48
14	there are many ways to fill up a saturated non-unique	11:11:52
15	dual-indexing matrix.	11:11:56
16	MR. RAICH: I'll move to strike that as	11:12:00
17	nonresponsive.	11:12:01
18	Q. I'm going to ask again. I'm not asking you	11:12:02
19	about whether or not something is rare or not or how	11:12:06
20	you would do it, just whether or not one could exclude	11:12:08
21	it or not, given the scenario I'm describing.	11:12:11
22	So you agree that sequences with incorrect	11:12:15

1	pairs of identifiers can be identified and excluded in	11:12:18
2	a non-unique dual-indexing study provided that the	11:12:22
3	identifier sequence pairs assigned to the original	11:12:25
4	samples are not saturated?	11:12:30
5	MR. MATTY: Objection, asked and answered.	11:12:34
6	A. I would say not by design choice. A POSA	11:12:40
7	would seek to minimize the gaps in a matrix and in	11:12:43
8	many cases would be able to fill out a saturated	11:12:50
9	non-unique dual-indexing schema, because, again, the	11:12:54
10	whole idea -- and this is what Gloor taught in the	11:12:57
11	introduction -- or in the paper, at least -- one can	11:13:03
12	sequence a large number of samples with a minimum	11:13:06
13	number of primers. And so in seeking to minimize the	11:13:09
14	number of primers one uses, one would try to fill out	11:13:12
15	a fully saturated non-unique dual-index matrix.	11:13:18
16	So maybe there's rare occasions when	11:13:24
17	there's an odd number of samples and that's just not	11:13:25
18	possible, but it wouldn't be a design choice, no.	11:13:29
19	Q. So in those situations where there is an odd	11:13:33
20	number of samples, one could exclude sequences with	11:13:36
21	incorrect pairs of identifiers in a non-unique	11:13:40
22	dual-indexing study, provided that you obtained	11:13:45

1	identifier sequence pairs -- strike that.	11:13:49
2	So in the situation where there is an odd	11:13:52
3	number of samples, one could identify and exclude	11:13:56
4	sequences with incorrect pairs of identifiers in a	11:14:03
5	non-unique dual-indexing study because the identifier	11:14:07
6	sequence pairs as originally assigned were not	11:14:12
7	saturated?	11:14:14
8	A. We could go down the path of prime numbers if	11:14:20
9	you'd like. But with nine samples, you could form	11:14:23
10	that with 3 by 3. So it's not just odd numbers of	11:14:25
11	samples that you would have an incomplete matrix.	11:14:30
12	Q. You don't want to answer my question, Doctor.	11:14:39
13	It's interesting.	11:14:42
14	MR. MATTY: You're asking him questions	11:14:42
15	about a theory that wasn't in Spellman and wasn't in	11:14:43
16	the petition. He's taking his time to think about it	11:14:46
17	and he's answering your questions fairly.	11:14:48
18	MR. RAICH: No speaking objections,	11:14:51
19	counsel. No colloquies.	11:14:52
20	MR. MATTY: Then don't be argumentative	11:14:54
21	with the witness, please.	11:14:56
22	Q. I'm handing you what's been marked as Exhibit	11:15:04

1	1001 in the 965 IPR.	11:15:07
2	Q. Now, this is the '200 patent that you opined	11:15:21
3	about in your declaration; correct?	11:15:31
4	A. That's correct.	11:15:36
5	Q. And one of the named inventors is George	11:15:40
6	Church; correct?	11:15:44
7	A. That's correct.	11:15:47
8	Q. Do you know him?	11:15:48
9	A. Not personally.	11:15:49
10	Q. Have you collaborated with him?	11:15:51
11	A. Not that I recall. He has a very big lab. I	11:15:56
12	don't recall -- certainly no direct collaboration with	11:16:07
13	him, no.	11:16:09
14	Q. Have you taught a class with him?	11:16:11
15	A. No, but he gives great lectures.	11:16:17
16	Q. Were you taught by him?	11:16:19
17	A. I was not.	11:16:21
18	Q. Have you published with him?	11:16:24
19	A. I don't believe so. Some of our author lists	11:16:26
20	are very long, but I don't have any recollection of	11:16:34
21	George Church being on those, no.	11:16:39
22	Q. Have you applied for funding with him?	11:16:41

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1	A. Again, no -- not directly with him, and I	11:16:45
2	don't believe with a member of his lab, either.	11:16:52
3	Q. What's his relationship to your current	11:16:57
4	employer, the Broad Institute?	11:16:59
5	A. I don't know his specific title.	11:17:02
6	Q. What is your understanding of his	11:17:10
7	relationship to the Broad Institute?	11:17:12
8	A. I don't interact with him there, so I really	11:17:15
9	don't know.	11:17:23
10	Q. To your knowledge, does he have a	11:17:25
11	relationship with the Broad Institute?	11:17:27
12	A. He might. There's, gosh, many, many	11:17:29
13	thousands of individuals who are just affiliated with	11:17:48
14	the community. It doesn't mean they're directly	11:17:52
15	involved in any of our science. Some investigators	11:17:59
16	are more engaged than others but effectively have	11:18:08
17	their own home institutions -- which for George I	11:18:13
18	understand is Harvard.	11:18:17
19	Q. One of the named inventors is Mark Umbarger.	11:18:18
20	Do you know him?	11:18:26
21	A. I don't know Mark.	11:18:27
22	Q. And another of the named inventors is Gregory	11:18:33

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1	Porreca. Do you know him?	11:18:36
2	A. I don't. Neither of them come to mind. I	11:18:38
3	don't know if we've crossed paths at some point --	11:18:43
4	maybe at a conference -- but I have no recollection of	11:18:45
5	them specifically.	11:18:49
6	Q. Now, the patent is assigned to Molecular Loop	11:18:50
7	Biosciences. Do you see that?	11:18:55
8	A. I see that.	11:18:56
9	Q. And before you were asked to work on these	11:18:57
10	proceedings, were you aware of Molecular Loop	11:18:59
11	Biosciences?	11:19:08
12	A. I'd heard of the name.	11:19:08
13	Q. And what was your understanding of Molecular	11:19:09
14	Loop Biosciences?	11:19:14
15	A. It just was a familiar name. They're a	11:19:14
16	Cambridge-based company. I didn't know much more	11:19:17
17	about them.	11:19:22
18	Q. Were you aware of the patents at issue in	11:19:23
19	these proceedings before you were asked to work on	11:19:27
20	them?	11:19:29
21	A. I don't believe so, but it's certainly in my	11:19:30
22	domain of expertise, so it's possible I've come across	11:19:40

1	it.	11:19:43
2	Q. Okay, could you turn to column 21 of the '200	11:19:49
3	patent, where the claims are listed.	11:19:54
4	A. I'm there.	11:20:05
5	Q. Now, claim 1 of the '200 patent does not	11:20:06
6	specify the number of identifier sequences used in the	11:20:10
7	multiplex sequencing reaction; correct?	11:20:16
8	A. Do you mean the total number?	11:20:21
9	Q. Total number.	11:20:28
10	A. I don't believe it does. It depends on the	11:20:30
11	number of samples and their reaction.	11:20:45
12	Q. Well, claim 1 does not specify the number of	11:20:50
13	samples used in the multiplex sequencing reaction;	11:20:53
14	correct?	11:21:05
15	A. I don't believe it specifies the number of	11:21:09
16	samples, but to perform a multiplex sequencing	11:21:33
17	reaction, it has to be more than one.	11:21:37
18	Q. Claim 1 does not specify the number of	11:21:45
19	nucleic acid analytes of interest sequenced in the	11:21:48
20	multiplex sequencing reaction; correct?	11:21:53
21	A. Again, it would have to be more than one, and	11:23:00
22	often it's considerably more in a multiplex sequencing	11:23:06

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1	reaction.	11:23:14
2	Q. And claims 2 to 6 of the '200 patent do not	11:23:19
3	specify the number of identifier sequences used in the	11:23:23
4	claimed multiplex sequencing reactions; correct?	11:23:29
5	A. Well, these are dependent claims that	11:23:36
6	would -- I would have the same answer as for claim 1,	11:24:01
7	that it's more than one.	11:24:05
8	Q. And claims 2 to 6 do not specify the number	11:24:09
9	of samples used in the multiplex sequencing reaction;	11:24:13
10	correct?	11:24:20
11	A. A similar response: These are dependent	11:24:20
12	claims, and I believe it would have to be more than	11:24:28
13	one to perform a multiplex sequencing reaction.	11:24:32
14	Q. And claims 2 to 6 do not specify the number	11:24:35
15	of nucleic acid analytes of interest sequenced in the	11:24:38
16	multiplex sequencing reaction; correct?	11:24:43
17	A. Sorry, could you repeat that?	11:24:54
18	Q. Claims 2 to 6 do not specify the number of	11:24:56
19	nucleic acid analytes of interest sequenced in the	11:24:59
20	multiplex sequencing reaction; correct?	11:25:02
21	A. Again, these are dependent claims, and I	11:25:13
22	believe it would have to be more than one, by	11:25:26

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1	definition, in a multiplex reaction.	11:25:28
2	Q. Let's turn back to claim 1 of the '200	11:25:30
3	patent. It recites three steps: a detecting step, a	11:25:33
4	sequencing step, and a validating step. Do you see	11:25:39
5	that?	11:25:41
6	A. I see that.	11:25:45
7	Q. I want you to take a look at the validating	11:25:48
8	step. The validating step of claim 1 of the '200	11:25:51
9	patent recites excluding the sequences of those	11:25:54
10	nucleic analytes of interest containing only one	11:26:00
11	identifier or an incorrect pair of identifiers from	11:26:03
12	sequence analysis of the multiplex sequencing	11:26:05
13	reaction. Do you see that?	11:26:09
14	A. I see that.	11:26:10
15	Q. And the last step is not limited to excluding	11:26:11
16	sequences of nucleic acid analytes of interest	11:26:13
17	containing an incorrect pair of identifiers; correct?	11:26:16
18	A. But in the context of the invention, a	11:26:32
19	sequence with only one identifier --	11:27:09
20	Sorry, could you repeat the question?	11:27:45
21	Q. The last step of claim 1 is not limited to	11:27:48
22	excluding sequences of nucleic acid analytes of	11:27:57

1	interest containing an incorrect pair of identifiers;	11:28:00
2	correct?	11:28:04
3	A. I believe that's correct.	11:28:04
4	Q. And you understand that if a prior art	11:28:22
5	reference disclosed all of the other steps of claim 1	11:28:24
6	and excluded the sequences of those nucleic acid	11:28:28
7	analytes of interest containing only one identifier,	11:28:32
8	that reference would anticipate claim 1; correct?	11:28:35
9	MR. MATTY: Objection to form.	11:28:40
10	A. Well, anticipation analysis is more involved	11:28:41
11	than just that.	11:29:20
12	Q. So you disagree that if a prior art reference	11:29:29
13	disclosed all of the other steps of claim 1 and	11:29:32
14	excluded the sequences of those nucleic acid analytes	11:29:35
15	of interest containing only one identifier, that	11:29:39
16	reference would anticipate claim 1?	11:29:43
17	A. Well, for a patent claim to be anticipated	11:29:46
18	and invalid, it's only if each and every element is	11:30:12
19	found in a single prior art reference range as in the	11:30:17
20	claim.	11:30:22
21	Q. So if a prior art reference disclosed each	11:30:31
22	and all of the other steps of claim 1 and it excluded	11:30:34

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1 the sequences of those nucleic acid analytes of 11:30:39
2 interest containing only one identifier, would that 11:30:43
3 reference anticipate claim 1 or not? 11:30:50

4 A. Again, anticipation analysis is more involved 11:30:53
5 than just that. It also requires that prior art 11:31:04
6 publications must enable a person of ordinary skill in 11:31:09
7 the art to make the invention without undue 11:31:12
8 experimentation. 11:31:16

9 Q. Okay. So if a prior art reference was 11:31:20
10 enabling and disclosed each and all of the other steps 11:31:23
11 of claim 1 and it excluded the sequences of those 11:31:27
12 nucleic acid analytes of interest containing only one 11:31:32
13 identifier, would that reference anticipate claim 1 or 11:31:34
14 not? 11:31:38

15 A. What I said previously was not limiting. 11:31:44
16 Anticipation analysis also requires that a disclosed 11:31:48
17 feature must either be necessarily present in the 11:31:51
18 prior art references or the natural result of elements 11:31:54
19 that are explicitly disclosed by the prior art 11:31:57
20 references. So again, it's more complicated than just 11:31:59
21 that. 11:32:03

22 Q. Other than whether or not a reference is 11:32:19

1	enabling and whether or not it expressly or inherently	11:32:20
2	discloses a particular limitation, what else would you	11:32:25
3	need to know to determine whether or not a reference	11:32:29
4	is anticipating or not?	11:32:31
5	A. It's everything I have in Paragraph 12 of my	11:32:33
6	'200 declaration.	11:32:40
7	Q. Okay. So if a prior art reference disclosed	11:32:58
8	all of the other steps of claim 1 and excluded the	11:33:06
9	sequences of those nucleic acid analytes of interest	11:33:14
10	containing only one identifier, could that reference	11:33:18
11	anticipate claim 1?	11:33:23
12	A. It would have to meet all the criteria that	11:33:25
13	are in Paragraph 12 of my declaration.	11:33:29
14	Q. And if it meets those criteria and the	11:33:33
15	sequences of those nucleic acid analytes of interest	11:33:38
16	containing only one identifier were excluded, would	11:33:43
17	that reference anticipate claim 1?	11:33:47
18	A. If we look at the big picture of this	11:33:50
19	invention, one would appreciate that the method for	11:34:54
20	validating the sequence of a nucleic analyte of	11:35:05
21	interest involves appending -- or, rather, detecting	11:35:10
22	the presence of two or more identifier sequences that	11:35:36

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1 are each uniquely associated with a nucleic acid 11:35:38
2 analyte of interest, and when sequenced, one would 11:35:42
3 want to do the exclusion step for sequences containing 11:35:49
4 only one identifier or an incorrect pair of 11:35:56
5 identifiers from sequence analysis. They're both very 11:35:59
6 important. 11:36:05

7 Q. Okay. So if a prior art reference taught 11:36:06
8 steps 1 and 2 of claim 1 of the '200 patent -- and I'm 11:36:16
9 asking you to assume that it does -- and for step 3 it 11:36:19
10 excluded sequences of those nucleic acid analytes of 11:36:24
11 interest containing only one identifier, would it 11:36:27
12 anticipate claim 1 if that reference was enabled? 11:36:31

13 MR. MATTY: Objection. It's an incomplete 11:36:37
14 hypothetical. 11:36:44

15 A. I did not consider hypothetical situations 11:36:57
16 like that in my analysis. 11:36:58

17 Q. Now, the validating step of claim 1 of the 11:37:01
18 '200 patent is not limited to excluding sequences of 11:37:04
19 nucleic acid analytes of interest containing only one 11:37:08
20 identifier; correct? 11:37:10

21 A. It says "only one or an incorrect pair of 11:37:12
22 identifiers." 11:37:24

1 Q. So if a prior art reference disclosed all of 11:37:25
2 the other steps of claim 1 and excluded the sequences 11:37:28
3 of those nucleic acid analytes of interest containing 11:37:31
4 an incorrect pair of identifiers, that reference would 11:37:34
5 anticipate claim 1, assuming that it's enabled; 11:37:39
6 correct? 11:37:44

7 A. Again, as I said, the anticipation analysis 11:37:44
8 is more involved than that. I have the additional 11:37:46
9 requirements of that spelled out in Paragraph 12 of my 11:37:50
10 declaration. 11:37:52

11 I'm also aware -- not aware of any such 11:37:52
12 references that anticipate the claims and did not 11:37:56
13 consider hypothetical scenarios in my analysis. 11:37:59

14 Q. So if a prior art reference disclosed all of 11:38:02
15 the other steps of claim 1 and excluded the sequences 11:38:05
16 of those nucleic acid analytes of interest containing 11:38:08
17 an incorrect pair of identifiers, could that reference 11:38:12
18 anticipate claim 1? 11:38:16

19 A. That's a big hypothetical. Again, all the 11:38:18
20 requirements of the anticipation that I have spelled 11:38:21
21 out in Paragraph 12 of my declaration -- it's more 11:38:25
22 involved than just that. And again, my analysis did 11:38:28

1	not involve hypothetical situations. I'm not aware of	11:38:31
2	any prior art reference that anticipates claim 1 of	11:38:39
3	this patent.	11:38:42
4	Q. You understand -- well, strike that.	11:38:44
5	Claim 1 does not recite any specific	11:38:45
6	barcode sequences to be used for its method; correct?	11:38:49
7	A. Well, it may not give an exact nucleic acid	11:38:53
8	sequence, but it teaches what should be done, and what	11:39:09
9	should be done is to append two or more identifier	11:39:12
10	sequences that are each uniquely associated with a	11:39:16
11	nucleic acid analyte of interest.	11:39:19
12	It also says the first and second	11:39:22
13	identifier sequences have four or more nucleotides and	11:39:25
14	are different.	11:39:30
15	There may be more in here about it, but	11:39:32
16	those are some examples of what it's teaching.	11:39:35
17	Q. Claim 1 does not set forth the specific	11:39:43
18	sequences of the identifier sequences that should be	11:39:48
19	used; correct?	11:39:51
20	A. Again, claim 1 teaches the types of	11:39:52
21	identifier sequences that should be used, and it's	11:40:00
22	very clear that those are -- that two or more	11:40:03

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1	identifier sequences should each be uniquely	11:40:09
2	associated with a nucleic acid analyte of interest, as	11:40:11
3	well as that the first and second identifier sequences	11:40:16
4	should have four or more nucleotides and are	11:40:19
5	different.	11:40:22
6	Q. Doctor, I'm not asking about the criteria	11:40:28
7	that are set forth. I'm asking whether the nucleic	11:40:49
8	acid sequences for the identifier sequences are	11:40:53
9	spelled out in claim 1 of the '200 patent.	11:40:56
10	A. Again, as I said, the specific A, T, G, C's,	11:40:59
11	et cetera, are not tabulated in the claim, but the	11:41:05
12	claim teaches how one should design those.	11:41:10
13	Q. And claims 2 to 6 of the '200 patent also do	11:41:16
14	not set forth the specific nucleic acid sequences to	11:41:20
15	be used for the identifier sequences; correct?	11:41:26
16	A. Well, there are some additional limitations	11:41:32
17	introduced in the dependent claims. I'm happy to go	11:41:36
18	through those if you'd like.	11:41:40
19	Q. Do any of the additional limitations set	11:41:41
20	forth the specific nucleic acid sequences to be used	11:41:45
21	for the identifier sequences in the claims of the '200	11:41:51
22	patent?	11:41:56

1	A. Again, the specific A's, T's, G's, and C's	11:41:57
2	aren't tabulated, but the claim teaches what should be	11:42:04
3	done, how to design those identifier sequences, so	11:42:06
4	that one can accomplish the goal of validating the	11:42:10
5	sequence of a nucleic acid analyte of interest in a	11:42:13
6	multiplex sequencing reaction.	11:42:17
7	Q. I'm about to move to a new line. Do you want	11:42:28
8	to take a break now, or do you want to continue?	11:42:31
9	We've been going about an hour.	11:42:34
10	A. I'm okay if you are.	11:42:37
11	THE REPORTER: I wonder if we could take a	11:42:40
12	break.	11:42:41
13	THE VIDEOGRAPHER: We are going off the	11:42:42
14	record. The time is 11:42.	11:42:43
15	(Recess taken.)	11:42:45
16	(Exhibit 1005 previously marked for	11:54:44
17	identification.)	11:55:33
18	THE VIDEOGRAPHER: We are back on the	11:55:33
19	record. The time is 11:55.	11:55:38
20	Q. Let's go ahead and hand out the Gloor	11:55:44
21	reference, Exhibit 1005. Everyone has it?	11:55:48
22	A. Yes.	11:55:51

1	Q. Okay. Now, Gloor used an Illumina sequencer	11:55:51
2	for a multiplex sequencing reaction; correct?	11:55:58
3	A. For multiplex sequencing, that's right.	11:56:03
4	Q. So you agree that by 2010 it was known that	11:56:09
5	an Illumina sequencer could be using for multiplex	11:56:14
6	sequencing; correct?	11:56:19
7	A. Yes, I agree.	11:56:25
8	Q. Now, Gloor amplified the rRNA V6 region from	11:56:30
9	272 microbiome samples using PCR primers containing	11:56:37
10	combinatorial sequence tags; correct?	11:56:46
11	A. 272 samples -- I'm sorry, could you repeat	11:56:54
12	the whole thing?	11:57:00
13	Q. Gloor amplified the rRNA V6 region from 272	11:57:01
14	microbiome samples using PCR primers containing	11:57:07
15	combinatorial sequence tags; correct?	11:57:12
16	A. Yes, the same non-unique dual-indexing we've	11:57:34
17	spoken of before -- combinatorial dual-indexing.	11:57:37
18	Q. And on Page 3 of Exhibit 105, Gloor provides	11:57:44
19	the sequences of the primers used to amplify the rRNA	11:57:49
20	V6 region; correct?	11:57:54
21	A. Well, I don't believe those are the entirety	11:57:58
22	of the primers, because they also have tags. But	11:58:07

1 those appear to be what I presume are -- I don't know 11:58:11
2 the sequences, of course -- but I presume these bind 11:58:17
3 that region of the V6 gene, that these are what we 11:58:20
4 would refer to as the gene-specific region of the 11:58:25
5 primer. 11:58:28

6 Q. Now, as of December 2010 the P5 and P7 11:58:29
7 adapters for Illumina sequencers were required for 11:58:35
8 binding the molecules to the oligonucleotides on the 11:58:39
9 surface of the flow-cell for an Illumina sequencer; 11:58:43
10 correct? 11:58:47

11 A. Yes, the P5 and P7 adapter sequences were 11:58:47
12 required to bind -- to bind the DNA template nucleic 11:58:59
13 acid containing -- which contained the adapters to the 11:59:18
14 surface of the flow-cell. But each individual 11:59:21
15 template nucleic acid would only bind with one 11:59:26
16 initially. 11:59:32

17 Q. The primers used to amplify the rRNA V6 11:59:35
18 regions in Gloor did not include the P5 and P7 11:59:40
19 adapters used for Illumina sequencing; correct? 11:59:46

20 A. Well, these sequences are partial sequences, 11:59:49
21 and then there's the tag. I believe the adapters were 11:59:55
22 added later. But I'm figuring we're coming back to 11:59:58

1	that earlier question.	12:00:04
2	If you could please give me a moment to	12:00:05
3	refamiliarize myself with the specifics of how those	12:00:07
4	adapters are added, I think I would be better	12:00:11
5	positioned to be able to address your questions.	12:00:13
6	Q. Of course.	12:00:15
7	A. Thank you. If you happen to know the section	12:00:16
8	of the article and could point me to it, that could	12:02:05
9	save a little bit of time.	12:02:07
10	Q. I can direct you to places in the article.	12:02:11
11	There's a section on sample preparation and	12:02:13
12	amplification at the bottom of -- on Page 23. That	12:02:19
13	might be what you're looking for.	12:02:25
14	A. That would have taken me a while to get to.	12:02:26
15	Thank you.	12:02:29
16	Okay, thank you for that.	12:02:59
17	Q. So Gloor did not mention attaching the P5 and	12:03:00
18	P7 adapters before sending the final sample for	12:03:28
19	Illumina sequencing; correct?	12:03:31
20	A. I don't see it mentioned, but it would be	12:03:34
21	understood to be required.	12:03:37
22	Q. If Gloor hadn't done it, then the sequencing	12:03:40

1	facility would have attached the P5 and P7 adapter to	12:03:43
2	the pooled sample?	12:03:52
3	A. That's my understanding.	12:03:53
4	Q. Could you turn to Page 7 of Gloor, Figure 2.	12:03:55
5	A. Yes.	12:04:26
6	Q. And Gloor in Figure 2 depicts the conceptual	12:04:28
7	work flow for his data analysis; correct?	12:04:33
8	A. At a high level, yes.	12:04:40
9	Q. And if you look at the middle of Page 7,	12:04:43
10	Gloor discusses the extraction of overlapping reads	12:04:49
11	with proper primer sequences and correct sequence	12:04:56
12	tags. Do you see that?	12:05:00
13	A. Which words does it begin with?	12:05:01
14	Q. "The extraction of overlapping reads."	12:05:07
15	A. Oh, I see it. Thank you. I see that.	12:05:10
16	Q. And in the last paragraph on Page 7, Gloor	12:05:16
17	discusses the inspection of sequences with incorrect	12:05:21
18	sequence tags; correct?	12:05:23
19	A. I see that.	12:05:35
20	Q. And one of the largest class of sequence tag	12:05:54
21	errors was complete lack of the left or right end	12:05:58
22	sequence tag; correct?	12:06:04

1	A. It says that was the next-largest class. I'm	12:06:09
2	just clarifying that I don't believe it was the	12:06:23
3	largest class. It just says the next-largest class of	12:06:25
4	sequence tag error was complete lack of the left or	12:06:28
5	right end sequence tag, yeah.	12:06:31
6	Q. So Gloor states that the next-largest class	12:06:33
7	of sequence tag error was complete lack of the left or	12:06:36
8	right end sequence tag; correct?	12:06:39
9	A. Correct.	12:06:44
10	Q. So these are sequences of nucleic acids	12:06:47
11	containing only one identifier sequence; correct?	12:06:54
12	A. I believe so.	12:07:27
13	Q. And Gloor also states that the remaining	12:07:31
14	missing reads are composed of a large number of	12:07:37
15	classes of sequence tag sequences, each containing	12:07:40
16	small number of errors, including additional 5' bases,	12:07:45
17	misincorporated bases, or difficult-to-classify errors	12:07:51
18	that presumably arose during the PCR amplification.	12:07:55
19	Do you see that?	12:07:58
20	A. I see that.	12:08:00
21	Q. And these are sequences of nucleic acids	12:08:00
22	containing an incorrect pair of identifier sequences;	12:08:07

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1	correct?	12:09:11
2	A. I'm not sure I'd consider that an incorrect	12:09:11
3	pair. It is not two of the expected tags, just in an	12:09:26
4	unexpected configuration that Gloor had no ability to	12:09:42
5	see. But these are sequences with only one valid	12:09:50
6	identifier, that we know for combinatorial	12:10:00
7	dual-indexing isn't enough to make a sample	12:10:03
8	assignment.	12:10:05
9	Q. Could we turn to Table 2 of Gloor, on Page 6.	12:10:08
10	Table 2 lists the identifier sequences used in Gloor;	12:10:18
11	correct?	12:10:26
12	A. Correct.	12:10:26
13	Q. And you agree that each of these --	12:10:30
14	Well, let me ask you this: In the context	12:10:34
15	of these patents, are you drawing any distinctions	12:10:38
16	between the term "identifier sequence" and "barcode	12:10:43
17	sequence"? I don't think you are, but I want to just	12:10:46
18	get your confirmation of that being the case.	12:11:00
19	A. I'm just thinking, there are instances in	12:11:07
20	Parameswarm, for instance, they refer to barcode	12:11:10
21	motif. There's a few terms like "barcode," "tag,"	12:11:14
22	"identifier sequence" that are I believe for the most	12:11:20

1	part interchangeable, but maybe I reserve to right to	12:11:26
2	look at if there's a specific instance of it or a	12:11:30
3	different definition of it in the context. I'd	12:11:33
4	appreciate that.	12:11:37
5	Q. Understood. I guess in the context of Gloor,	12:11:37
6	are you drawing any distinctions between Table 2	12:11:41
7	listing sequence tags versus identifier sequence	12:11:45
8	versus barcode sequence, in terms of the nomenclature?	12:11:49
9	A. No, I don't believe these are non-unique	12:12:05
10	identifier sequences.	12:12:07
11	Q. Now, the barcode sequences used in Gloor do	12:12:09
12	not include two of the same bases in a row; correct?	12:12:16
13	A. I would have to go through each and every	12:12:21
14	one. It doesn't look like it. And I don't believe	12:12:44
15	they do, but I also recall Gloor being silent on the	12:12:49
16	matter whether they need to include homopolymers or	12:12:53
17	not.	12:12:57
18	Q. Why don't you take a minute and confirm that	12:12:58
19	the barcode sequences used in Gloor do not include two	12:13:00
20	of the same bases used in a row.	12:13:06
21	A. I recall looking at this in my analysis and	12:13:27
22	believe that is right, that none of those have two or	12:13:43

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1	more in a row. But again, Gloor was silent on the	12:13:45
2	matter of whether that's important or not.	12:13:49
3	Q. Now, I will represent to you that in Table 2	12:13:52
4	there are nine barcodes that are three bases in	12:13:56
5	length, nine barcodes that are four bases in length,	12:13:59
6	eight barcodes that are five bases in length, and	12:14:02
7	eight barcodes that are six bases in length.	12:14:05
8	If each of these nucleotides was adding to	12:14:10
9	the barcodes by chance, what are the odds of not	12:14:13
10	having two or more of the same nucleotides in a row in	12:14:16
11	any of the barcodes used in Gloor?	12:14:20
12	A. Well, there was a whole other reason why they	12:14:23
13	designed three, four -- was it five and six base pair	12:14:39
14	tags, and that had to do with the cluster	12:14:46
15	identification on a nonpatterned flow-cell requiring	12:14:52
16	base diversity at every nucleotide position.	12:14:56
17	So I wouldn't consider this a random	12:14:59
18	collection of tags that we could apply just, you know,	12:15:03
19	sampling statistics to it. But this seems like a	12:15:11
20	rationed, at least in regard to length, set of tags,	12:15:15
21	and it would be difficult to estimate in light of that	12:15:19
22	the probability that two or more nucleotides arose --	12:15:25

1	would arise in a row or what they did. They're just	12:15:29
2	silent on the matter.	12:15:33
3	Q. So the rules that you're referring to for	12:16:36
4	sequence tag choice are set forth at Pages 5 to 6; is	12:16:39
5	that correct?	12:16:47
6	A. That's right, yes. Yes, that's right.	12:16:47
7	So in fact, when we think about this, it	12:17:02
8	further underscores how -- the additional constraints	12:17:05
9	that Gloor imposed on the sequence tag choice.	12:17:17
10	Q. So do those roles set forth in Gloor require	12:17:21
11	or prohibit two consecutive bases that are the same?	12:17:34
12	A. I'm not sure I could say either way, just	12:17:49
13	like Gloor was silent on the matter. All they say is	12:18:33
14	they want base diversity at every cycle. They don't	12:18:36
15	say among how many tags or --	12:18:39
16	It's, I think, just all they say is, "We	12:18:44
17	chose sequence tags to ensure all four nucleotides	12:18:47
18	represented in each of the four positions using	12:18:51
19	parameters similar to those" in barcrawl. This was	12:18:53
20	achieved in part by varying the length of the tags of	12:18:56
21	the nucleotides.	12:18:59
22	So I think we'd almost have to write a	12:19:00

1	Python script to be able to figure that one out.	12:19:03
2	Q. Let's go ahead -- I'm going to hand you what	12:19:32
3	was marked as Exhibit 1001 in the 964 IPR. This is	12:19:35
4	the '852 patent that you opined on in your	12:19:41
5	declaration.	12:19:45
6	(Exhibit 1001 previously marked for	12:20:02
7	identification.)	12:20:05
8	Q. Could you turn to column 20 of the '852	12:20:05
9	patent, just where the claims are listed.	12:20:10
10	A. Sure.	12:20:12
11	Q. Now, claim 1 of the '852 patent does not	12:20:32
12	recite any specific identifier sequences for use in	12:20:35
13	its method; correct?	12:20:39
14	A. Specific sequences such as A, T, G, C, et	12:20:41
15	cetera, aren't tabulated in the claim, but ample	12:20:53
16	instruction is given as to how one would design the	12:20:59
17	indices to be able to achieve the claimed invention.	12:21:02
18	Q. None of the claims of the '852 patent recite	12:21:07
19	any specific identifier sequences for use in their	12:21:11
20	methods; correct?	12:21:14
21	A. Is this the same question, just for all the	12:21:16
22	dependent claims?	12:21:23

1	Q. Correct.	12:21:23
2	A. I would have the same response, that, again,	12:21:24
3	there's not a table of A, T, G, C's, et cetera, that	12:21:29
4	must be used, but ample instruction is given. It's	12:21:35
5	crystal clear how one would go about designing	12:21:40
6	identifier sequences to be able to achieve the claimed	12:21:44
7	invention.	12:21:48
8	Q. Claim 1 does not recite a specific number of	12:21:52
9	identifier sequences used in the sequencing work flow;	12:21:55
10	correct?	12:22:50
11	A. Not specifically, but it does say a plurality	12:22:50
12	of identifier sequences as well as at least two	12:22:56
13	members of a plurality, which I take to mean a	12:23:00
14	collection of identifier sequences. Certainly more --	12:23:08
15	in this case it has to be more than four, because	12:23:15
16	there's at least two members of a plurality that are	12:23:17
17	each unique and each associated with a template	12:23:25
18	nucleic acid, and there must be at least two samples	12:23:29
19	in a multiplex sequencing reaction.	12:23:32
20	So I believe at minimum -- I'd have to	12:23:35
21	think more about it. But I believe at minimum there	12:23:43
22	would be four, but it depends on the number of	12:23:45

1	samples, and, of course, one would understand each of	12:23:50
2	these identifier sequences needs to be unique.	12:23:53
3	And so depending on the number of samples,	12:24:01
4	you could imagine how that could grow in number.	12:24:03
5	Q. Claim 1 doesn't recite a specific number of	12:24:07
6	samples to be sequenced in the sequencing work flow;	12:24:10
7	correct?	12:24:15
8	A. Again, this is a multiplex -- excuse me.	12:24:15
9	Give me one minute, please.	12:24:22
10	It does say at least two different	12:24:25
11	samples.	12:24:30
12	Q. So claim 1, in your view, encompasses	12:24:32
13	sequencing two or more samples in the sequencing work	12:24:38
14	flow; correct?	12:24:41
15	A. I believe that's right.	12:24:44
16	Q. Now, none of the claims of the '852 patent	12:25:07
17	recite a specific number of samples to be sequenced in	12:25:11
18	the sequencing work flow. It's just two or more.	12:25:16
19	Correct?	12:25:19
20	A. I believe that's correct -- at least two or	12:25:51
21	more.	12:26:02
22	Q. And none of the claims of the '852 patent	12:26:06

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1	recites a specific number of identifier sequences used	12:26:14
2	in the sequencing work flow; correct?	12:26:18
3	A. Well, again, it depends on the number of	12:26:20
4	samples. There's a requirement that there must be at	12:26:25
5	least two members of a plurality of identifier	12:26:29
6	sequences incorporated into the template nucleic acids	12:26:33
7	obtained from at least two different samples wherein	12:26:37
8	the two members constitute a distinct pair associated	12:26:40
9	with said template.	12:26:49
10	And implicitly there's a requirement --	12:26:55
11	I'd like to correct -- not "implicitly." Clearly	12:27:01
12	there's a requirement that each of the identifier	12:27:05
13	sequences be unique. And thus the number of	12:27:09
14	identifier sequences scales with the number of	12:27:14
15	samples.	12:27:17
16	Q. So under your interpretation of the claims,	12:27:17
17	the specific number of identifier sequences would be	12:27:23
18	four or more?	12:27:26
19	A. I believe that's right.	12:27:58
20	Q. I'd like to ask you about your claim	12:28:00
21	construction position for the '852 patent. So could	12:28:04
22	you turn -- keep the claim in front of you, but also	12:28:07

1	turn in your declaration to Paragraph 23. Are you	12:28:10
2	there?	12:28:24
3	A. I'm there.	12:28:24
4	Q. Who first proposed the construction set forth	12:28:37
5	in Paragraph 23 of your '852 patent -- excuse me.	12:28:40
6	Who first proposed the construction set	12:28:45
7	forth in Paragraph 23 of your declaration? Paragraph	12:28:48
8	24 of your declaration.	12:28:58
9	A. Sorry, are you asking about Paragraph 24?	12:28:59
10	Q. Yeah. Who first set forth the construction	12:29:02
11	set forth in Paragraph 24 -- strike that.	12:29:06
12	One more time. Who first proposed the	12:29:11
13	construction set forth in Paragraph 24 of your	12:29:14
14	declaration in the '852 patent?	12:29:18
15	A. I'd say the majority came from me, but it was	12:29:26
16	further refined through discussion with counsel. But	12:29:38
17	I stand by what I have in my declaration.	12:29:43
18	Q. Have you ever construed a claim term before?	12:29:48
19	A. Formally, in an IPR proceeding? No.	12:29:55
20	Q. So you interpreted the terms "template	12:30:03
21	cross-over error" and "cross-over error" to mean error	12:30:07
22	from sequences from chimeric molecules created during	12:30:11

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1	cluster amplification and made from template nucleic	12:30:14
2	acids derived from different samples; correct?	12:30:18
3	A. That's correct. It's based on looking at the	12:30:26
4	claim language as well as the intrinsic evidence in	12:30:29
5	the patent, including the abstract specification, so	12:30:32
6	forth; looking also to the prosecution history, which	12:30:35
7	wasn't all that informative in this case but	12:30:38
8	reinforced the notion that the amplification	12:30:42
9	corresponds to cluster amplification on the flow-cell.	12:30:46
10	Q. Let's go ahead and take a look at column 1 of	12:30:49
11	the '852 patent. Now, the preamble of claim 1 doesn't	12:30:53
12	specify that the errors were created during cluster	12:31:03
13	amplification; correct?	12:31:07
14	A. Well, it includes template cross-over error,	12:31:10
15	which is not a conventional term in the art. And so I	12:31:14
16	looked to the specification, the intrinsic evidence in	12:31:20
17	the patent application, to establish its definition.	12:31:23
18	Q. Okay. I understand you looked at the	12:31:27
19	intrinsic evidence -- the text of the specification,	12:31:29
20	and we will get there. But looking at the words of	12:31:32
21	the preamble themselves, it doesn't specify the errors	12:31:35
22	were created during cluster amplification; it simply	12:31:40

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1	references the sequencing work flow. Correct?	12:31:43
2	A. Well, but again, there's a term in here	12:31:46
3	that's not plain and ordinary, and therefore to	12:31:49
4	understand what the preamble of claim 1 is saying, one	12:31:54
5	must look to the intrinsic evidence and establish the	12:31:58
6	definition, which I believe is very clear for what	12:32:01
7	"template cross-over error" means in this patent.	12:32:04
8	Q. Let's keep working through the steps of claim	12:32:07
9	1. I want to understand your position. Now, the	12:32:10
10	incorporation step of claim 1 doesn't state that the	12:32:14
11	cross-over error is created during cluster	12:32:18
12	amplification; correct?	12:32:22
13	A. The incorporating step does not.	12:32:30
14	Q. Now, the combining step doesn't state that	12:32:33
15	the cross-over error is created during cluster	12:32:36
16	amplification; correct?	12:32:39
17	A. That's correct.	12:32:46
18	Q. The amplifying step doesn't state that	12:32:51
19	cross-over error is created during cluster	12:32:54
20	amplification; correct?	12:32:56
21	A. Well, the chimeric sequence includes the type	12:32:58
22	of chimera associated with template cross-over error	12:33:15

1	that's formed on the surface of the flow-cell.	12:33:20
2	Q. The amplification step states that at least	12:33:24
3	one of the clusters comprises a chimeric sequence;	12:33:26
4	correct?	12:33:32
5	A. It does, but I understand based on the whole	12:33:32
6	claim the chimeric sequence this is referring to	12:33:48
7	includes a type of chimera associated with template	12:33:54
8	cross-over error.	12:33:58
9	Q. Well, the amplification step states that at	12:34:03
10	least one of the clusters comprises a chimeric	12:34:05
11	sequence. It doesn't specify that the chimeric	12:34:08
12	sequence is created during cluster amplification;	12:34:11
13	correct?	12:34:19
14	A. Perhaps very narrowly speaking. But when we	12:34:19
15	zoom out and looking at the claim overall, we can see	12:34:21
16	it very clearly. And when we look to, as I laid out	12:34:28
17	in Paragraph 24 of my definition, my understanding of	12:34:35
18	template cross-over error -- when we look to the	12:34:38
19	intrinsic evidence to define that, it's very clear	12:34:41
20	that the chimeric sequence referred to in that step	12:34:43
21	includes the type of chimera that's formed during	12:34:46
22	cluster amplification on the surface of the flow-cell.	12:34:48

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1	Q. Doctor, you said that your understanding of	12:34:58
2	template cross-over is that when you look at the	12:35:38
3	intrinsic evidence to define that, it's very clear	12:35:41
4	that the chimeric sequence referred to in that step	12:35:44
5	includes the type of chimera that's formed during	12:35:48
6	cluster amplification on the surface of the flow-cell.	12:35:52
7	A. My point is, it's not limited to. Other	12:35:56
8	types of chimeras can arise in the sequencing process,	12:36:00
9	but this claim is very clearly directed at the type of	12:36:04
10	chimera that forms during cluster amplification on the	12:36:08
11	surface of a flow-cell, the type of which can lead to	12:36:12
12	template cross-over error.	12:36:16
13	Q. If we go to the discarding step: The	12:36:26
14	discarding step doesn't specify that the cross-over	12:36:30
15	error is created during cluster amplification;	12:36:33
16	correct?	12:36:41
17	A. I would disagree. It includes "thereby to	12:36:41
18	reduce cross-over error," and that is a term I've	12:36:44
19	defined in Paragraph 24 of my declaration based on the	12:36:50
20	intrinsic evidence in the patent, which very clearly	12:36:55
21	shows, in order to reduce cross-over error -- or,	12:36:59
22	rather, it very clearly shows that cross-over error	12:37:08

1 corresponds to the error from sequences of chimeric 12:37:14
2 molecules created during cluster amplification and 12:37:19
3 made from template nucleic acids derived from 12:37:22
4 different samples. Figures 1 and 2 of the 12:37:26
5 specification very clearly show that. 12:37:28

6 Q. When you look at data from an Illumina 12:37:34
7 sequencer, can you tell the difference between 12:37:40
8 cross-over that occurs on the flow-cell or if it 12:37:43
9 occurred before the flow-cell? 12:37:48

10 A. Are you asking me today? At the time of the 12:37:54
11 invention there was no clue template cross-over error 12:37:59
12 was a thing, and so a POSA would have no understanding 12:38:02
13 to be able to evaluate that question. 12:38:06

14 Q. Would a person of skill in the art reading 12:38:12
15 the '852 patent be able to distinguish cross-over 12:38:14
16 errors that were created on the flow-cell versus those 12:38:21
17 that were created before the flow-cell? 12:38:26

18 A. So the '852 patent is not -- the claims of 12:38:32
19 the '852 patent are very clearly directed at reducing 12:38:51
20 template cross-over error, which is the error from the 12:38:55
21 chimeric sequences that arise during cluster 12:38:58
22 amplification on the surface of the flow-cell. 12:39:01

1	It's possible that other chimeras can be	12:39:04
2	formed and sequenced, too, but the method of the	12:39:08
3	invention -- or, rather, the invention is directed at	12:39:11
4	reducing template cross-over error, and that's what's	12:39:14
5	reflected in the claims.	12:39:18
6	Q. Having the knowledge of the disclosure of the	12:39:22
7	'852 patent, would a person of skill in the art be	12:39:52
8	able to distinguish cross-over errors that were	12:39:56
9	created on the flow-cell versus those that were	12:39:59
10	created before the flow-cell?	12:40:02
11	A. Did you say a POSA?	12:40:03
12	Q. A person of skill in the art.	12:40:12
13	A. Okay. If a person of ordinary skill in the	12:40:14
14	art were aware of template cross-over error, which at	12:40:22
15	the time was a completely unappreciated problem -- if	12:40:28
16	they had seen the '852 patent, the disclosure within,	12:40:33
17	one could imagine potential ways to pinpoint where	12:40:55
18	chimeras are being formed, but would also have an	12:41:10
19	understanding that chimeras can form in many parts of	12:41:15
20	the process. And at the time of the invention, in	12:41:19
21	2010, what people were really concerned about with	12:41:23
22	chimeras were those that arise in the amplification of	12:41:27

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1 each individual sample on its own and not -- did not 12:41:30
2 have any awareness that there could be chimeras formed 12:41:36
3 between samples, including in studies like Gloor, 12:41:42
4 where each sample was amplified on its own, not 12:41:45
5 amplified together before being loaded on the 12:41:51
6 sequencer. In Gloor their suspicion was chimeras was 12:41:55
7 purely those formed during the amplification of each 12:41:59
8 individual sample -- nothing about recombination 12:42:02
9 between samples. 12:42:09
10 So I think with that in mind, I think this 12:42:10
11 would all be very new to a POSA in 2010. If they were 12:42:16
12 to see the '852, I think it would be eye-opening, just 12:42:19
13 the way many years later, when the Illumina white 12:42:25
14 paper came out in 2018, that was eye-opening to the 12:42:28
15 field, that this sort of issue could arise, and 12:42:31
16 prompted a set of solutions that just weren't aware at 12:42:39
17 the time of the invention. 12:42:42
18 Q. If you look at the last step of claim 1 of 12:42:45
19 the '852 patent, it recites discarding sequences that 12:42:48
20 contain a combination of identifier sequences that are 12:42:52
21 different than any of the distinct pairs. Correct? 12:42:54
22 A. That's right. 12:43:01

1 Q. And that means combination of identifier 12:43:01
2 sequences that were different than any of the pairs of 12:43:03
3 identifier sequences that were assigned to the 12:43:07
4 samples? 12:43:09

5 A. So each sample was assigned at least two 12:43:09
6 members of a plurality of identifier sequences, which 12:43:13
7 means those two sequences were fully unique and not 12:43:16
8 ever repeated among any other samples that were being 12:43:19
9 sequenced together. And the same was done for at 12:43:23
10 least two different samples. So effectively every 12:43:28
11 sample that's being sequenced together has a fully 12:43:31
12 unique barcode on each end. And it's that which 12:43:35
13 enables one to do the discarding step and to reduce 12:43:41
14 cross-over error. 12:43:45

15 Q. So during unique dual-indexing, sequences 12:43:50
16 with a pair of mismatched barcodes could be created 12:43:56
17 due to barcode contamination prior to cluster 12:44:00
18 amplification; correct? 12:44:03

19 A. But that's not template cross-over error. 12:44:04

20 Q. That wasn't my question. My question was: 12:44:16
21 During unique dual-indexing, sequences with a pair of 12:44:19
22 mismatched barcodes could be created due to barcode 12:44:22

1	contamination prior to cluster amplification; correct?	12:44:26
2	A. Yes, that was one of the reasons Parameswarm	12:44:34
3	speculated for the perfect error-free mismatched	12:44:36
4	barcodes. I don't know it was definitively proven or	12:44:41
5	not. That's something can be hard to prove. But	12:44:47
6	it -- sorry, I lost my train of thought there.	12:44:58
7	Could you repeat the question? Or did I	12:45:01
8	answer it already?	12:45:04
9	Q. I think you answered it. During unique	12:45:07
10	dual-indexing, sequences with a pair of mismatched	12:45:10
11	barcodes could be created due to sample contamination	12:45:13
12	prior to cluster amplification; correct?	12:45:17
13	A. Thank you. Yes. So as I was saying, in	12:45:19
14	Parameswarm that was one of the reasons speculated for	12:45:23
15	the occurrence of perfect mismatched barcodes. But	12:45:26
16	that phenomenon is entirely different than the	12:45:33
17	template cross-over error that's disclosed in the '852	12:45:37
18	patent.	12:45:40
19	Q. During unique dual-indexing, sequences with a	12:45:41
20	pair of mismatched barcodes could be created during	12:45:44
21	PCR amplification of pooled samples prior to cluster	12:45:47
22	amplification; correct?	12:45:51

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1	A. Today we know that. At the time of the	12:45:52
2	invention that wasn't appreciated. There are exhibits	12:46:05
3	showing that libraries pooled and amplified together	12:46:20
4	did not show signs of reads that were assigned to the	12:46:28
5	wrong samples. It wasn't after -- until after the	12:46:35
6	time of the invention, I believe Kircher, Exhibit two	12:46:38
7	thousand -- I need to get the exact number -- it was a	12:46:49
8	paper in 2011, after the time of the invention, I	12:46:53
9	believe was one of the first to shed light on that	12:46:56
10	possibility you mention -- which even that isn't	12:47:00
11	template cross-over error.	12:47:05
12	And I recall Kircher also suspected	12:47:06
13	something was going on on the Illumina sequencers,	12:47:09
14	too, but even then didn't pinpoint that as template	12:47:13
15	cross-over error. That I may be more than you asked	12:47:16
16	for.	12:47:18
17	Q. During unique dual-indexing, sequences with a	12:47:19
18	pair of mismatched barcodes could be created during	12:47:22
19	cluster amplification; correct?	12:47:26
20	A. That was not understood at the time of the	12:47:29
21	invention.	12:47:33
22	Q. But could it occur? Yes or no.	12:47:33

1 A. Based on what we know today, we understand 12:47:35
2 that absolutely that's a serious pitfall in multiplex 12:47:39
3 sequencing reactions, that even if you do everything 12:47:45
4 you can to avoid cross-contamination, to avoid -- you 12:47:47
5 know, to amplify each sample carefully on its own, 12:47:54
6 maybe even in isolation in different labs around the 12:47:57
7 world, you send them together and you load them on a 12:47:59
8 sequencer, that you could have cross-over, is a 12:48:03
9 serious issue. And that just was not appreciated at 12:48:08
10 the time of the invention. 12:48:11

11 Q. The method of claim 1 doesn't allow a person 12:48:12
12 of skill in the art to discard sequences with a pair 12:48:15
13 of mismatched barcodes created during cluster 12:48:20
14 amplification, as opposed to chimeric sequences 12:48:24
15 created at other steps during the sequencing work 12:48:30
16 flow. Correct? 12:48:33

17 A. As I mentioned -- sorry to jump in. 12:48:33

18 As I mentioned, template cross-over error 12:48:35
19 is very specifically referring to the error from 12:48:38
20 sequences of chimeric molecules created during cluster 12:48:42
21 amplification and made from template nucleic acids 12:48:46
22 derived from different samples. 12:48:50

1	So by definition claim 1 is directed at	12:48:51
2	those types of chimeras specifically.	12:48:55
3	Q. But does the method allow one to discard only	12:48:57
4	sequences with a pair of mismatched barcodes created	12:49:01
5	during cluster amplification, as opposed to chimeric	12:49:05
6	sequences created in other steps during the sequencing	12:49:08
7	work flow?	12:49:11
8	A. I think we've come to learn that unique	12:49:15
9	dual-indexing can be a powerful approach that could	12:49:18
10	address other weaknesses in the sequencing work flow,	12:49:27
11	too. But the claims of this invention and the spec	12:49:31
12	very clearly show this is talking about the template	12:49:35
13	cross-over error that arises during cluster	12:49:39
14	amplification on the surface of a flow-cell.	12:49:42
15	MR. RAICH: Why don't we go ahead and	12:49:46
16	break for lunch.	12:49:47
17	THE VIDEOGRAPHER: We are going off the	12:49:48
18	record. The time is 12:50.	12:49:49
19	(Recess for lunch.)	12:49:55
20	THE VIDEOGRAPHER: We are back on the	13:31:50
21	record. The time is 13:32.	13:31:52
22	Q. Dr. Adalsteinsson, we were talking about the	13:31:57

1	'852 patent before the break, and I want to pick back	13:32:01
2	up. So could you get out the '852 patent and turn,	13:32:05
3	please, to column 8. At about line 54 there's a	13:32:12
4	section titled Barcode Sequences. Do you see that?	13:32:30
5	A. I see that.	13:32:34
6	Q. And if you look down to line 65 it states	13:32:39
7	that, "Exemplary methods for designing sets of barcode	13:32:46
8	sequences and other methods for attaching barcode	13:32:50
9	sequences are shown in" previously published patents.	13:32:53
10	Do you see that?	13:32:57
11	A. I see that.	13:32:58
12	Q. The '852 patent doesn't specify the specific	13:33:00
13	barcode sequences that one must use for the claimed	13:33:03
14	methods; correct?	13:33:06
15	A. The '852 patent does not provide a list of	13:33:18
16	sequences for the nucleic acid tags but provides ample	13:33:28
17	instruction as it pertains to how one should go about	13:33:38
18	designing those to overcome template cross-over	13:33:47
19	errors -- or, rather, to reduce template cross-over	13:33:54
20	error.	13:33:57
21	Q. And could you identify for me in terms of	13:33:57
22	column number and line number what the ample	13:34:02

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1	instruction is that you're referring to?	13:34:07
2	A. Well, at a high level, beginning with the	13:34:08
3	claims, I believe the claims are very clear about	13:34:13
4	that. First, if we turn to those, we have a method	13:34:18
5	for validating the sequence of a nucleic acid --	13:34:22
6	sorry, a method -- I was reading the wrong one here.	13:34:27
7	A method for reducing template cross-over error	13:34:34
8	introduced during the sequencing work flow and the	13:34:38
9	method comprising the steps of.	13:34:41
10	So template cross-over error, as I've	13:34:44
11	defined in Paragraph 24 of my declaration, is the	13:34:53
12	error from sequences of chimeric molecules created	13:34:59
13	during cluster amplification and made from template	13:35:03
14	nucleic acids derived from different samples. And	13:35:06
15	that definition is supported by figures such as figure	13:35:09
16	1 and figure 2 of the spec, which show how barcodes	13:35:14
17	have to be unique in order to identify and ultimately	13:35:18
18	reduce template cross-over error which arises on the	13:35:24
19	surface of a flow-cell.	13:35:29
20	In addition to that, the claims include	13:35:33
21	several additional informative elements, including --	13:35:38
22	including that you have at least two members of a	13:35:56

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1 plurality of identifier sequences that are 13:36:11
2 incorporated into the nucleic acid template, as well 13:36:14
3 as dependent claims around the specific order and 13:36:24
4 configuration of those. 13:36:29

5 As for other places within the 13:36:34
6 specification, I don't know those at the top of my 13:36:38
7 mind. If you'd like, I can read through it and flag 13:36:41
8 additional places where I see that. 13:36:46

9 Q. Please. 13:36:49

10 A. Column 2, line 5, describes the invention 13:37:24
11 utilizes two or more identifiers that are uniquely 13:37:26
12 associated with the analyte of interest and describes 13:37:30
13 how those can be used to avoid errors in sequencing. 13:37:37

14 Line 16 discusses two or more identifiers 13:37:49
15 uniquely associated with the analyte. The following 13:38:10
16 line describes them flanking the sequence of interest, 13:38:14
17 consistent with the drawing in figure 1 and 2. 13:38:16

18 Q. Would you agree that the '852 patent leaves 13:38:37
19 it up to the person of ordinary skill in the art to 13:38:42
20 design appropriate barcode sequences for use in the 13:38:45
21 claimed method? 13:38:50

22 A. Well, as I said, the claim is very specific 13:38:56

1	about the types of barcodes that must be used in order	13:39:02
2	to reduce template cross-over error. So I would say	13:39:08
3	one would have to be very deliberate about their	13:39:19
4	choice of barcode sequences to achieve the goals of	13:39:29
5	the invention.	13:39:33
6	Q. In the -- in your view, is the '852 patent,	13:39:41
7	claim 1, directed to a unique dual-indexing approach?	13:39:51
8	A. Could you clarify what you mean, "directed	13:39:56
9	to"?	13:40:00
10	Q. Does it require a unique dual-indexing	13:40:01
11	approach?	13:40:05
12	A. It requires -- or, rather, involves	13:40:06
13	incorporating at least two members of a plurality of	13:40:17
14	identifier sequences, as it says, from at least two	13:40:19
15	different samples where the two members constitute a	13:40:23
16	distinct pair associated with said template.	13:40:26
17	So as we've discussed before, it's very	13:40:29
18	important that the sequence identifiers be unique and	13:40:31
19	not repeated among any other sample. And that's	13:40:35
20	critical. Otherwise one could not accomplish the	13:40:41
21	discarding step and achieve the goal of the patent to	13:40:46
22	reduce cross-over error.	13:40:49

1	Q. So I think what you said is that claim 1 of	13:40:51
2	the '852 patent requires a unique dual-indexing	13:40:55
3	approach. Correct?	13:40:59
4	A. Just to be clear, could I ask how you're	13:41:02
5	defining "unique dual-indexing approach"?	13:41:18
6	Q. It requires -- well, let me flip that back on	13:41:31
7	you. What do you understand unique dual-indexing to	13:41:40
8	be?	13:41:46
9	A. Assigning unique tags, commonly at least two	13:41:46
10	or more, based on how it's used today, to each sample,	13:42:12
11	where no unique tag is repeated among samples. But	13:42:23
12	that is simply the act of indexing, and that simply	13:42:32
13	describes adding the indices to the template nucleic	13:42:40
14	acid.	13:42:44
15	Q. Does claim 1 require assigning unique tags to	13:42:48
16	each sample where no unique tag is repeated?	13:42:56
17	A. It involves incorporating at least two	13:43:00
18	members of a plurality of identifier sequences into	13:43:05
19	the template nucleic acids obtained from at least two	13:43:09
20	samples wherein the said two members constitute a	13:43:13
21	distinct pair associated with said template -- which,	13:43:16
22	as I said before, involves each sequence identifier	13:43:18

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1 must be unique and the sequence identifier -- each 13:43:22
2 sequence identifier cannot be repeated among samples. 13:43:28
3 Otherwise one could not achieve what's claimed in this 13:43:33
4 invention. 13:43:37

5 Q. Is that unique tag approach that you've 13:43:37
6 defined required by claim 1 of the '200 patent? 13:43:41

7 A. So claim 1 of the '200 patent, step i, is, I 13:44:13
8 believe, what you're referring to. And I read step i 13:44:22
9 as detecting the presence of two or more identifier 13:44:28
10 sequences that are each uniquely associated with a 13:44:32
11 nucleic acid analyte of interest. That is my read of 13:44:37
12 this claim. 13:44:40

13 Q. Do you agree that the '852 patent assumes 13:44:55
14 that as of December 2010 it was within the capacity of 13:45:00
15 a person of skill in the art to design suitable 13:45:04
16 barcodes for different sequencing platforms? 13:45:09

17 A. As we discussed before, I believe it's column 13:45:12
18 8, line 65. The '852 patent does include reference to 13:45:46
19 prior patents that have involved designing sets of 13:46:00
20 barcode sequences and for attaching barcode sequences. 13:46:05

21 So by and large, I'd say that was known in 13:46:09
22 the art. But there are additional considerations when 13:46:14

1 it comes to designing barcodes for each sequencing 13:46:20
2 platform. For instance, the requirements one could 13:46:25
3 consider for designing barcodes for pyrosequencing 13:46:29
4 would look very different than what one may consider, 13:46:33
5 for instance, when designing barcodes for Illumina 13:46:36
6 sequencing. As Parameswarm taught, one has to 13:46:39
7 consider the error mode of the sequencer and factor 13:46:43
8 that into the design of barcode sequences. And we 13:46:47
9 looked earlier today at Gloor. Even Gloor had 13:46:50
10 different length of sequences to be tailored to the 13:46:54
11 Illumina platform. 13:46:57

12 Q. Can you turn to column 20 of the '852 patent, 13:47:04
13 line 37. And it states, "The invention is not 13:47:11
14 intended to be limited to use of the sequencing method 13:47:17
15 outlined above, as essentially any sequencing 13:47:20
16 methodology which relies on successive incorporation 13:47:24
17 of nucleotides into a polynucleotide chain can be 13:47:26
18 used." Do you see that? 13:47:30

19 A. I see that. 13:47:32

20 Q. It then lists the Roche/454 and SOLiD 13:47:36
21 systems; correct? 13:47:44

22 A. I see that, but I read the claims of this 13:47:45

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1	invention as being directed towards the Illumina	13:47:47
2	sequencer, in particular with the amplification being	13:47:51
3	on the surface of a flow-cell, and the way figure 1	13:47:53
4	and 2 depict what we all well know as bridge	13:47:58
5	amplification.	13:48:09
6	Q. Let's go ahead and mark or get out Exhibit	13:48:09
7	1004, which is Parameswarm.	13:48:13
8	(Exhibit 1004 previously marked for	13:48:17
9	identification.)	13:48:53
10	Q. And if you could also turn to Paragraph 59 of	13:48:53
11	your declaration in the 964 IPR. You state in the	13:48:58
12	beginning of the paragraph, "Parameswarm discusses	13:49:30
13	three different sequencing systems available in 2007."	13:49:32
14	Do you see that?	13:49:36
15	A. I see that.	13:49:37
16	Q. And then the next sentence, which is at the	13:49:39
17	top of Page 37, you state, "Parameswarm acknowledges	13:49:42
18	that at the time the Illumina and SOLiD sequencing	13:49:47
19	systems provided many more, shorter reads than the	13:49:54
20	Roche/454 pyrosequencers." Correct?	13:49:57
21	A. Yes.	13:50:03
22	Q. Now, "at the time" refers to 2007; correct?	13:50:04

1	A. That's when Parameswarm was published.	13:50:09
2	Q. And then midway down the page, on Page 37, in	13:50:23
3	Paragraph 59, you wrote, "A person of skill in the art	13:50:28
4	would recognize that Parameswarm developed a barcoding	13:50:32
5	approach for pyrosequencing microbiomes as opposed to	13:50:35
6	Illumina sequencing systems because, at the time of	13:50:40
7	Parameswarm, Illumina's sequencing reads were too	13:50:43
8	short to sequence regions of interest. Do you see	13:50:46
9	that?	13:50:50
10	A. I see that.	13:50:55
11	Q. And "at the time of Parameswarm" refers to	13:50:57
12	2007?	13:51:07
13	A. That's when Parameswarm was published.	13:51:07
14	Q. And then the last sentence in the same	13:51:10
15	paragraph states, "A person of skill in the art would	13:51:18
16	further understand that in 2007, further advancements	13:51:21
17	to the Illumina sequencers were needed to adapt	13:51:25
18	Parameswarm's barcoding approach to Illumina	13:51:28
19	sequencers." Do you see that?	13:51:32
20	A. I see that.	13:51:37
21	Q. And again, you refer to 2007, the time when	13:51:38
22	Parameswarm was published; correct?	13:51:41

1	A. This particular section of the declaration	13:51:49
2	refers to Parameswarm, yes.	13:51:51
3	Q. Now, in analyzing patentability of the '852	13:51:52
4	and '200 patents, what date did you use to assess the	13:52:00
5	disclosure of Parameswarm?	13:52:04
6	A. All my analysis was done based on the	13:52:08
7	priority date of the invention, December 23rd, 2010,	13:52:11
8	considering everything that was known in the art up to	13:52:18
9	and including that date.	13:52:21
10	Q. All right. Let's look at figure 1 of Exhibit	13:52:24
11	104, the Parameswarm reference. And Figure 1C depicts	13:52:33
12	the construct sequenced in Parameswarm; correct?	13:53:05
13	A. Correct.	13:53:11
14	Q. Now, Dr. Spellman calculated the read lengths	13:53:14
15	required for sequencing each Parameswarm template	13:53:18
16	nucleic acid as between 71 and 81 nucleotides. Do you	13:53:23
17	recall that?	13:53:28
18	A. I don't. Could you point me to that, please?	13:53:30
19	Q. Sure. It's in Paragraph 171 of Exhibit 1003,	13:53:32
20	which is Dr. Spellman's report I handed you earlier.	13:53:39
21	A. 171. Yes, I'm there.	13:54:06
22	Q. You didn't dispute his calculation of the	13:54:21

1	read lengths required for sequencing each Parameswarm	13:54:25
2	template nucleic acid as being between 71 and 81	13:54:28
3	nucleotides; correct?	13:54:33
4	A. That's right. Parameswarm sequenced	13:54:34
5	exceptionally small fragments of DNA, much smaller	13:54:49
6	than I'd say most would be sequencing in other	13:54:54
7	applications. But yes.	13:54:57
8	Q. Now, the read length of the Illumina	13:55:03
9	sequencer used in Gloor was 76 nucleotides; correct?	13:55:07
10	You acknowledge this in Paragraph 76 of your	13:55:25
11	declaration, if you want to look at it.	13:55:28
12	A. Yes, that's right.	13:56:01
13	Q. So with paired end sequencing, the Illumina	13:56:02
14	sequencer used in Gloor sequenced about 150	13:56:06
15	nucleotides; correct?	13:56:09
16	A. In total, that's right.	13:56:11
17	Q. And by December 2010 read lengths of up to	13:56:31
18	150 nucleotides had been reported using an Illumina	13:56:43
19	sequencer; correct?	13:56:48
20	A. That's right. But the inserts in Gloor were	13:56:50
21	also considerably longer than those in Parameswarm,	13:56:54
22	and for microbiome sequencing, for instance, that	13:57:01

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1 placed some major restrictions on the sorts of regions 13:57:05
2 one could look at. One would have to focus on 13:57:09
3 amplicons that were not too big to be sequenced by the 13:57:13
4 Illumina machine, and also consider the length of the 13:57:20
5 sequence tags, because if you make your sequence tags 13:57:25
6 very long and if you also have other regions, such as 13:57:29
7 of a cloning linker to sequence, before you know it 13:57:33
8 you're eating far into that 150 base pair allotment 13:57:37
9 and constraining the amount of sequencing one can do. 13:57:42
10 So with Parameswarm's exceptionally short 13:57:48
11 DNA fragments, it might be somewhat of a unique case. 13:57:51
12 It would be more challenging with longer DNA 13:57:59
13 fragments. If your insert is, you know, cell-free DNA 13:58:02
14 is 166 bases in size, and with 150 nucleotides a read, 13:58:11
15 it would be very difficult to analyze a sequence and 13:58:17
16 identifiers that weren't exceptionally short. 13:58:21
17 Q. Do the claimants of the '852 or '200 patents 13:58:25
18 say anything about the length of the nucleic acid 13:58:31
19 analytes being sequenced? 13:58:39
20 A. I don't believe they do. But in thinking 13:58:52
21 about what it would mean for a POSA, this would be a 13:58:54
22 consideration -- a person of ordinary skill in the 13:59:03

1 art, a consideration that would come to mind in 13:59:06
2 thinking about what types of analyses can be done. 13:59:08
3 Read lengths were still limiting at the time of the 13:59:12
4 invention, and that made it difficult to sequence all 13:59:16
5 the types of sample sets you would want to sequence in 13:59:20
6 a multiplex reaction. 13:59:26
7 Q. And you agree that by 2010, December 2010, a 13:59:27
8 person of skill in the art would have understood that 13:59:32
9 an Illumina sequencer could be used to sequence about 13:59:34
10 300 nucleotides using pair end sequencing; correct? 13:59:41
11 A. I understand there is a press release 13:59:47
12 announcing that. I don't know when exactly that 13:59:49
13 became broadly available, though. 13:59:52
14 Q. Earlier you referenced some Illumina white 13:59:56
15 papers. Do you recall that? 14:00:12
16 A. I do. 14:00:13
17 Q. Did you locate those Illumina white papers, 14:00:14
18 or were they provided by counsel? 14:00:18
19 A. The one in 2018 announcing this issue was one 14:00:20
20 I vividly remember. By that time I was -- met the 14:00:29
21 definition of a person of ordinary skill of the art -- 14:00:36
22 and well before that, in fact, as a PI of a lab -- and 14:00:42

1 remember vividly the shocking realization that things 14:00:48
2 could go wrong in a multiplex sequencing reaction. So 14:00:54
3 that is one that I distinctly remember. 14:01:00

4 The other white papers -- I believe there 14:01:04
5 were some prior to 2010, including some which 14:01:07
6 showed -- or showed -- or suggested that single index 14:01:12
7 barcoding was sufficient for highly accurate multiplex 14:01:18
8 sequencing on Illumina. That I believe I located, 14:01:21
9 because I don't recall the exact date unique dual 14:01:27
10 indices were introduced by Illumina. I think that was 14:01:31
11 probably mid-2010s. I really don't know. But just 14:01:34
12 it -- I was looking to see was there anything around 14:01:41
13 the time of the invention from Illumina to that 14:01:45
14 regard, and everything I could find was about single 14:01:50
15 index barcoding for multiplex sequencing being 14:01:53
16 accurate enough. 14:01:57

17 Q. So I've handed you what's been marked as 14:02:34
18 Exhibit 2004. This is another one of the materials 14:02:37
19 cited in your declaration. Correct? 14:02:41

20 A. Correct. 14:02:43

21 (Exhibit 2004 previously marked for 14:02:44
22 identification.) 14:02:50

1	Q. Now, I guess same question: Did you locate	14:02:50
2	this paper, or was it provided to you by counsel?	14:03:07
3	A. I located it. And I can't recall exactly	14:03:12
4	when I first saw this, but I do recall seeing it	14:03:20
5	before this case.	14:03:25
6	Q. In the right column of the first page, second	14:03:31
7	full paragraph, Exhibit 2004 states, "While sample	14:03:39
8	multiplexing greatly increases experimental	14:03:47
9	scalability, it also introduces the danger of falsely	14:03:49
10	assigning sequences to their original samples. Some	14:03:54
11	applications, however, require highly accurate	14:03:58
12	genotyping, particularly if conclusions are drawn from	14:04:01
13	the occurrence of rare sequence variants." Do you see	14:04:05
14	that?	14:04:09
15	A. I see that.	14:04:09
16	Q. Do you agree that some applications of sample	14:04:12
17	multiplexing require highly accurate genotyping and	14:04:17
18	that others do not?	14:04:20
19	A. Yes. I would consider applications like	14:04:22
20	Gloor had shown, for instance, microbiome sequencing,	14:04:25
21	as an application that would require highly accurate	14:04:29
22	sequencing, but would agree, not every application	14:04:34

1	would necessarily require, you know, the same level of	14:04:37
2	accuracy.	14:04:43
3	Q. So Exhibit 2004 goes on to state that things	14:04:46
4	like cancer research, ancient DNA research, as two	14:04:52
5	examples of things that may require highly accurate	14:05:10
6	genotyping; is that right?	14:05:13
7	A. Yes, in addition to microbiome sequencing,	14:05:15
8	which just comes to mind given the exhibits in this	14:05:18
9	case, there's, of course, many other applications that	14:05:22
10	retire highly accurate sequencing.	14:05:27
11	Q. You can set that aside.	14:05:40
12	So you've been handed what's marked as	14:06:12
13	Exhibit 2010. This is another one of the materials	14:06:15
14	cited in your declaration. Correct?	14:06:17
15	A. That's right.	14:06:22
16	(Exhibit 2010 previously marked for	14:06:23
17	identification.)	14:06:43
18	Q. Did you locate Exhibit 2010, or was it	14:06:43
19	provided to you by counsel?	14:06:46
20	A. I can't recall for this one.	14:06:49
21	Q. Could you turn to Paragraph 125 of your	14:06:51
22	declaration in the 964 IPR. Are you there?	14:06:56

1	A.	I'm there. Thank you.	14:07:22
2	Q.	And the last sentence of Paragraph 125	14:07:26
3		states, "Meyer 2007, which is Exhibit 2010," quote,	14:07:36
4		"'explains that errors can be easily identified and	14:07:47
5		eliminated when closely related sequences are	14:07:51
6		available for comparison with the single index PTC	14:07:53
7		method described.'" Correct?	14:07:58
8	A.	I see that.	14:08:01
9	Q.	Let's take a look at that sentence in Exhibit	14:08:02
10		2010. It's at Page 4. It's at the bottom of the	14:08:07
11		page, third line from the bottom. And you quoted,	14:08:24
12		"Errors can be easily identified and eliminated when	14:08:39
13		closely related sequences are available for	14:08:42
14		comparison." Correct?	14:08:44
15	A.	I see that, yeah.	14:08:48
16	Q.	The sentence actually starts with "These	14:08:49
17		errors." Correct?	14:08:52
18	A.	That's right.	14:08:59
19	Q.	And in the previous sentence, Exhibit 2010	14:08:59
20		mentions single base-pair insertion and deletion	14:09:04
21		errors; correct?	14:09:07
22	A.	That's right.	14:09:15

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1	Q. And so when read in context, the errors that	14:09:15
2	can be easily identified and eliminated refers to the	14:09:20
3	single base-pair insertion and deletion errors;	14:09:27
4	correct?	14:09:41
5	A. Yes, it appears to be referring to those	14:09:41
6	specific types of errors within the resulting sequence	14:09:44
7	obtained from the sequencer.	14:09:58
8	Q. That sentence is not referring to false-	14:10:03
9	assignment errors; correct?	14:10:08
10	A. That's right. I don't believe this exhibit	14:10:20
11	talks about false assignment. So I believe that's	14:10:36
12	correct. I believe that's focused on sequencing	14:10:39
13	errors as in the wrong bases being detected when the	14:10:50
14	sequence is being read.	14:10:58
15	That, by the way, was the main cause for	14:10:59
16	concern for sample misassignment in general in the art	14:11:02
17	up to the time of the invention, was that the barcode	14:11:08
18	could be read wrong. That's why Parameswarm designed	14:11:12
19	their barcodes to be four nucleotides distinct from	14:11:15
20	one another. And that was really what everybody was	14:11:19
21	worried about at the time of the invention.	14:11:24
22	But yeah, I believe this paper doesn't get	14:11:27

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1 into that. They had dual-indexing, but they only used 14:11:30
2 a single index, and they found that that was -- that 14:11:35
3 that was sufficient to obtain the complete consensus 14:11:38
4 sequences for all -- of the vast majority of samples, 14:11:42
5 underscoring the notion that single indexing was 14:11:46
6 perfectly good enough. 14:11:50

7 Q. Earlier today you mentioned that you did a 14:11:56
8 literature search, searching for references that cited 14:11:58
9 Parameswarm. Do you recall that? 14:12:02

10 A. Well, I looked at some references that were 14:12:04
11 cited in Parameswarm and vice versa, in addition to 14:12:12
12 other papers that have gone into the exhibits. 14:12:19

13 Q. Do you recall seeing references that cited 14:12:24
14 Parameswarm to improve an assay being run on an 14:12:29
15 Illumina sequencer? 14:12:38

16 A. No, but by the time of Gloor, the field had 14:12:40
17 moved beyond pyrosequencing. So a person of skill in 14:12:44
18 the art would not look to a pyrosequencing reference 14:12:47
19 like Parameswarm to improve Gloor's already 14:12:51
20 high-performing non-unique dual-indexing method, which 14:12:56
21 they claimed gave saturating coverage of the 14:12:59
22 microbiome and had very few chimeric sequences in its 14:13:02

1	dataset, which the chimeric sequences Gloor of course	14:13:09
2	was referring to had nothing to do with template	14:13:13
3	cross-over error. Those were simply the errors	14:13:16
4	arising when each sample was amplified on its own.	14:13:18
5	So, no, a person of skill in the art would	14:13:22
6	see Gloor, would see multiplex sequencing working	14:13:26
7	exceptionally well with non-unique dual-indexing, and	14:13:29
8	would have no reason to look back to Parameswarm or	14:13:34
9	pyrosequencing for that matter.	14:13:39
10	Q. So you did not see references that cited	14:13:41
11	Parameswarm in the context of improving an assay to be	14:13:45
12	run on an Illumina sequencer?	14:13:49
13	A. Well, I would have to go back through the	14:13:51
14	various exhibits to tell you that. What I can say is,	14:13:55
15	not every paper cited in a publication is formative	14:14:06
16	in -- to the matter of the publication. In other	14:14:11
17	words, a lot of papers are cited. When we write	14:14:14
18	publications, we cite a lot of papers, just because in	14:14:19
19	some cases it might even be just an early concept	14:14:22
20	that's obsolete right now but was envisioned in the	14:14:29
21	past and of relevance to the matter, and so we include	14:14:33
22	it in the paper, whether or not it had any bearing on	14:14:36

1	what we actually did in terms of the study.	14:14:39
2	And so I could look through the exhibits	14:14:41
3	and see, but I think just because an Illumina -- you	14:14:43
4	know, I don't know if Gloor cited other papers. If	14:14:48
5	Parameswarm were cited, it doesn't necessarily mean	14:14:53
6	that Parameswarm were used.	14:14:55
7	In fact, what I would say with Parameswarm	14:14:59
8	is, Parameswarm taught that non-unique dual-indexing	14:15:03
9	was the way to go. That's ultimately what Gloor used,	14:15:07
10	and that's what worked beautifully well.	14:15:11
11	MR. RAICH: Let's go ahead and take a	14:15:14
12	break.	14:15:16
13	THE VIDEOGRAPHER: We are going off the	14:15:16
14	record. The time is 14:15.	14:15:17
15	(Recess taken.)	14:26:37
16	THE VIDEOGRAPHER: We are back on the	14:26:46
17	record. The time is 14:26.	14:26:48
18	Q. Doctor, did you discuss the substance of your	14:26:53
19	testimony with counsel for Molecular Loop at any time	14:26:55
20	today?	14:27:01
21	A. Could you clarify what you mean by "my	14:27:02
22	testimony"? Is it whatever was in my declaration?	14:27:04

1 Q. Did you discuss the substance of the 14:27:08
2 deposition at any point today during any of our 14:27:10
3 breaks? 14:27:13

4 A. Oh. No. 14:27:13

5 MR. RAICH: I pass the witness. 14:27:15

6 MR. MATTY: We have no questions for 14:27:17
7 today. So we're done. 14:27:19

8 THE VIDEOGRAPHER: This marks the end of 14:27:21
9 the deposition of Dr. Viktor Adalsteinsson. We are 14:27:22
10 going off the record at 14:27. 14:27:26

11 (The deposition concluded at 2:27 p.m.)

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1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2
3 I, Alan H. Brock, Certified Reporter
4 and Notary Public within and for the Commonwealth of
5 Massachusetts, do hereby certify:

6 That Viktor Adalsteinsson, Ph.D., the
7 witness whose deposition is hereinbefore set forth,
8 was duly sworn by me before the commencement of such
9 deposition and that such deposition was taken before
10 me and is a true record of the testimony given by such
11 witness.

12 I further certify that the adverse
13 party, Molecular Loop Biosciences, Inc., was
14 represented by counsel at the deposition.

15 I further certify that the deposition
16 of Viktor Adalsteinsson, Ph.D. occurred at the offices
17 of Finnegan, Henderson, Farabow, Garrett & Dunner LLP,
18 Two Seaport Lane, Boston, Massachusetts on Friday, June
19 20, 2025, commencing, at 9:09 a.m. to 2:27 p.m.

20 I further certify that I am not
21 related to any of the parties to this action by blood
22 or marriage, I am not employed by or an attorney to

1 any of the parties to this action, and that I am in no
2 way interested, financially or otherwise, in the
3 outcome of this matter.

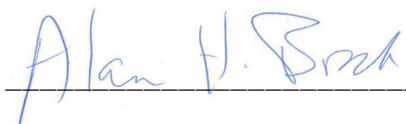
4 IN WITNESS WHEREOF, I have hereunto
5 set my hand this 21st day of June, 2025

6 My commission expires: March 25, 2027.

7

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Alan H. Brock, RDR, CRR

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