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 and IPR2024-00965

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

VIDEOTAPED DEPOSITION OF PAUL SPELLMAN, Ph.D.

Friday, August 1, 2025

Videotaped Deposition of PAUL SPELLMAN, Ph.D., a Witness herein, called for examination by counsel for Patent Owner in the above-entitled matter, pursuant to notice, the witness being duly sworn by MICHELE E. EDDY, RPR, CRR, a Notary Public in and for the District of Columbia, taken at the law firm of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, 901 New York, Avenue, Northwest, Washington, D.C., 20001, at 9:22 a.m.

A P P E A R A N C E S

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E X H I B I T S

(Retained by Counsel)

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1 P R O C E E D I N G S
2 Friday, August 1, 2025
3 - - -
4 VIDEO TECHNICIAN: Good morning. We 09:21:57
5 are going on the record at 9:22 a.m. on August 1st, 09:21:57
6 2025. This is Media Unit 1 of the recorded 09:22:03
7 deposition of Dr. Paul Spellman in the matter of 09:22:06
8 Illumina Inc. versus Molecular Loop Biosciences, 09:22:10
9 Inc., filed before the United States Patent and 09:22:14
10 Trademark Office, Case No. IPR2024-00964. 09:22:16
11 My name is Orson Braithwaite, 09:22:25
12 representing Henderson Legal Services. I'm the 09:22:27
13 videographer. The court reporter is Michele Eddy 09:22:31
14 from the firm Henderson Legal Services. 09:22:33
15 Counsel will now state their 09:22:36
16 appearances and affiliations for the record. 09:22:37
17 MR. MATTY: Brian Matty from 09:22:39
18 Desmarais LLP on behalf of Molecular Loop. 09:22:42
19 MR. RAICH: Bill Raich of Finnegan 09:22:45
20 for Petitioner Illumina. With me today is my 09:22:47
21 colleague, Yoonjin Lee, also with Finnegan, as well 09:22:49
22 as Marcus Burch from Illumina. 09:22:54

1 VIDEO TECHNICIAN: Thank you. Will 09:22:57
2 the court reporter please swear in the witness. 09:22:57
3 - - - 09:23:07
4 PAUL SPELLMAN, Ph.D., 09:23:07
5 having been duly sworn, testified as follows: 09:23:07
6 EXAMINATION BY COUNSEL FOR RESPONDENT 09:23:07
7 BY MR. MATTY: 09:23:08
8 Q. Good morning, Dr. Spellman. 09:23:13
9 **A. Good morning.** 09:23:16
10 Q. You understand you've taken an oath to 09:23:17
11 tell the truth today just as if you were in front of 09:23:19
12 a judge or jury? 09:23:21
13 **A. Yes.** 09:23:22
14 Q. And you know you're being videotaped 09:23:23
15 today, right? 09:23:25
16 **A. Yes.** 09:23:26
17 Q. Is there any reason you can't give full 09:23:26
18 and truthful answers to my questions today? 09:23:28
19 **A. No.** 09:23:31
20 Q. I see you brought in a couple documents 09:23:32
21 with you. Could you hand those to me? 09:23:34
22 **A. Absolutely. (handing).** 09:23:37

Q. (handing). 09:24:16
All right. So you have in front of you 09:24:49
two reply declarations that you submitted in the two 09:24:51
IPRs that we're here about today, right? 09:24:55
A. That's correct. 09:24:57
Q. And I think we got this all down, but just 09:24:58
to make sure, if I refer to the '852 patent, you 09:25:00
understand that is the patent that is at issue in 09:25:04
the 964 IPR? 09:25:05
A. Yes. 09:25:08
Q. And if I refer to the '200 patent today, 09:25:08
you understand that's the patent that's at issue in 09:25:12
the 965 IPR? 09:25:14
A. I do. 09:25:16
Q. All right. What did you do to prepare for 09:25:17
your deposition today? 09:25:18
**A. I read the prior art, read the patents, 09:25:22
read my previous declarations, read my reply 09:25:24
declarations, met with counsel.** 09:25:28
Q. When you say you read prior art, what 09:25:32
prior art did you read? 09:25:34
A. I believe the set of exhibits already 09:25:35

1 **presented in this case.** 09:25:41
2 Q. All of them? 09:25:42
3 **A. No, I don't believe I read them all** 09:25:42
4 **completely.** 09:25:45
5 Q. So you read some of the prior art, some of 09:25:45
6 the exhibits that are cited in your prior 09:25:47
7 declaration, that's the prior art that you're 09:25:50
8 referring to? 09:25:52
9 **A. I read -- sorry, can you repeat the** 09:25:54
10 **question?** 09:25:59
11 Q. Yes. When you said you read the prior 09:25:59
12 art, some of the exhibits, that's prior art and 09:26:01
13 exhibits that are cited in your declarations, right? 09:26:04
14 **A. In my declaration, reply declaration, yes.** 09:26:06
15 Q. Did you review any documents or materials 09:26:11
16 to prepare for today that are not cited in your 09:26:12
17 declarations? 09:26:16
18 **A. I don't believe so.** 09:26:17
19 Q. When you prepared these reply reports that 09:26:22
20 you have in front of you, you cited a number of new 09:26:24
21 exhibits. And when I say new, I mean they hadn't 09:26:29
22 been cited in your first declaration. You're 09:26:32

1 familiar with that, right? 09:26:34
2 **A. Yes.** 09:26:35
3 Q. Is it fair to assume that those new 09:26:35
4 exhibits that you cited in your second declaration, 09:26:37
5 you had not considered those when you signed your 09:26:39
6 first declaration? 09:26:42
7 **A. What do you mean "not considered"?** 09:26:43
8 Q. The exhibits that you submitted new in 09:26:45
9 your second declaration, when did you first become 09:26:48
10 aware of those? 09:26:51
11 **A. Some of them I have known about for a very** 09:26:52
12 **long time. Some of them may have been new. I can't** 09:26:54
13 **remember.** 09:26:57
14 Q. Okay. So back when you signed your 09:26:58
15 original declaration, you knew about some of the 09:27:00
16 exhibits that were submitted in your reply 09:27:04
17 declaration, but you didn't cite those in your 09:27:06
18 original declaration, true? 09:27:08
19 **A. I believe that's correct, yes.** 09:27:10
20 Q. The new exhibits that are cited in your 09:27:19
21 reply declaration, had you reviewed or considered 09:27:23
22 any of those when you were preparing your original 09:27:27

1 declaration? 09:27:30
2 **A. Inasmuch as they informed my knowledge of** 09:27:34
3 **the prior art, I had considered contents in them or** 09:27:36
4 **related to them, yes.** 09:27:40
5 Q. Had you reviewed those documents 09:27:41
6 themselves when you were preparing your original 09:27:43
7 declaration? 09:27:45
8 **A. Not inasmuch as they formed my** 09:27:46
9 **understanding of the prior art.** 09:27:48
10 Q. Okay, I don't think that answers my 09:27:54
11 question, though. 09:27:56
12 The new exhibits that you submitted with 09:27:56
13 your reply declaration, that set of exhibits, had 09:27:59
14 you reviewed any of those documents back at the 09:28:02
15 beginning when you were preparing your original 09:28:05
16 declaration? 09:28:07
17 **A. My understanding of the prior art is** 09:28:11
18 **governed by nearly 20 years of experience in high** 09:28:14
19 **throughput sequencing technologies, and I have a** 09:28:20
20 **concept of the field that endures for that length of** 09:28:24
21 **time. It's very difficult for me to think about** 09:28:28
22 **this field without including lots of prior art, so I** 09:28:30

1 **did not explicitly review those pieces at the time** 09:28:36
2 **of the initial declaration, but in the concept that** 09:28:39
3 **they inform my understanding of the prior art, I was** 09:28:45
4 **aware of some of those pieces.** 09:28:47
5 Q. Which of the new exhibits that you cite in 09:28:49
6 your reply declaration were you aware of from your 09:28:50
7 past 20 years of experience? 09:28:54
8 **A. I have been a long-term collaborator of** 09:28:58
9 **Dr. Campbell, the first author, the Campbell** 09:29:01
10 **reference. And he and I have published through the** 09:29:05
11 **PCOG network dozens, if not perhaps 30 to 50 papers** 09:29:07
12 **together, so I -- and I served as an external** 09:29:12
13 **advisor for the sequencing program that Mike** 09:29:17
14 **Stratton, the senior author of that publication. So** 09:29:21
15 **I was broadly aware of the work that they were doing** 09:29:24
16 **at the Sanger Wellcome Trust. Similarly, Dr. Xian** 09:29:26
17 **Chen's lab was a collaborator of ours. We had a** 09:29:31
18 **grant with Dr. Xian Chen from Stand Up to Cancer,** 09:29:38
19 **and so -- and Dr. Grasso, who is a middle author on** 09:29:42
20 **that paper, actually was a member of my lab in the** 09:29:43
21 **2012 to 2013 time frame. So, I'm broadly aware of** 09:29:45
22 **the work that those two groups were doing.** 09:29:49

1 Q. So you were familiar with the Campbell 09:30:13
2 group and their work back at the time you signed 09:30:15
3 your original declaration; is that what you're 09:30:17
4 saying? 09:30:19
5 **A. Deeply and intimately familiar with** 09:30:20
6 **Dr. Campbell. My post-op, Tim Butler, was a -- my** 09:30:23
7 **graduate student Tim Butler was a post-doc with** 09:30:27
8 **Dr. Campbell. I'm a long-term collaborator of** 09:30:31
9 **Dr. Campbell in the PCOG network, as I said, and I** 09:30:32
10 **had an explicit grant with Dr. Xian Chen.** 09:30:37
11 Q. And you were familiar with the Campbell 09:30:43
12 publication that you submitted with your reply 09:30:45
13 declaration, you were familiar with that one back 09:30:48
14 when you signed your original declaration too? 09:30:52
15 **A. Whether or not I could have described the** 09:30:55
16 **contents of that, I'm not certain, but the contents** 09:30:56
17 **that are in there, I am broadly familiar with.** 09:31:00
18 Q. The new exhibits that were submitted with 09:31:04
19 your reply declaration, did you go out and find 09:31:07
20 those or did counsel provide those to you? 09:31:09
21 **A. I believe they were suggested by counsel.** 09:31:13
22 Q. Including the Campbell paper? 09:31:16

1 **A. I believe so.** 09:31:17
2 Q. Okay. Aside from reviewing documents and 09:31:32
3 materials from this case, what else did you do to 09:31:36
4 prepare for your deposition today? 09:31:38
5 **A. I met with counsel.** 09:31:42
6 Q. And those are just the lawyers in the room 09:31:43
7 right now? 09:31:45
8 **A. Correct.** 09:31:45
9 Q. Since the time that you had your first 09:31:52
10 deposition in this case, have you spoken with anyone 09:31:54
11 from Illumina? 09:31:56
12 **A. I don't believe so. Other than counsel.** 09:32:00
13 Q. And that's Mr. Burch? 09:32:05
14 **A. Yes.** 09:32:07
15 Q. Since your first deposition, have you 09:32:15
16 spoken with any other experts who have been retained 09:32:16
17 for Illumina in cases against Molecular Loop? 09:32:21
18 **A. I don't know of any such individuals, so** 09:32:25
19 **I'm not sure.** 09:32:27
20 Q. Aside from your declarations and the 09:32:36
21 exhibits in this case, have you reviewed any of the 09:32:40
22 briefs that have been filed by either of the 09:32:41

1 parties? 09:32:43
2 **A. Do you have an example of such a brief?** 09:32:46
3 Q. Yes, I'm referring to things like the 09:32:48
4 patent owner response, the petitioner's reply. Have 09:32:50
5 you reviewed any of those papers? 09:32:54
6 **A. I don't recall.** 09:32:55
7 Q. Have you reviewed Illumina's petition in 09:32:56
8 this case? 09:32:57
9 **A. I'm not sure.** 09:32:59
10 Q. At the end of your declarations, each of 09:33:15
11 them has a list of materials considered that lists 09:33:19
12 certain exhibits that have been submitted in these 09:33:23
13 cases. Are you familiar with that? 09:33:27
14 **A. Yes, that's my understanding.** 09:33:28
15 Q. Is that a -- 09:33:30
16 MR. RAICH: Sorry, counsel. Can I 09:33:31
17 just get a copy of the declarations if you're going 09:33:33
18 to start asking him about them? 09:33:35
19 MR. MATTY: Sure. 09:33:37
20 MR. RAICH: These are the opening 09:34:06
21 reports? Do you have the reply versions? 09:34:07
22 MR. MATTY: I'm sorry. I think I 09:34:10

only have a reply of the 964, an extra copy. 09:34:38

MR. RAICH: If you start asking about 09:34:42

the other one, I'll take a break. 09:34:44

MR. MATTY: We can figure it out. 09:34:47

BY MR. MATTY: 09:34:48

Q. At the back of your reply declarations, 09:34:49

you have a list of materials considered that lists 09:34:52

certain exhibits that have been submitted in this 09:34:55

case, right? 09:34:58

A. In the 964? 09:34:59

Q. Yes. 09:35:01

A. Appendix A. 09:35:07

Q. Are you there? 09:35:11

A. Appendix A, yes. 09:35:12

Q. And my question is, is that a full list of 09:35:13

the materials that you considered in forming the 09:35:15

opinions that are expressed in your reply 09:35:19

declaration? 09:35:21

A. As explicit sources, yes, beyond my, you 09:35:23

know, not including the knowledge I have as a -- as 09:35:27

a scientist. 09:35:30

Q. Are you aware of any materials that you 09:35:31

1 considered in forming the opinions for your reply 09:35:32
2 report that are not cited in this list? 09:35:36
3 **A. I don't believe so.** 09:35:39
4 Q. And is the same true of the list of 09:35:41
5 materials considered included in your reply 09:35:44
6 declaration for the 965 IPR? 09:35:48
7 THE WITNESS: Counsel, did you want 09:35:54
8 the 965? 09:35:54
9 MR. RAICH: You can answer the 09:35:57
10 question. 09:35:58
11 **A. I believe that's correct, yes.** 09:35:58
12 Q. Okay. All right. You talk about some 09:36:11
13 general concepts of Illumina sequencing in your 09:36:29
14 declarations that I want to talk about. You're well 09:36:32
15 familiar with Illumina sequencing, true? 09:36:36
16 **A. I believe so, yes.** 09:36:38
17 Q. And you mention in your declaration 09:36:39
18 there's at least a few steps in the typical Illumina 09:36:43
19 sequencing workflow. One of those is something 09:36:47
20 called enrichment PCR. You're familiar with that, 09:36:51
21 right? 09:36:54
22 **A. What page of the declaration are you** 09:36:55

1 **referring to?** 09:36:56
2 Q. I'm not referring to a specific page right 09:36:58
3 now. I'm asking you are you familiar with the 09:36:59
4 concept of enrichment PCR in Illumina sequencing? 09:37:01
5 **A. By enrichment PCR you mean a step prior to** 09:37:05
6 **placing material to be sequenced on the flow-cell?** 09:37:09
7 Q. Yes, I think that's right. There's 09:37:17
8 generally a PCR enrichment step in Illumina 09:37:19
9 sequencing prior to placing a sample on the 09:37:22
10 flow-cell, right? 09:37:27
11 **A. There are often many enrichment steps.** 09:37:28
12 **That's why I want to be precise about which one you** 09:37:31
13 **are referring to. PCR is routinely used throughout** 09:37:35
14 **the process.** 09:37:38
15 Q. Okay. So PCR is routinely used to enrich 09:37:39
16 a sample before it is placed on a flow-cell in 09:37:43
17 Illumina sequencing, right? 09:37:46
18 **A. PCR is used at numerous steps in many** 09:37:48
19 **different sequencing processes, so it's a little** 09:37:53
20 **hard to answer your exact question because not all** 09:37:59
21 **practitioners will do exactly the same thing.** 09:38:04
22 Q. Is it true or not -- is it true that PCR 09:38:08

is routinely used to enrich a sample before Illumina 09:38:12
sequencing. Is that true? 09:38:16
A. It would depend on the time frame. It 09:38:18
would depend on the technology being utilized. It 09:38:20
would depend upon the goals of what the person was 09:38:23
doing, so you would have to ask a very specific 09:38:27
question about a specific assay and a specific time. 09:38:29
Q. In December 2010, was it routine to 09:38:49
perform PCR enrichment on a sample before placing 09:38:58
that sample on an Illumina sequencer? 09:39:03
A. Broadly speaking, at that time frame, I 09:39:08
believe a typical workflow on an Illumina sequencer 09:39:11
would be to do one of two methods. One would be to 09:39:15
ligate adapters on and PCR from the ligated adapters 09:39:23
across the insert. The other might be to perform 09:39:30
PCR with adapters already on them. In that sense, 09:39:35
the second version would be in a target enrichment 09:39:39
PCR and would absolutely have a PCR step in it. In 09:39:43
the first version, it would be typical to then 09:39:47
amplify those ligated adapters that have been added 09:39:51
to the library prior to sequencing. 09:39:58
Q. And you amplify them by PCR, right? 09:40:00

1 **A. Nearly universally, yes.** 09:40:03
2 Q. And in both of those examples, that's PCR 09:40:04
3 that is not being performed on the surface of a 09:40:08
4 flow-cell yet, right? 09:40:11
5 **A. In nearly all circumstances that would be** 09:40:14
6 **the case, I believe.** 09:40:16
7 Q. So in a typical Illumina sequencing 09:40:27
8 workflow as of December 2010, it was normal practice 09:40:31
9 to perform at least one PCR enrichment step prior to 09:40:39
10 placing the sample on an Illumina sequencer, right? 09:40:45
11 **A. I believe that would be the most common** 09:40:50
12 **thing to do, yes.** 09:40:52
13 Q. Then moving ahead in the workflow, after 09:41:00
14 PCR enrichment in December 2010, it was standard to 09:41:04
15 load samples onto a flow-cell in the Illumina 09:41:10
16 sequencing platform, right? 09:41:15
17 **A. That is correct.** 09:41:17
18 Q. And then there is an amplification known 09:41:18
19 as bridge PCR or bridge amplification that occurs on 09:41:22
20 the surface of the flow-cell in the Illumina 09:41:27
21 machine, right? 09:41:29
22 **A. That is correct.** 09:41:30

1 Q. After that amplification, there's a step 09:41:33
2 of sequencing commonly referred to as a sequencing 09:41:37
3 by synthesis method. You're familiar with that on 09:41:42
4 the Illumina flow-cell? 09:41:45
5 **A. Illumina sequencers would perform** 09:41:47
6 **sequencing by -- sequencing by synthesis, that's** 09:41:49
7 **correct.** 09:41:52
8 Q. And the sequencing by synthesis, 09:41:52
9 nucleotides are detected one at a time based on 09:41:57
10 colors that the different nucleotides emit as 09:42:01
11 they're added to a sample being sequenced, right? 09:42:05
12 **A. The technical details are a little off,** 09:42:11
13 **but broadly speaking, yes.** 09:42:13
14 Q. What did I have wrong? 09:42:16
15 **A. Can you ask your question again?** 09:42:23
16 Q. Yes. 09:42:25
17 **A. It's quite complicated. I don't know how** 09:42:25
18 **much of the detail you want.** 09:42:29
19 Q. I understand. 09:42:30
20 In sequencing by synthesis, let's start 09:42:31
21 here, nucleotides are added and detected one at a 09:42:33
22 time to determine the sequence of an amplicon, true? 09:42:38

1 **A. Generally speaking, that's correct.** 09:42:46
2 Q. And the way the Illumina machine can tell 09:42:48
3 for a particular amplicon what nucleotide is being 09:42:51
4 added is by detecting a certain color that's 09:42:56
5 associated with either an A, a G, a C, or a T, 09:42:59
6 right? 09:43:04
7 **A. In the 2010 time frame, I believe that is** 09:43:04
8 **fairly accurate, yes.** 09:43:10
9 Q. Okay. And the way the Illumina machine 09:43:13
10 does that detection is by detecting clusters on the 09:43:15
11 flow-cell, and with each round, detecting what color 09:43:21
12 each cluster emits, right? 09:43:26
13 **A. That is technically a lot more complicated** 09:43:29
14 **than that in the 2010 time frame. At the highest** 09:43:30
15 **level, I would say that that is mostly correct.** 09:43:36
16 Q. Okay. So I appreciate there's a lot of 09:43:38
17 chemistry and optics and all other kinds of things 09:43:43
18 going on on the machine. 09:43:47
19 **A. There is also the actual mechanism of** 09:43:49
20 **cluster detection in the 2010 time frame, which is** 09:43:52
21 **quite complicated and is not -- it is done semi** 09:43:58
22 **retrospectively.** 09:44:02

1 Q. Let's talk about that. What do you mean 09:44:04
2 by semi retrospectively? 09:44:06
3 **A. The locations of clusters are unknown on** 09:44:14
4 **an Illumina sequencer in 2010, and a substantial** 09:44:16
5 **fraction of the technical effort is to determine** 09:44:22
6 **their locations. That is done using information** 09:44:27
7 **from several cycles of sequencing in the 2010 time** 09:44:34
8 **frame. The exact number, I'm not sure of off the** 09:44:39
9 **top of my head. I would have to look at a reference** 09:44:42
10 **for it. But it does not detect the locations of the** 09:44:44
11 **clusters first and then determine their sequence.** 09:44:52
12 **It determines -- it collects data and then** 09:44:54
13 **identifies the locations of clusters at some point.** 09:44:57
14 **And I believe it's -- I believe it's somewhere** 09:45:00
15 **around cycle 10. I believe it's in one of the** 09:45:02
16 **references in the case if we want to look for it.** 09:45:05
17 Q. And that process, the way that cluster 09:45:09
18 detection, I'll call it, works on an Illumina 09:45:13
19 machine has changed over time, right? 09:45:17
20 **A. Partially.** 09:45:22
21 Q. And I think one of the differences is back 09:45:23
22 in 2010, the flow-cells were non-patterned 09:45:25

1 flow-cells, right? 09:45:30
2 **A. That is correct.** 09:45:31
3 Q. And that's the reason why they were doing 09:45:31
4 this semi retrospective analysis to determine where 09:45:34
5 the clusters actually fell, right? 09:45:39
6 **A. Roughly speaking, that's correct. Again,** 09:45:45
7 **I think it's a little more complicated than that.** 09:45:47
8 **Early in Illumina, I don't know the exact** 09:45:53
9 **cluster center distance, but my impression was it** 09:45:57
10 **was two or three or even more radiuses from one** 09:46:01
11 **another. Later on the intra-cluster distance** 09:46:04
12 **becomes extremely dense. I would have to look at** 09:46:11
13 **the time frame of when that happens. But in order** 09:46:14
14 **to both improve sequencing, quality, and throughput,** 09:46:19
15 **the Illumina is switched to a pattern flow-cell** 09:46:26
16 **later on.** 09:46:29
17 Q. Help me understand that. How does a 09:46:29
18 pattern flow-cell improve your sequencing quality? 09:46:33
19 What's the connection there? 09:46:36
20 **A. It makes the process of finding the** 09:46:37
21 **clusters easier.** 09:46:40
22 Q. And it's easier to find the clusters on 09:46:45

the later patterned flow-cells because due to the 09:46:48
pattern, you know where to expect the clusters to be 09:46:53
located? Is that the idea? 09:46:56
A. I would have to actually check the 09:46:58
technical details. I did not review that for this 09:46:59
case. 09:47:02
Q. Okay. In the non-pattern flow cells, it 09:47:04
was important to go through the process of 09:47:10
retrospectively determining where the clusters are 09:47:14
to make sure that what the machine is analyzing are 09:47:19
true single clusters, right? 09:47:21
A. Partly. I mean, that is necessary, yes, 09:47:28
but it's also just to figure out what the -- what 09:47:31
the -- where the boundaries of the clusters are, 09:47:38
which is slightly different than what are single 09:47:40
clusters. 09:47:43
Q. When you say "boundaries of the clusters," 09:47:44
you mean boundaries of each individual cluster? 09:47:47
A. Clusters were allowed to overlap one 09:47:52
another. And so my understanding was that 09:47:54
Illumina's infrastructure could separate overlapping 09:47:57
clusters with some reasonably high degree of 09:48:02

1 **accuracy. So even if two clusters touched, they** 09:48:05
2 **could -- they could separate them.** 09:48:08
3 Q. So if two clusters on a non-patterned 09:48:10
4 flow-cell were initially seeded too close together, 09:48:13
5 through the bridge amplification they could overlap 09:48:19
6 each other, right? 09:48:22
7 **A. That is my understanding, yes.** 09:48:24
8 Q. Are you familiar with the concept of a 09:48:25
9 mixed cluster? 09:48:27
10 **A. Yes.** 09:48:28
11 Q. And when on a non-patterned flow-cell, 09:48:28
12 when two clusters are seeded too close together and 09:48:31
13 they amplify and overlap with each other, that's 09:48:35
14 commonly referred to as a mixed cluster, right? 09:48:38
15 **A. I'm -- I would have to look at the** 09:48:42
16 **literature. I don't know if you have some examples** 09:48:46
17 **of literature on that one. It could be. I think** 09:48:48
18 **the Illumina software did a pretty good job of** 09:48:52
19 **de-convolving those, so a mixed cluster might be** 09:48:55
20 **called that or it might be called a cluster in which** 09:48:59
21 **the information was garbled and so that you didn't** 09:49:03
22 **get accurate sequence from it, or it could be one in** 09:49:10

which the two different reads were somehow mixed. 09:49:12

Q. The reason that a mixed cluster, the data 09:49:17
can be garbled -- this goes back to the colors idea. 09:49:20
If they're overlapping and on a certain step of the 09:49:26
sequencing by synthesis those two clusters that are 09:49:30
overlapping are adding a different nucleotide, 09:49:35
they're emitting two different colors, right? 09:49:37

A. Yes. I think in this particular case, if 09:49:40
-- in the simplest case in which the clusters 09:49:43
completely overlap but maintain their identity 09:49:47
somehow, you would have at every cycle the potential 09:49:49
for two different bases or more being detected at 09:49:52
each round of the chemistry so that it would be -- 09:49:56
you wouldn't know if it was an A or a G, if they 09:50:00
were both present on two different molecules in that 09:50:02
step. 09:50:05

Q. Got it. 09:50:05

So if you have two clusters that 09:50:06
completely overlap on a certain step where they're 09:50:07
adding different nucleotides, the colors sort of mix 09:50:11
together, and that's why it's hard for the machine 09:50:14
to know exactly what base is added to each cluster, 09:50:16

1 right? 09:50:20
2 MR. RAICH: Object to form. 09:50:21
3 **A. Roughly speaking, I think that's correct.** 09:50:22
4 Q. Are mixed clusters a problem on patterned 09:50:33
5 flow-cells? 09:50:37
6 MR. RAICH: Object to scope. 09:50:41
7 **A. I think they could be. I don't** 09:50:45
8 **actually -- I haven't read the literature on it** 09:50:46
9 **because I didn't think it was germane to this case.** 09:50:49
10 Q. Let's -- going back to the time frame, we 09:50:55
11 were talking about December 2010. Do you know when 09:50:57
12 patterned flow-cells were first used in Illumina 09:51:01
13 machines? 09:51:04
14 **A. It was after 2010. The exact date I can't** 09:51:07
15 **give you. I remember roughly the location I was in,** 09:51:10
16 **and that was after 2010, but I can't give you an** 09:51:14
17 **actual date.** 09:51:19
18 Q. Okay. So when we're looking at the '200 09:51:19
19 patent, the '852 patent in December 2010, and we're 09:51:22
20 looking at the prior art before that, all the 09:51:25
21 discussion of Illumina machines and Illumina 09:51:28
22 sequencing, it's fair to assume those were all 09:51:31

occurring on non-patterned flow-cells, true? 09:51:34

A. I think that's correct, yes. 09:51:36

Q. Sticking with this idea of detecting the 09:52:00
colors from clusters on the flow-cell, are you 09:52:04
familiar with the concept of optical duplicates on 09:52:06
the Illumina non-patterned flow-cells? 09:52:10

A. Yes. I might not have referred to them as 09:52:13
optical, but you mean two separate identified 09:52:17
clusters that really seeded from the same template 09:52:19
source? 09:52:24

Q. Yes. Is there another term for that that 09:52:24
you would use? 09:52:25

A. PCR duplicates on the flow-cell I might 09:52:26
prefer. Optical duplicates may -- (interruption by 09:52:33
court reporter). 09:52:33

Just because optical makes it sound like 09:52:33
it's something in the optical light path rather 09:52:35
than -- rather than a physical thing, when I think 09:52:38
of it usually as a physical thing or a software 09:52:40
problem, right? This is separating boundaries of a 09:52:43
cluster. 09:52:47

Q. I'm happy to use your language. In your 09:52:48

words, what -- what are PCR duplicates on the 09:52:50
flow-cell? 09:52:53
A. These would be places in which a cluster 09:52:56
was seeded and then a molecule from that cluster 09:53:03
either went a little further than it might have been 09:53:07
expected to in the bridge PCR step or -- and then 09:53:10
seeded effectively a new cluster somehow. Or it 09:53:15
could be the position in which the software failed 09:53:19
to -- over-segmented a cluster into two clusters so 09:53:24
that one cluster, which should have been detected in 09:53:30
some reasonable way, was split into two separate 09:53:34
things. 09:53:38
Q. And when you say over-segmented, you mean 09:53:38
the software is seeing signal that in reality is 09:53:41
coming from one cluster but it's segmenting those 09:53:46
into two different clusters based on where they're 09:53:51
located or something that's going on in the 09:53:55
software? 09:53:57
A. Roughly speaking, yes. 09:53:58
Q. So in the context of the PCR duplicates on 09:54:10
the flow-cell, that's a situation where you have one 09:54:13
molecule that's seeded but in the analysis at the 09:54:19

end, it's seen as two different clusters? That's 09:54:25
what a PCR duplicate is, right? 09:54:27
MR. RAICH: Object to form. 09:54:30
A. Yes, I think in this context, I would -- I 09:54:34
would call it that. There's another use of the 09:54:35
phrase PCR duplicate that probably is very different 09:54:38
than that one, so we need to distinguish that. But 09:54:41
in this context, a bridge PCR duplicate maybe is a 09:54:44
better way to say it, is -- is the same molecule 09:54:49
seeding somewhat larger distances than expected and 09:54:53
the software over-segmenting them. 09:54:55
Q. Okay. And you say bridge PCR because 09:55:02
that's the PCR that's happening on the flow-cell, 09:55:03
right? 09:55:05
A. Correct. 09:55:06
Q. So a bridge PCR duplicate is a situation 09:55:06
where you have one molecule that's seeded, but at 09:55:11
the analysis stage it's seen as two different 09:55:16
clusters, right? 09:55:19
A. I think that would be accurate, yes. 09:55:20
Q. Okay. For the mixed cluster that we 09:55:26
talked about before, that's a situation where two 09:55:27

molecules are seeded, but at the analysis stage, 09:55:31
they might be seen as just one cluster because they 09:55:35
overlap, right? 09:55:39
MR. RAICH: Objection to form. 09:55:42
A. Yes, I think that's correct. 09:55:42
Q. Let me just close the loop on the flow 09:56:10
cells. Do you have an understanding even at a high 09:56:12
level what the difference is between a non-patterned 09:56:17
flow-cell and a patterned flow-cell? 09:56:19
A. In what context? 09:56:26
Q. I guess just in the context of what they 09:56:30
are. When you think of non-patterned flow-cell and 09:56:31
patterned flow-cell, what is the difference between 09:56:35
those two in your mind? 09:56:37
MR. RAICH: I'll object to scope. 09:56:39
A. Broadly speaking, an -- the original 09:56:40
flow-cells could seed clusters anywhere on the 09:56:44
surface, whereas the patterned flow cells had 09:56:49
specific regions that could seed clusters and 09:56:53
boundary regions that could not, and exact chemistry 09:56:57
I can't give you, and I have not reviewed, that 09:57:01
allows the Illumina to create the pattern, but there 09:57:04

is a place where clusters can form. What shape it is, I actually don't know. I don't know if it's a square or a circle. But within that boundary, you can form, and then there's some boundary element that is not available if the cluster is seeding so the clusters are somewhat constrained in size and location. 09:57:10 09:57:14 09:57:16 09:57:19 09:57:25 09:57:30 09:57:33

Q. For the non-patterned, you mentioned the step of retrospectively determining where the clusters are. Is that retrospective determination something that's also done on patterned flow-cells or is that not needed anymore? 09:57:34 09:57:36 09:57:40 09:57:45 09:57:47

MR. RAICH: Object to scope. 09:57:49

A. I actually don't know. I think the Illumina went through several rounds of technology, and I didn't review the exact time frames. The original machines had clustering -- cluster generation and sequencing on different instruments, and that created some indexing fiducial problems sometimes is my understanding. The later machines integrated that to reduce the amount of movement between image steps. And I believe that that's 09:57:50 09:57:54 09:57:56 09:58:03 09:58:09 09:58:13 09:58:19 09:58:24 09:58:29

1 **further reduced by the patterned flow-cells, so --** 09:58:32
2 **but the exact accuracy of how those is not something** 09:58:37
3 **I'm deeply familiar with.** 09:58:43
4 Q. Do you know in December 2010 if the 09:58:44
5 clustering and the sequencing for Illumina were done 09:58:48
6 on different instruments or on the same instrument? 09:58:53
7 **A. I actually don't remember. I'm sure there** 09:58:57
8 **were commercially available instruments that used** 09:59:00
9 **the CBOT available. I don't remember if the** 09:59:03
10 **instrument that did clustering on the sequencer was** 09:59:05
11 **commercially available yet. I don't remember what** 09:59:09
12 **version that was.** 09:59:11
13 Q. We talked about the amplification that 10:00:04
14 happens on the flow-cell is bridge amplification, 10:00:07
15 right? 10:00:10
16 **A. Bridge PCR amplification, yes.** 10:00:12
17 Q. The PCR enrichment that occurs before 10:00:15
18 loading onto the flow-cell is not bridge PCR, right? 10:00:18
19 **A. It would be uncommon for it to be, yes.** 10:00:24
20 Q. It's the PCR enrichment that happens 10:00:28
21 before you load the sample onto the flow-cell, 10:00:30
22 happens in an Eppendorf tube or maybe it's some 10:00:35

other tube that's containing the sample, right? 10:00:39

MR. RAICH: Object to the form. 10:00:42

A. Most commonly. I would -- the distinction I would make is in solution versus in solid phase. 10:00:44 10:00:46

Q. The PCR that happens in solution before being loaded onto the flow-cell is not bridge PCR, right? 10:00:50 10:00:54 10:00:57

A. It would be uncommon for it to be -- perhaps someone did it on-solid phase. I don't know. 10:01:00 10:01:02 10:01:04

Q. But generally PCR in-solution is different than bridge PCR, right? 10:01:05 10:01:08

A. PCR in solution is distinct from bridge PCR on the surface of a flow-cell in that the -- during the cycles of amplification, the templates are in solution and can diffuse, and all of the reagents are in solution and diffuse. Whereas on bridge PCR, the templates are attached to the surface and oftentimes the -- I believe in the Illumina context, the primers aren't also attached to the surface, so there is a degree of freedom difference on what can bind to what. 10:01:15 10:01:21 10:01:26 10:01:33 10:01:40 10:01:44 10:01:48 10:01:51 10:01:56 10:02:01

1 **In solution, in principle, anything within** 10:02:06
2 **the diffusion radius, given the amount of time,** 10:02:12
3 **could find something else. I don't know that I know** 10:02:14
4 **the calculation on how fast molecules diffuse in** 10:02:19
5 **solution, but ostensibly it's a complex mixture.** 10:02:22
6 **On the surface you would be much more** 10:02:27
7 **constrained. You could only bind to what is nearby** 10:02:29
8 **you, and that is the entire principle of how** 10:02:36
9 **Illumina clusters are generated, that it limits the** 10:02:39
10 **scope of where things can move, but it has other --** 10:02:42
11 **it can create density issues because there are** 10:02:48
12 **specific regions on the flow-cell that are now** 10:02:51
13 **extremely concentrated for molecules and others that** 10:02:55
14 **are depleted. Many of the components are freely** 10:02:57
15 **diffusible, the enzymes are diffusible, the** 10:03:00
16 **nucleotides are diffusible during the steps. So it** 10:03:05
17 **mirrors PCR in solution in many ways and adds some** 10:03:09
18 **distinct differences.** 10:03:12
19 Q. So the bridge amplification on the 10:03:13
20 flow-cell forms clusters because things are fixed to 10:03:15
21 the solid state, right? 10:03:19
22 MR. RAICH: Object to the form. 10:03:21

1 **A. One end of the molecules is fixed and so** 10:03:24
2 **they're generally -- we normally would think of them** 10:03:29
3 **as covalently bound, although I'm sure there are** 10:03:33
4 **sequencing chemistries when they are non-covalently** 10:03:37
5 **bound. And they stay in that location and can only** 10:03:42
6 **sort of move -- in general they can only move the** 10:03:46
7 **length of their physical size, although I think it** 10:03:55
8 **is possible for them to break or move around or** 10:03:59
9 **cross-hybridize with other molecules.** 10:04:02
10 Q. They form clusters because when they're 10:04:06
11 amplified, the amplicons can't diffuse away because 10:04:09
12 they have at least one end connected to the 10:04:13
13 flow-cell, right? 10:04:14
14 **A. They form clusters because they are** 10:04:15
15 **substantially inhibited from diffusing away, yes.** 10:04:19
16 Q. Are you familiar with the concept of 10:04:25
17 limiting dilution PCR? 10:04:26
18 **A. Yes.** 10:04:29
19 Q. What is limiting dilution PCR in your 10:04:29
20 understanding? 10:04:33
21 **A. Broadly speaking, limiting dilution PCR is** 10:04:33
22 **where you put fewer and fewer molecules into a PCR** 10:04:37

until a specific set of conditions are reached that you're trying to achieve. That's how I would define it. 10:04:41 10:04:45 10:04:50

Q. Can you give me an example of what you mean by a specific set of conditions are reached? 10:04:50 10:04:53

A. You may, for example -- I think this is the use case you are asking about. There may be other uses of the phrase "limiting dilution PCR" where you want there to only be one -- one molecule of the thing you care about in your PCR reaction. So you put so little DNA into it that there is by limiting dilution only one molecule. A very common version of this would be something like digital droplet PCR where in a thousand molecules -- a thousand droplets, only one molecule -- one droplet has a molecule at all. People have used this for a variety of techniques to measure all sorts of things around individual molecules of DNA. I think that's what you're asking about. If you have a different use case, there might be one. 10:04:58 10:05:02 10:05:05 10:05:09 10:05:16 10:05:19 10:05:23 10:05:26 10:05:29 10:05:32 10:05:36 10:05:40 10:05:46 10:05:51 10:05:53

Q. I think so. my understanding is that limiting dilution PCR is a method that's used to get 10:05:54 10:05:56

1 down to a scenario where you have only one seed 10:06:02
2 molecule in the PCR reaction. Is that at a high 10:06:06
3 level true? 10:06:09
4 **A. That is the way I was using the term, yes.** 10:06:10
5 Q. Okay. One more. 10:07:43
6 Are you familiar with the concept of 10:07:45
7 mispriming in a PCR reaction? 10:07:46
8 **A. Sadly, yes.** 10:07:49
9 Q. I don't want to bring up bad memories. 10:07:52
10 What's your understanding of mispriming in PCR? 10:07:55
11 **A. Mispriming broadly is when the thing you** 10:07:57
12 **are trying to extend, the primer, binds to somewhere** 10:08:00
13 **that you did not want it to bind and extends off of** 10:08:06
14 **that. It happens in any primer-dependent polymerase** 10:08:09
15 **reaction. It's a problem of kinetics and thermo** 10:08:17
16 **chemistry, so it just happens.** 10:08:23
17 Q. So when you are using a primer, your hope 10:08:25
18 is that the primer attaches to a certain place on a 10:08:34
19 nucleic acid and extends that nucleic acid so that 10:08:40
20 you can create a copy, basically, right? 10:08:43
21 MR. RAICH: Object to the form. 10:08:49
22 **A. I would likely put in a lot more technical** 10:08:51

1 **details, but at the highest level, I'm comfortable** 10:08:54
2 **with that definition.** 10:08:56
3 Q. For the mispriming, is it -- is the "mis", 10:08:57
4 is it where it attaches or is it in the extension 10:09:05
5 phase? 10:09:08
6 **A. Normally when we talk about mispriming, we** 10:09:13
7 **would talk about conditions in which the primer** 10:09:15
8 **itself inappropriately -- it bound to a location** 10:09:18
9 **that was not the intended one in a -- bound to a** 10:09:24
10 **sequence that was not the intended sequence and** 10:09:29
11 **extended that -- extended it -- polymerase extended** 10:09:34
12 **it.** 10:09:38
13 **I think formally mispriming could also be** 10:09:38
14 **a process in which something moved and happened** 10:09:43
15 **somewhere else. Though, I think most people would** 10:09:50
16 **use mispriming to refer to an unexpected or** 10:09:54
17 **inappropriate binding and extension.** 10:09:58
18 Q. So generally when you see mispriming, you 10:10:02
19 think of a primer that attached to the wrong place. 10:10:05
20 **A. In most contexts, yes.** 10:10:10
21 Q. Okay. Going back to the sequencing by 10:10:41
22 synthesis, on the surface of a flow-cell in an 10:10:44

1 Illumina machine, we mentioned as nucleotides are 10:10:50
2 being added, the colors are being emitted and 10:10:57
3 detected, right? 10:11:00
4 **A. Again, at the highest level, correct.** 10:11:04
5 Q. And the goal is or in an ideal situation, 10:11:12
6 each cluster emits one color for each round of 10:11:16
7 sequencing by synthesis, right? 10:11:20
8 **A. On an Illumina machine, that's not quite** 10:11:26
9 **correct. Illumina machines have -- sequencing by** 10:11:30
10 **synthesis can work many different ways, so I'm just** 10:11:37
11 **restricting myself to Illumina. There are typically** 10:11:40
12 **hundreds if not thousands of copies of the thing** 10:11:46
13 **being sequenced in the cluster. And as a** 10:11:48
14 **consequence, they are all generating information.** 10:11:54
15 **And it is -- no chemical reaction is 100 percent** 10:11:57
16 **efficient. And as a consequence, at any given cycle** 10:12:08
17 **of sequencing, some of the molecules did not** 10:12:12
18 **incorporate a base. Sometimes those bases are dark.** 10:12:17
19 **Sometimes the bases don't de-protect properly, so** 10:12:20
20 **there is a process of both the amount of signal** 10:12:24
21 **being generated is not necessarily constant on** 10:12:30
22 **Illumina sequencer Circa 2010. And again, this** 10:12:34

1 **changes later on. So, I'm just talking about** 10:12:38
2 **Illumina sequences 2010. There is spectral overlap** 10:12:42
3 **between the dyes such that one has to de-convolve** 10:12:48
4 **fluorescent signals to figure how which signal you** 10:12:53
5 **actually measured. And there is a process of** 10:12:55
6 **dephasing in which -- in which sequencing reactions** 10:12:58
7 **that did not -- sequencing steps that did not** 10:13:02
8 **complete in a previous cycle can get caught up in a** 10:13:06
9 **later cycle. And so as the sequencing reaction** 10:13:09
10 **continues, there is signal from previous cycles that** 10:13:12
11 **also is emitted.** 10:13:17
12 **So action -- one of the ways Illumina** 10:13:21
13 **sequencers work is to explicitly model that** 10:13:23
14 **underlying dephasing information and to generate it.** 10:13:26
15 **Especially late in a sequencing reaction, there is** 10:13:35
16 **an enormous amount of computational work on the part** 10:13:37
17 **of Illumina to figure out what the actual base is** 10:13:41
18 **that's being emitted.** 10:13:44
19 Q. Why does that change later in the 10:13:45
20 sequencing reaction? 10:13:47
21 **A. If one is sequencing 30 bases and 5** 10:13:50
22 **percent of the molecules don't extend at each step,** 10:13:55

1 **then the third step, 15 percent of the molecules,** 10:13:58
2 **are one step behind. A small fraction might even be** 10:14:01
3 **two steps behind. And so you get a little bit of** 10:14:06
4 **signal from the preceding base that compounds over** 10:14:08
5 **time. Illumina's chemistry got astonishingly good,** 10:14:11
6 **and my understanding is that later on their** 10:14:17
7 **extension rates are above 98, 99 percent.** 10:14:21
8 **Nonetheless, at 150 bases, some significant fraction** 10:14:27
9 **of molecules might be one base behind.** 10:14:30
10 Q. That's all helpful. 10:14:37
11 Within a cluster there's many different 10:14:41
12 copies of the molecule that's being sequenced, 10:14:46
13 right? 10:14:50
14 **A. Yes.** 10:14:50
15 Q. And at each cycle of sequencing by 10:14:53
16 synthesis, the hope is that you add one base to each 10:14:57
17 of those molecules, right? 10:14:59
18 **A. Correct.** 10:15:03
19 Q. In an ideal world, it would all be the 10:15:03
20 same base because it would be the same step of the 10:15:06
21 reaction, right? 10:15:09
22 **A. Correct.** 10:15:10

Q. And the idea is to have at least 10:15:14
predominantly one color emitted from each of those 10:15:16
molecules because you hope that most of them are at 10:15:21
the same step and that's why the machine can detect 10:15:23
a predominant color from that cluster at each step, 10:15:26
right? 10:15:30

**A. Again, mostly correct. I'm not sure 10:15:34
exactly how the optics on the Illumina work, but 10:15:36
there is spectral overlap between the colors, and so 10:15:41
most instruments don't actually detect color. They 10:15:44
detect the presence of photons, and so they're 10:15:47
sorting photons by their wavelengths, which involves 10:15:50
complex optics, including band-pass filters and 10:15:54
other things in the optics base. So I have never 10:15:59
spent much time figuring out how Illumina solves 10:16:01
this problem. It's a general problem in the field 10:16:03
when one is doing multicolor imaging for microscopy 10:16:06
or anything. And there's lots -- I believe there 10:16:10
are lots of technical solutions to it. 10:16:11**

Q. Let's talk about the filters. Are you 10:16:13
familiar with the concept of a purity filter on the 10:16:15
Illumina machine? 10:16:19

1 **A. Sorry, is this in an optic system?** 10:16:23
2 Q. Yes. Are you familiar with the concept of 10:16:25
3 a purity filter in Illumina sequencing? 10:16:26
4 **A. In the optic system?** 10:16:30
5 Q. In the Illumina sequencer when it does its 10:16:32
6 analysis. 10:16:35
7 **A. Purity filter is something completely** 10:16:36
8 **different if you're asking about the thing that's** 10:16:39
9 **called a purity filter.** 10:16:40
10 Q. What's a purity filter in your 10:16:43
11 understanding? 10:16:45
12 **A. The exact mechanics of it I'm not sure I** 10:16:45
13 **could describe, but it's a process for determining** 10:16:48
14 **whether or not a cluster is a good cluster, but it** 10:16:49
15 **has nothing to do with optics to the best of my** 10:16:52
16 **understanding.** 10:16:54
17 Q. Okay. I think we're talking about the 10:16:55
18 same thing, but maybe I'm just describing it wrong. 10:16:56
19 So in your understanding of a purity 10:17:01
20 filter in the Illumina sequencing workflow, what is 10:17:03
21 that purity filter? 10:17:06
22 **A. It's a process for figuring out if the** 10:17:09

1 **cluster is a good cluster or not, but it has nothing** 10:17:13
2 **to do with optics per se to the best of my** 10:17:19
3 **understanding.** 10:17:21
4 Q. Okay. What do you mean by figuring out if 10:17:21
5 a cluster is a good cluster? 10:17:23
6 **A. Is it measured well? Does it have good** 10:17:26
7 **boundaries? Is it sequenced properly?** 10:17:28
8 Q. Is one of the purposes of a purity filter 10:17:33
9 to weed out things like mixed clusters? 10:17:36
10 **A. I believe that's correct, yes. Again, it** 10:17:39
11 **has nothing to do with optics.** 10:17:42
12 Q. Okay. Do you have any understanding of 10:17:44
13 how a purity filter determines what is or is not a 10:17:45
14 good cluster? 10:17:49
15 MR. RAICH: Object to the scope. 10:17:54
16 **A. Illumina may have published its white** 10:17:55
17 **papers on this, and I may have read them a long time** 10:17:57
18 **ago. I did not review them for this case.** 10:18:00
19 Q. Did you review any prior art that talks 10:18:02
20 about purity filters on Illumina machines? 10:18:04
21 **A. It's referred to in Bentley and I believe** 10:18:08
22 **it is also referred to in Campbell. I can't** 10:18:10

1 **remember if it's referred to other places.** 10:18:13
2 Q. So when Bentley talks about a purity 10:18:15
3 filter, do you have an understanding of how that 10:18:20
4 purity filter that it's referring to works? 10:18:23
5 **A. Can I please have a copy of Bentley?** 10:18:25
6 Q. I'll hand you Exhibit 1006, which I 10:18:46
7 believe is the Bentley paper you are referring to. 10:18:51
8 (Exhibit 1006 was previously marked 10:18:53
9 and referred to.) 10:18:53
10 **A. Yes, I believe that's correct.** 10:18:55
11 Q. Let me take you to -- there's an exhibit 10:19:08
12 stamped page in the bottom right, page 2 of 67. I 10:19:12
13 don't know if you see that stamping. 10:19:16
14 **A. Yes. Page 2.** 10:19:19
15 Q. And this is the middle of a paragraph, so 10:19:23
16 you can read it on page 1 too if you need context, 10:19:25
17 but at the top of the left column, it says, "We 10:19:28
18 discarded all reads from mixed clusters and used the 10:19:31
19 remaining 'purity filtered reads for analysis.'" Do 10:19:35
20 you see that? 10:19:38
21 **A. Yes.** 10:19:38
22 Q. Do you have an understanding of how purity 10:19:39

filtering as it's described in Bentley is done to 10:19:43
discard mixed clusters? 10:19:47
A. Bentley has a discussion of this on page 10:19:50
6. I could read it for you or if you have a 10:19:52
question about it. 10:19:56
Q. Do you have an understanding at a high 10:19:57
level how the purity filter identifies mixed 10:19:58
clusters? 10:20:02
A. What it says is we defined a measure of 10:20:03
signal purity at a given cycle by taking the 10:20:06
brightest of the four corrected color intensities as 10:20:08
a fraction of the sum of the brightest and next 10:20:11
brightest intensities. We discarded reads whose 10:20:14
corrected brightness in any of the first 12 10:20:17
sequencing cycles was less than 60 percent of the 10:20:19
sum of the brightest intensity, et cetera. 10:20:22
Q. Okay. So why is that measure of 10:20:25
brightness a way to weed out mixed clusters as it's 10:20:27
described in Bentley? 10:20:34
A. I think they're looking for examples where 10:20:35
there's more signal than they expect in some 10:20:42
channels, broadly speaking. 10:20:44

1 Q. And there might be more signal in some 10:20:46
2 channels because the signal might be coming from two 10:20:49
3 overlapping clusters rather than just one normal 10:20:51
4 cluster; is that fair? 10:20:54
5 **A. I think that's correct, yes.** 10:20:55
6 Q. And when it sees the higher brightness 10:20:56
7 from what it determines are two overlapping 10:20:59
8 clusters, it can identify that as a mixed cluster 10:21:01
9 rather than a, quote unquote, good cluster, right? 10:21:05
10 MR. RAICH: Object to the form. 10:21:10
11 **A. I believe that's correct, yes.** 10:21:11
12 Q. I've seen elsewhere discussion in Illumina 10:21:23
13 sequencing of a chastity filter. Are you familiar 10:21:26
14 with that term? 10:21:30
15 **A. I think chastity was the name that** 10:21:31
16 **Illumina gave it. I think it's a very equivalent** 10:21:34
17 **concept. The exact technical details I'm not sure** 10:21:37
18 **are exactly the same, but roughly speaking that's my** 10:21:39
19 **understanding, that they're similar concepts.** 10:21:41
20 Q. Those can be like -- so when you say 10:21:43
21 purity filter and chastity filter, roughly those 10:21:46
22 refer to the same thing? 10:21:50

1 **A. The technical basis might be slightly** 10:21:52
2 **updated or different, but I think the concepts are** 10:21:52
3 **similar.** 10:21:53
4 Q. One more filter. How about a passing 10:22:22
5 filter? Are you familiar with what a passing filter 10:22:25
6 is in Illumina sequencing? 10:22:28
7 **A. I think it's a very common term. I'm not** 10:22:32
8 **sure -- you would have to point me to an exact** 10:22:32
9 **example. We use pass filter a lot.** 10:22:32
10 Q. In the context of Illumina sequencing, 10:22:36
11 have you seen the term pass filter/passing filter? 10:22:39
12 **A. We use it a lot in a lot of different** 10:22:42
13 **steps. You would have to point me to an explicit** 10:22:43
14 **example.** 10:22:45
15 Q. Is a purity filter an example of a passing 10:22:47
16 filter in your mind? 10:22:51
17 **A. It could be. Again, you would have to** 10:22:52
18 **point me to an explicit use case for me to tell you** 10:22:56
19 **what it is.** 10:23:00
20 Q. Now, in a number of the prior art 10:23:47
21 references that you cite, they discuss changes in 10:23:49
22 genetic sequences causing problems like cancer from 10:23:57

1 genetic mutations. Are you generally familiar with 10:24:01
2 that concept? 10:24:04
3 **A. Yes.** 10:24:05
4 Q. Do you know what a point mutation is? 10:24:07
5 **A. Yes.** 10:24:10
6 Q. What is a point mutation? 10:24:10
7 **A. Broadly speaking geneticists would** 10:24:14
8 **describe a point mutation as most commonly a** 10:24:17
9 **substitution in the DNA sequence where the ancestral** 10:24:21
10 **sequence was set, for example, a G and it is now** 10:24:25
11 **changed and some -- new sequence derived from the** 10:24:29
12 **ancestral sequence to a C or a T or something other** 10:24:34
13 **than the G. People might also refer to the deletion** 10:24:37
14 **of the G as a point mutation. Those would be the** 10:24:42
15 **most common use cases. I think the single most** 10:24:46
16 **common would be to refer to a point mutation as a** 10:24:49
17 **single nucleotide variant.** 10:24:52
18 Q. Sometimes shortened SNV? 10:24:56
19 **A. Correct.** 10:24:59
20 Q. And it's called a point mutation because 10:24:59
21 it's just at one base in the genetic code, right? 10:25:04
22 **A. Correct.** 10:25:07

1 Q. Okay. So one example of a point mutation 10:25:07
2 is an expected base, or I'll call it a normal base, 10:25:10
3 is changed to something different. That's one 10:25:13
4 example of a point mutation, right? 10:25:17
5 **A. Geneticists would definitely say ancestral** 10:25:21
6 **base changed to a new base, but yes.** 10:25:23
7 Q. Okay. So, again, ancestral base changed 10:25:26
8 to a new base is an example of a point mutation, 10:25:30
9 right? 10:25:32
10 **A. Yes.** 10:25:33
11 Q. And similarly, an ancestral base that's 10:25:34
12 deleted is also a point mutation, right? 10:25:38
13 **A. Pretty commonly. Some people --** 10:25:40
14 **geneticists like to split hairs, so some people** 10:25:41
15 **might call that an insertion deletion. Technically** 10:25:45
16 **there's often different mechanisms for them, and** 10:25:48
17 **technically there are different ways of detecting** 10:25:51
18 **them. So sometimes they're distinguished between** 10:25:56
19 **SNVs and indels.** 10:25:58
20 Q. So what's a distinction? What is an 10:26:01
21 indel? 10:26:03
22 **A. An indel is -- a short indel, a one-base** 10:26:04

1 **indel would be the removal of the G from the** 10:26:10
2 **sequence, so if the ancestral sequence was ATGC, the** 10:26:12
3 **derived sequence would be ATC.** 10:26:18
4 Q. Okay. And an insertion would be, I 10:26:24
5 assume, adding a base to the ancestral sequence? 10:26:26
6 **A. Correct.** 10:26:30
7 Q. And sometimes either insertions or 10:26:33
8 deletions can be longer than just one base, right? 10:26:35
9 **A. Correct.** 10:26:38
10 Q. Do have an understanding of what a 10:26:43
11 duplication mutation is? 10:26:46
12 **A. Duplication is a very broad term that** 10:26:48
13 **would encompass anything from the sequence ATGC** 10:26:50
14 **becoming ATGGC where a single G was duplicated, all** 10:26:59
15 **the way to an entire chromosome having two copies** 10:27:04
16 **instead of one copy. So it's a very broad term in** 10:27:08
17 **genetics, and most geneticists would put some bound** 10:27:12
18 **on it or talk about it in a specific context.** 10:27:16
19 Q. Okay. How about tandem duplications, are 10:27:19
20 you familiar with that term? 10:27:22
21 **A. Tandem duplications are caused by one of** 10:27:23
22 **several mechanisms in which usually larger than a** 10:27:28

1 **single base-pair sequence is expanded. So sometimes** 10:27:34
2 **we would talk about a sequence like ATGATGATG** 10:27:41
3 **becoming ATGATGATGAKG, right? Adding a whole three** 10:27:52
4 **units of sequence to it. Other times a tandem** 10:28:00
5 **duplication can refer to the sequence in which a** 10:28:04
6 **gene or a gene region or a locus is -- a second copy** 10:28:12
7 **of that is put in right next to where it was. And** 10:28:20
8 **there's many mechanisms for that as well.** 10:28:24
9 Q. I've seen the term copy number variation. 10:28:27
10 Is that the -- an example of what you're talking 10:28:29
11 about? 10:28:32
12 **A. Copy number variation does not have to be** 10:28:35
13 **tandem duplication. Tandem duplications can be copy** 10:28:38
14 **number changes, but copy number change has a** 10:28:43
15 **different connotation from tandem duplication.** 10:28:50
16 Q. Okay. At a high level, is copy number 10:29:09
17 variation a variation in gene number? Is it gene 10:29:13
18 specific? 10:29:20
19 **A. Copy number variation in my opinion is a** 10:29:26
20 **user-defined term that is operational to the context** 10:29:30
21 **in which you are discussing it. And you would have** 10:29:35
22 **to give me a specific context for me to give you a** 10:29:42

1 **really good definition of what I think most people** 10:29:45
2 **in the field would understand. Geneticists are** 10:29:47
3 **extremely semantic about such things. Broadly** 10:29:52
4 **speaking, copy -- you said copy number variation or** 10:29:56
5 **copy number duplication?** 10:30:02
6 Q. I said variation, but -- let's start 10:30:04
7 there. Copy number variation. 10:30:06
8 **A. So, are you limiting this to cancer or are** 10:30:07
9 **you open to all uses of copy number variation?** 10:30:09
10 Q. So, in the context of mutations that cause 10:30:12
11 cancer, what's your understanding of what 10:30:15
12 cancer-causing copy number variations are? 10:30:19
13 MR. RAICH: Object to the scope. 10:30:25
14 **A. It is an extremely broad term, and it** 10:30:26
15 **would -- it would encompass the addition of** 10:30:28
16 **additional whole chromosomes. It would refer to** 10:30:32
17 **rearrangements amongst chromosomes in which the** 10:30:39
18 **derived cells carried part of an additional** 10:30:42
19 **chromosome. It could refer to tandem duplications.** 10:30:48
20 **It could refer to deletions. It has a very wide** 10:30:53
21 **scope that probably is not germane to this** 10:30:57
22 **conversation.** 10:31:02

Q. Okay. Let's go back one other type of 10:31:03
mutation. Do you have an understanding of what an 10:31:08
inversion is? 10:31:10
A. Broadly speaking, an inversion is a 10:31:13
situation in which the sequence of DNA through -- 10:31:15
again, through many plausible mechanisms. I don't 10:31:20
know I could give you a full list. A segment of DNA 10:31:25
-- DNA has a -- has a -- has a direction, and it is 10:31:31
a case in which the -- a unit of DNA has been 10:31:40
flipped around, so as if you were on a one-way 10:31:44
street and in the middle of the block someone had 10:31:49
sent the signs pointing the other direction. 10:31:51
Q. So an example would be, in a particular 10:31:54
DNA molecule, you expect a particular sequence, say 10:31:59
from three prime to five prime, and you find that 10:32:04
sequence in the backward order if you're reading 3' 10:32:08
to 5'. Is that generally what you're saying with the 10:32:14
one-way street? 10:32:18
A. In general, yes. Well as always use 5' to 10:32:19
3', but yes. 10:32:23
Q. Okay. So an inversion is you're expecting 10:32:25
a certain sequence reading 5' to 3' and when you 10:32:27

1 read it, you get the expected sequence but in 10:32:31
2 backward order? 10:32:36
3 **A. I would say we would get the reverse** 10:32:37
4 **complement of that sequence, yes.** 10:32:38
5 Q. Okay. How about translocation? Do you 10:32:44
6 have an understanding of what a translocation is? 10:32:46
7 **A. A translocation is the movement of a piece** 10:32:49
8 **of DNA from one place in the genome to somewhere** 10:32:53
9 **else in the genome.** 10:32:58
10 Q. At your first deposition in this case, I 10:34:52
11 asked you if you knew when Illumina first became 10:34:54
12 aware of index hopping happening on its machines. 10:34:56
13 Do you remember that? 10:34:59
14 **A. I believe you, but I don't recall.** 10:35:01
15 Q. Okay. Since your first deposition, have 10:35:03
16 you tried to determine when Illumina first became 10:35:06
17 aware of index hopping potentially causing errors on 10:35:09
18 its sequencers? 10:35:13
19 **A. I'm not sure how to answer the question.** 10:35:15
20 **I mean, have I thought about it? I'm sure I have.** 10:35:19
21 **I don't know that I have done any research on it.** 10:35:22
22 Q. Since your first deposition, have you 10:35:25

1 tried to determine when Illumina first acknowledged 10:35:27
2 index hopping happening on its machines? 10:35:31
3 **A. No.** 10:35:36
4 Q. Since your first deposition, did you try 10:35:36
5 to determine whether Illumina was aware of index 10:35:38
6 hopping on its machines at the time of the invention 10:35:40
7 of these patents in December 2010? 10:35:44
8 **A. I have not attempted to determine what** 10:35:46
9 **Illumina did.** 10:35:49
10 Q. Since your first deposition, have you 10:35:51
11 asked anyone at Illumina whether they had any 10:35:53
12 evidence of Illumina being aware of index hopping on 10:35:56
13 its machines in December 2010? 10:36:01
14 **A. No.** 10:36:04
15 Q. Since your first deposition, have you 10:36:12
16 tried to determine what types of sample indexes 10:36:13
17 Illumina was instructing its customers to use with 10:36:17
18 their sequencers? 10:36:20
19 **A. No.** 10:36:22
20 MR. MATTY: All right. Let's take a 10:36:26
21 short break. 10:36:27
22 VIDEO TECHNICIAN: The time is 10:36 10:36:28

a.m. This ends Unit 1. We are off the record. 10:36:30

(A brief recess was taken.) 10:36:33

VIDEO TECHNICIAN: The time is 10:52 10:52:25

a.m. This begins Unit number 2. We are on the 10:52:27

record. 10:52:30

BY MR. MATTY: 10:52:31

Q. Dr. Spellman, your understanding of 10:53:23

cross-over error as it's used in the '852 patent 10:53:24

claims requires sequences of chimeric molecules made 10:53:27

from template nucleic acids derived from different 10:53:37

samples. Right? 10:53:39

A. Are you using my interpretation from my 10:53:44

reply declaration? 10:53:46

Q. I think so. I guess that's what I'm 10:53:49

asking. 10:53:51

A. Can you point me to that? Or I can find 10:53:52

it. 10:53:54

Q. I was looking at paragraph 26 of your 10:53:55

'852. 10:53:56

So your understanding of cross-over error 10:54:09

as it's used in the '852 patent claims requires 10:54:12

sequences of chimeric molecules made from template 10:54:16

1 nucleic acids derived from different samples, right? 10:54:23
2 **A. That's what I've gotten in 26. Can I have** 10:54:25
3 **a copy of the '852 as well, please?** 10:54:30
4 Q. Here is the '852 patent. 10:54:45
5 So, when you read cross-over error in the 10:54:47
6 '852 patent claims, in your interpretation, it 10:54:49
7 requires chimeric molecules; and those chimeric 10:54:53
8 molecules have to be made from template nucleic 10:54:56
9 acids derived from different samples. True? 10:55:00
10 **A. I'm just reading the claims and making** 10:55:11
11 **sure I got them against my reply declaration.** 10:55:13
12 **Can you repeat the question, please?** 10:55:34
13 Q. When you read cross-over error in the '852 10:55:36
14 patent claims, in your interpretation, it requires 10:55:40
15 there that -- it requires that there be chimeric 10:55:45
16 molecules, and it requires that those chimeric 10:55:49
17 molecules be made from template nucleic acids 10:55:52
18 derived from different samples. True? 10:55:56
19 **A. Yes, that's correct.** 10:55:58
20 Q. Okay. Now, in the obviousness 10:56:04
21 combinations that you have advanced for the '852 10:56:06
22 patent, one of the reasons that you said there would 10:56:08

1 have been motivation to combine your references is 10:56:12
2 that there would be motivation to use Illumina 10:56:15
3 machines instead of pyro-sequencing because Illumina 10:56:18
4 machines gave accurate sequencing data, right? 10:56:22
5 **A. If you want to point me to a specific** 10:56:27
6 **place in the reply declaration or the original** 10:56:31
7 **declaration, I'd be happy to go there. But broadly** 10:56:33
8 **speaking, Illumina sequencers are more accurate at** 10:56:35
9 **individual bases than the 454 and are particularly** 10:56:42
10 **more accurate in some contexts. And so sequencing** 10:56:46
11 **accuracy of the Illumina machines is extremely high,** 10:56:52
12 **and it would be a very clear reason to use them.** 10:56:54
13 Q. Okay. In December 2010, sequencing 10:56:58
14 accuracy of the Illumina machines was extremely 10:57:01
15 high. That's your opinion, right? 10:57:03
16 **A. On individual-based determinations, yes.** 10:57:06
17 Q. Do you know what the error rate of 10:57:10
18 pyro-sequencing was in December of 2010? 10:57:11
19 **A. It would depend upon the context of the** 10:57:15
20 **sequence. It would typically be somewhere between** 10:57:18
21 **-- sequencing technology is normally used something** 10:57:25
22 **called a Q value as their quality assessment more** 10:57:29

1 **commonly than a percent accuracy because it both** 10:57:33
2 **measures the quality of a sequence as well as its** 10:57:36
3 **accuracy. So in the best contexts, the Q-value is** 10:57:41
4 **associated with individual reads on a 454 would** 10:57:47
5 **surely be around 30 or perhaps even a little better.** 10:57:52
6 **But there would be many bases that would have** 10:57:55
7 **Q-values well under 10 and would always have values** 10:57:59
8 **under 10 no matter how you sequenced them or when** 10:58:03
9 **you sequenced them. And A Q-value of 10 is** 10:58:07
10 **approaching -- is low quality sequence.** 10:58:10
11 Q. Do you understand how Q-values are 10:58:18
12 determined? 10:58:20
13 **A. Q-values are generally -- they are** 10:58:22
14 **heuristic interpretations of lots of things, and** 10:58:27
15 **they would be machine dependent. The original** 10:58:34
16 **definition of the Q-value is like the true accuracy,** 10:58:36
17 **but when they're applied with individual sequences,** 10:58:44
18 **you don't have the true accuracy. You can only** 10:58:46
19 **estimate their likely quality if you were to** 10:58:48
20 **sequence the same things. And so they're** 10:58:52
21 **approximated from the underlying data.** 10:58:55
22 Q. Okay. Stepping back, you mentioned 10:59:04

1 earlier that you're familiar with a number of the 10:59:07
2 authors on the Campbell paper that you rely on in 10:59:10
3 your reply declaration, right? 10:59:15
4 **A. Yes.** 10:59:16
5 Q. When was the last time you spoke with any 10:59:18
6 of the authors on the Campbell paper? 10:59:20
7 **A. Can you hand me a copy of Campbell,** 10:59:23
8 **please?** 10:59:25
9 **(Exhibit 1057 was previously marked** 10:59:43
10 **and referred to.)** 10:59:43
11 BY MR. MATTY: 10:59:44
12 Q. Here you go. I'll hand you Exhibit 1057. 10:59:45
13 Do you recognize that as the Campbell paper you 10:59:47
14 relied on? 10:59:49
15 **A. Yes.** 10:59:51
16 Q. All right. When was the last time you 10:59:51
17 spoke with any of the authors on the Campbell paper? 10:59:52
18 **A. Hard to answer for sure. Peter changed** 11:00:01
19 **institutions early in this year, and I don't believe** 11:00:11
20 **I've talked to him since then. I may have talked to** 11:00:15
21 **him in 2024. I would be surprised if I hadn't** 11:00:23
22 **talked to him since 2023. I do occasionally email** 11:00:29

1 **with him. I would have to try to dig that out. I** 11:00:33
2 **haven't talked to him within the last two years to** 11:00:40
3 **the best of my recollection. And he is the person I** 11:00:42
4 **would have most likely talked to most recently.** 11:00:45
5 **It's possible it could have been Mike Stratton or I** 11:00:50
6 **haven't -- I don't think I talked -- Andy Futreal** 11:00:57
7 **moved to MD Anderson in -- maybe ten years ago, and** 11:01:02
8 **I was at MD Anderson in 2024. It's possible he was** 11:01:09
9 **there, but I don't recall him being there.** 11:01:12
10 Q. And just to be make sure I'm clear, when 11:01:16
11 you said Peter, you mean Peter Campbell, right? 11:01:17
12 **A. Correct. I've talked to lots of people** 11:01:21
13 **who have talked to Peter since that. I saw Inigo** 11:01:23
14 **Martincorena, who was a post-doc with Peter and Mike** 11:01:25
15 **Stratton at ACR this year. And I talked to him. I** 11:01:31
16 **asked him explicitly about Peter, but I did not talk** 11:01:33
17 **to Peter at ACR. He was at his new company.** 11:01:37
18 Q. Okay. Have you ever talked with any of 11:01:40
19 the authors on the Campbell paper about this paper? 11:01:41
20 **A. It's an excellent question. So, as I** 11:01:48
21 **mentioned before, I was an external site reviewer** 11:01:50
22 **for the program that Stratton and Futreal had, and I** 11:01:54

1 **visited the Wellcome Trust Sanger Center I believe** 11:01:58
2 **around 2007, and talked to -- and met Peter for the** 11:02:03
3 **first time there. And I saw the science that they** 11:02:07
4 **were doing, so they may have talked to me about this** 11:02:12
5 **paper at this time because I believe this is dated** 11:02:15
6 **2008, so I think -- I think I was there right before** 11:02:18
7 **this paper came out. That was a long time ago. And** 11:02:20
8 **I don't remember exactly what they presented.** 11:02:26
9 Q. Okay. The time frame is helpful. 11:02:28
10 Have you talked to any of the authors on 11:02:30
11 the Campbell paper as part of your work in these 11:02:32
12 cases? 11:02:35
13 **A. No.** 11:02:36
14 Q. Now, you note a number of times in your 11:03:20
15 analysis that Campbell obtained 1.2 million sequence 11:03:23
16 reads that you say are chimeric sequences, right? 11:03:34
17 **A. Looking at Campbell on page 2 of the** 11:03:41
18 **exhibit number, there's a section under** 11:03:44
19 **rearrangements, and the exact quote is there. I can** 11:03:47
20 **read it for you if you wish. It's a little more** 11:03:50
21 **nuanced than what you said.** 11:03:53
22 Q. What do you mean by it's a little more 11:03:56

1 nuanced than what I said? What's different than 11:03:58
2 what I said? 11:04:00
3 **A. Well, the last clause of that sentence is** 11:04:00
4 **"Suggested a possible rearrangement."** 11:04:02
5 Q. Right. And what's the difference between 11:04:05
6 possible rearrangements and chimeric sequences in 11:04:08
7 your view? 11:04:11
8 **A. I didn't notice that you included the word** 11:04:14
9 **"suggested."** 11:04:16
10 Q. Got it. 11:04:21
11 So it's your opinion that Campbell 11:04:22
12 obtained 1.2 million reads that suggested a possible 11:04:25
13 chimera. Is that what you're saying? 11:04:31
14 **A. A rearrangement is a structural change in** 11:04:35
15 **the DNA that could either be a real change in the** 11:04:40
16 **DNA sequence or an artifact created by some other** 11:04:44
17 **process. And the Campbell paper is explicitly** 11:04:48
18 **looking for real rearrangements that are present in** 11:04:55
19 **the inherited DNA of the sample they have got. So,** 11:04:58
20 **the detection on the Illumina sequencer could be a** 11:05:04
21 **real change of the ones they care about, something** 11:05:13
22 **that's in the sample. It could be something that** 11:05:17

1 **happened later on that is an artifact of some** 11:05:19
2 **flavor.** 11:05:23
3 Q. What's the difference between a 11:05:24
4 rearrangement and a chimeric sequence? 11:05:25
5 MR. RAICH: Objection to the form. 11:05:31
6 **A. Technically nothing. They're used** 11:05:37
7 **slightly differently in the field for complicated** 11:05:40
8 **reasons.** 11:05:43
9 Q. Looking at the sentence that you pointed 11:05:56
10 to, it says that it got 1.2 million reads from 11:05:59
11 NCI-H2171 and 770,000 from NCI-H1770. 11:06:06
12 Do you see that? 11:06:21
13 **A. I do.** 11:06:22
14 Q. It goes on to say, "In which mapping of 11:06:23
15 the two ends of the genome suggested a possible 11:06:26
16 rearrangement." 11:06:30
17 Do you see that? 11:06:31
18 **A. I do.** 11:06:32
19 Q. Why did you focus only on the 1.2 million 11:06:32
20 and not the 770,000? 11:06:35
21 **A. No particular reason. I could have** 11:06:39
22 **described them both.** 11:06:41

1 Q. You said the 1.2 million are possible 11:06:43
2 chimeric sequences, right? 11:06:47
3 **A. Do you want to point me to the text in the** 11:06:53
4 **reply declaration?** 11:06:56
5 Q. You can look wherever you need to. I just 11:07:00
6 -- 11:07:06
7 **A. I don't think I have a specific reason for** 11:08:24
8 **only talking about the data from NCI-H2171.** 11:08:26
9 Q. Okay. Is it your understanding that the 11:08:36
10 770,000 reads from NCI-H1770 were not possible 11:08:38
11 chimeras? 11:08:49
12 **A. The sentence says exactly the opposite.** 11:08:50
13 **It says the reads from NCI-H1770 suggested a** 11:08:53
14 **possible rearrangement.** 11:08:58
15 Q. Right. But your declaration over and over 11:09:00
16 and over again says Campbell got 1.2 million 11:09:02
17 possible chimeras. Are you saying that number is 11:09:07
18 wrong? 11:09:11
19 MR. RAICH: Objection, foundation. 11:09:12
20 **A. I'm saying it's referring to NCI-H2171. I** 11:09:15
21 **don't see a problem.** 11:09:20
22 Q. And you have no explanation for why you 11:09:20

1 focused on that one and didn't talk about the 11:09:22
2 770,000? 11:09:28
3 **A. In paragraph 42 you'll see it starts,** 11:09:29
4 **"Among these -- those 18.8 million reads, about 1.2** 11:09:31
5 **million reads." So I've limited myself just to the** 11:09:35
6 **NCI-H2171. You'll see earlier on page 2 of Exhibit** 11:09:39
7 **1057 that the NCI-H2171 is the one that has 18.8** 11:09:46
8 **million reads, so I'm talking just about the 18.8** 11:09:52
9 **million reads that came from the NCI-H1271 and the** 11:09:57
10 **1.2 reads that suggested a possible rearrangement in** 11:10:01
11 **that sample.** 11:10:05
12 Q. Well, if you had chosen to focus on the 11:10:07
13 other one, NCI-H1770, you would have been 11:10:10
14 highlighting a lower number of what you say are 11:10:16
15 chimeras, right? 11:10:18
16 MR. RAICH: Objection, foundation. 11:10:20
17 **A. I don't understand the point.** 11:10:23
18 Q. I'm asking why you focused on the highest 11:10:25
19 number of what you say are potential chimeras 11:10:29
20 without mentioning the NCI-H1770. 11:10:34
21 **A. My recollection is that the number of** 11:10:51
22 **reads they generated for NCI-H1770 is actually** 11:10:52

1 **smaller, but I don't -- I am not seeing that on the** 11:11:01
2 **results there quickly. I can spend the time to** 11:11:02
3 **actually confirm that.** 11:11:04
4 Q. Let me ask, the sentence that you just 11:11:08
5 read to me from your declaration about the 1.2 11:11:09
6 million reads, did you write that sentence? 11:11:15
7 **A. I don't recall if I wrote it or if I** 11:11:31
8 **edited it or I -- but it is -- I agree that it is** 11:11:33
9 **correct.** 11:11:37
10 Q. Okay. The NCI-H2171, what does that refer 11:11:38
11 to? 11:11:50
12 **A. NCI-H2171 is a lung cancer cell line. In** 11:11:54
13 **this case it's a small cell lung cancer cell line.** 11:11:59
14 Q. Okay. So NCI-H2171 is one cell line, 11:12:03
15 right? 11:12:08
16 **A. Correct.** 11:12:09
17 Q. And NCI-H1770 is a second cell line, 11:12:10
18 right? 11:12:16
19 **A. That's correct.** 11:12:16
20 Q. Go to paragraph 41 in your '852 11:12:23
21 declaration that you are looking at. 11:12:27
22 **A. Paragraph 41?** 11:12:31

Q. 41. 11:12:34

A. Yes. 11:12:35

Q. Do you see there, you say, "Campbell, for 11:12:35
example, sequenced two cancer cell lines to identify 11:12:37
cancer causing chimeras"? 11:12:42

A. Yes. 11:12:44

Q. Those two cancer cell lines that you're 11:12:45
referring to refer to the 2171 and the 1770 that we 11:12:47
just mentioned, right? 11:12:54

A. Can you repeat the question, please? 11:12:56

Q. The two cancer cell lines that you refer 11:12:59
to in paragraph 41 of your declaration refer to the 11:13:02
2171 and the 1770 cell lines that we were just 11:13:06
talking about. Those are the two cell lines, right? 11:13:11

A. That's correct. 11:13:14

Q. At the bottom of page 22 in your '852 11:13:17
declaration, paragraph 41, you say, "From the two 11:13:22
cell lines, Campbell generated 36.2 million paired 11:13:28
reads of 29 to 36 bases at each end," right? 11:13:33

A. Yes, that's correct. 11:13:38

Q. And then you say, "About 18.8 million out 11:13:43
of those 36 million reads were of sufficient quality 11:13:46

that both ends mapped back to the current reference genome assembly," right? 11:13:49 11:13:54

A. You're reading what's written there, yes. 11:13:57

Q. Is that all accurate? 11:13:59

A. No. 11:14:00

Q. Okay. So you said you don't know why you focused on the 1.2 million from the 2171 cell line, right? 11:14:10 11:14:13 11:14:18

MR. RAICH: Objection. Mischaracterizes the prior testimony. 11:14:19 11:14:20

A. I think I'm being succinct. I don't see a problem with just choosing one of the two cell lines to discuss. You noted an error, the data that I referred to at the bottom of line 22 from the two cell lines, Campbell generated 36.2. It's not from the two cell lines. It's just from the 2171. 11:14:22 11:14:26 11:14:29 11:14:31 11:14:34 11:14:37

Q. All right. But in your declaration it says you were focused, you thought at least, on the two cell lines, right? 11:14:42 11:14:43 11:14:45

A. That's -- yes, I made a mistake. 11:14:47

Q. Okay. The number of possible rearrangements in the 1770 cell line was lower than 11:15:54 11:15:56

1 the 2171 cell line. You understand that now, right? 11:16:03
2 **A. The number -- yes.** 11:16:08
3 Q. Okay. So let's focus on the 2171. I need 11:16:12
4 some help with the numbers. I'm on page 2 of 11:16:20
5 Campbell. 11:16:24
6 Do you see the left column, the paragraph 11:16:25
7 sort of in the middle starts with "from the 11:16:30
8 NCI-H2171 library"? 11:16:34
9 **A. Yes.** 11:16:37
10 Q. So it says they generated 36.2 million 11:16:38
11 paired-end reads of 29 to 36 bases at each end, 11:16:42
12 right? 11:16:49
13 **A. Yes.** 11:16:49
14 Q. And I understand that as sort of the 11:16:51
15 biggest number, the total number of reads that they 11:16:53
16 got from the 2171 cell line. Is that your 11:16:56
17 understanding? 11:16:59
18 **A. Yes.** 11:17:00
19 Q. Okay. Then it says, "Out of those 36.2, 11:17:04
20 18.8 million reads were of sufficient quality that 11:17:08
21 both ends mapped back to the current reference 11:17:13
22 genome assembly." 11:17:16

1 Do you see that? 11:17:18
2 **A. Yes.** 11:17:19
3 Q. I understand that to be sort of a quality 11:17:20
4 filter that they used to discard a little under half 11:17:23
5 of the 36.2 million reads. Is that your 11:17:28
6 interpretation? 11:17:32
7 **A. Paired reads, yes.** 11:17:34
8 Q. Okay. So they got 36.2 million total 11:17:35
9 paired reads, right? 11:17:39
10 **A. Yes.** 11:17:40
11 Q. Then they applied a quality filter. Then 11:17:40
12 18.8 million paired reads got past the quality 11:17:44
13 filter, right? 11:17:47
14 **A. I'm not quite sure that's how it works,** 11:17:49
15 **but it's a reasonable approximation.** 11:17:52
16 Q. Okay. Their measure of quality is that 11:17:55
17 both ends mapped back to the current reference 11:18:02
18 genome assembly. Do you see that? 11:18:05
19 **A. Yes.** 11:18:07
20 Q. Can you explain to me why that's a useful 11:18:07
21 quality screen? 11:18:10
22 **A. One could have many sources of error in** 11:18:19

1 the sequence, and this is a -- this paper is a very 11:18:26
2 early paper on Illumina technology. I am not sure 11:18:31
3 exactly what the error rate is at this time. It's 11:18:35
4 probably a little higher than it would be in later 11:18:38
5 publications, like Circa 2010 in Gloor. I don't 11:18:40
6 know exactly when the Stratton lab generated this -- 11:18:47
7 the Stratton lab generated these data, but they 11:18:53
8 could have been as early as 2006 to 2007 if this 11:18:54
9 paper is published in 2008. So you could have 11:19:00
10 sequences that were of sort of low quality. You 11:19:07
11 could -- the actual methods, I believe -- I would 11:19:14
12 have to check if they used ELAND or if they used 11:19:20
13 Mac, but the ability to align these extremely short 11:19:24
14 sequences to the human genome can be a problem 11:19:27
15 sometimes. And so a combination of low-quality 11:19:30
16 sequence or a combination of mapping challenges with 11:19:35
17 the software algorithms could lead to mapping 11:19:43
18 problems. It could even be that there's like, you 11:19:47
19 know, E. coli or some other non-human DNA mixed in 11:19:52
20 with this material. So there's a whole set of 11:19:57
21 things whereby mapping to the human genome is a 11:20:00
22 really good first thing to do. 11:20:04

1 Q. At the time of the Campbell paper, why 11:20:08
2 could aligning the short sequences to the genome be 11:20:14
3 a problem? 11:20:18
4 **A. Why would it be a problem?** 11:20:20
5 Q. What would cause that problem? 11:20:22
6 **A. I mean, these sequences are very short,** 11:20:25
7 **right? This is one of the earliest sequencers out** 11:20:28
8 **there. 29 base pairs are right at the edge of what** 11:20:32
9 **we would call genome unique, so the general** 11:20:39
10 **threshold for being genome unique is one part in 3** 11:20:48
11 **billion, which I believe is roughly four to the 20th** 11:20:56
12 **if I'm doing my math -- if I'm remembering my math.** 11:20:58
13 **I would have to work it out. So somewhere around 20** 11:21:00
14 **base pairs is where you expect a sequence to become** 11:21:03
15 **genome unique if it's not part of a sequence that's** 11:21:07
16 **repeated. But there are lots of segments of the** 11:21:11
17 **genome at 29 base pairs that are repeats.** 11:21:15
18 **And if one allows one or two or even three** 11:21:18
19 **base pair mismatches against the reference genome,** 11:21:22
20 **29 base pairs is really getting hard to align** 11:21:26
21 **uniquely. So there can be problems in that space.** 11:21:30
22 **36 is substantially better. But, again, it is right** 11:21:33

1 **on the edge of what's technically possible. The** 11:21:37
2 **aligners themselves are heuristic.** 11:21:43
3 **The computational expense of doing full** 11:21:46
4 **accurate alignment is not tenable today. It wasn't** 11:21:49
5 **tenable then. And so the heuristic algorithms they** 11:21:54
6 **use can make mistakes. They normally use something** 11:21:57
7 **like a seed of the sequence, say 10 bases or 12** 11:22:01
8 **bases. If there's an error in that 10 or 12 bases,** 11:22:05
9 **it does not -- it might not align.** 11:22:07
10 **So there's lots of reasons for the** 11:22:09
11 **technical mapping problems. And it could be that** 11:22:12
12 **the sequence of NCI-H2171 is different from the** 11:22:13
13 **human reference in some meaningful way, which leads** 11:22:20
14 **to a mapping problem. That's still a problem today.** 11:22:23
15 Q. Okay. This might be related to that. I'm 11:22:28
16 not sure. 11:22:30
17 In that 18.8 million reads sentence that 11:22:31
18 we wrote -- that we read, it refers to the current 11:22:34
19 reference genome assembly NCBI Build 36. Do you see 11:22:37
20 that? 11:22:42
21 **A. Yes.** 11:22:42
22 Q. Do you have an understanding of what that 11:22:43

is? 11:22:44

A. The human genome was "published" -- I put that in quotes -- as a sequence in the early 2000s. That sequence was a single haplotype of a single individual, and sometimes it's composited from a few different people, but mostly it's just a single person and it's just one set of their chromosomes. And so it -- it could have different -- it could have substantial differences from a typical human because it's a single individual. And it also had technical errors in it, and over time the NCBI, the National Center for Bioinformatics or Biomedical Informatics would curate the human genome sequencing, provide more accurate, more updated maps of that sequence. It continues to this day. There are continued builds of the genome being released because we're trying to capture as much of it as possible, as accurately as possible. And the Build 36 is a specific build. 11:22:48 11:22:54 11:23:01 11:23:08 11:23:12 11:23:15 11:23:21 11:23:26 11:23:32 11:23:36 11:23:44 11:23:49 11:23:54 11:23:58 11:24:01 11:24:05 11:24:07 11:24:10

Q. So that the reference genome assembly starting from when it was first published in the early 2000s sort of gets better over time, right? 11:24:12 11:24:16 11:24:18

1 **A. There's a lot of debate of whether or not** 11:24:24
2 **it gets different over time. Not everyone is always** 11:24:25
3 **sure that it gets better over time. There's -- I** 11:24:30
4 **have a colleague who has a paper showing that Build** 11:24:32
5 **37 performs better on some metrics than Build 38** 11:24:35
6 **when you are trying to do problems like this. Why** 11:24:38
7 **that is, I'm not sure he can explain, but, you know,** 11:24:41
8 **as a practical matter, sometimes historical builds** 11:24:46
9 **are better than new builds. It could be because the** 11:24:49
10 **tools are better configured for them. It's our --** 11:24:52
11 **ostensibly errors are corrected, more complexity is** 11:24:54
12 **introduced, the accuracy is increased, but that's a** 11:25:00
13 **complicated question.** 11:25:03
14 Q. I think you just said it. What does NCBI 11:25:18
15 stand for? 11:25:22
16 **A. It's either the National Center for** 11:25:22
17 **Bioinformatics or National Center for Biomedical** 11:25:24
18 **Informatics. I'm not exactly sure. I can't** 11:25:29
19 **actually remember. We always just call it NCBI.** 11:25:33
20 Q. Do you have an understanding of how 11:25:51
21 accurate the human reference genome assembly was in 11:25:53
22 June of 2008? 11:25:59

1 **A. What do you mean by accuracy?** 11:26:00
2 Q. How reliable it was, how complete it was. 11:26:01
3 **A. You're going to have to be much more** 11:26:08
4 **specific in your question for me to even attempt to** 11:26:09
5 **answer that one.** 11:26:12
6 Q. Do you know if there were gaps in the 11:26:13
7 human reference genome assembly in June of 2008? 11:26:14
8 **A. I am nearly certain there were. Even if** 11:26:24
9 **there weren't, I don't -- I think your question is** 11:26:28
10 **very complicated because the sequence of one** 11:26:31
11 **individual is different than the sequence of another** 11:26:35
12 **individual. And in this case, the reference genome** 11:26:38
13 **is just one haplotype and therefore since most** 11:26:43
14 **humans are composed of two haplotypes, even a** 11:26:47
15 **sequence of one person can't be represented by the** 11:26:52
16 **sequence of -- by a single sequence. We have** 11:26:54
17 **learned an enormous amount about the structure and** 11:26:59
18 **variation of the genome at the point of this paper** 11:27:02
19 **but also since then, and you would have been very** 11:27:05
20 **specific about what you were asking.** 11:27:10
21 Q. Okay. So let's go back. 11:27:11
22 18.8 million of the reads that Campbell 11:27:14

1 got for the 2171 cell line passed their quality 11:27:19
2 screen for both ends mapping, right? 11:27:25
3 **A. Yes.** 11:27:29
4 Q. It goes on to say, "Of the reads for which 11:27:33
5 both ends mapped back to the genome, about 7.2 11:27:36
6 million were excluded from further analysis because 11:27:40
7 they precisely duplicated other sequences from the 11:27:43
8 library." Right? 11:27:47
9 **A. Yes, it does say that.** 11:27:49
10 Q. And you understand that to say that an 11:27:52
11 additional 7.2 million out of the 18.8 million reads 11:27:54
12 were excluded essentially because they were PCR 11:28:00
13 duplicates, right? 11:28:04
14 **A. That's what it says, yes.** 11:28:06
15 Q. Okay. So that leaves us with 11.6 million 11:28:08
16 paired-end reads that get past the quality mapping 11:28:12
17 screen and the duplicate screen in Campbell, right? 11:28:17
18 **A. Correct. I believe that's correct.** 11:28:21
19 Q. Do you see Campbell then says they 11:28:43
20 excluded several other classes of sequence reads and 11:28:45
21 the first one they say is reads with missed priming 11:28:49
22 of the sequencing, which is about 50,000 reads? Do 11:28:52

you see that? 11:28:55

A. I do. 11:28:56

Q. Do you have an understanding of what 11:28:57
Campbell is referring to when he is saying he 11:28:58
excluded reads with missed priming of the 11:29:02
sequencing? 11:29:06

A. That is not something I'm deeply familiar 11:29:06
with. My assumption is that they infer this because 11:29:08
it primarily sequences the adapter sequence or 11:29:15
something like that, but I don't know for sure. 11:29:20

Q. Okay. Campbell then says that sequences 11:30:11
from gaps in the reference genome estimated to 11:30:13
encompass about 160 mega-bases in total generated 11:30:17
many mapping errors. Do you see that? 11:30:24

A. Yes. 11:30:26

Q. Do you have an understanding of what that 11:30:26
means in Campbell? 11:30:28

A. Most of the gaps in the human genome were 11:30:33
around very large repetitive sequences. Oh, sorry. 11:30:36
So a very clear example of that is the centromeres 11:30:41
at each chromosome have pseudo -- they have repeated 11:30:45
sequences or near perfect -- near-repeated sequences 11:30:52

1 over and over and over again. And we have learned 11:30:55
2 again a lot about this in the last couple of years 11:30:59
3 with new sequencing technologies that can resolve 11:31:01
4 these. But at the time of Campbell, we had an idea 11:31:04
5 of what these sequences were like, and we had an 11:31:09
6 estimate of how big they were, but we didn't know 11:31:12
7 exactly what the sequences were, and we didn't know 11:31:17
8 -- and there was occasionally non-repeated DNA 11:31:26
9 sequence sort of buried within the repeated 11:31:29
10 sequence, so you might have 100,000 base pairs of an 11:31:33
11 extremely repeated set of sequences that are the -- 11:31:39
12 they're not exactly the same over and over and over 11:31:45
13 again, but they're very close, 30 or 50 or 70 base 11:31:47
14 pairs with one substitution or something like that. 11:31:52
15 Just over and over. And no sequencing at the time 11:31:55
16 of this could handle that problem. But then after 11:32:02
17 100 kb of this, there might be 10,000 base pairs of 11:32:05
18 unique sequence that did not have great numbers of 11:32:09
19 repeats in it, and then it might go back to the 11:32:14
20 repeat sequence again. So, these are the sort of 11:32:16
21 gaps that are present in Build 36, Build 37, Build 11:32:18
22 38 and only got resolved in the last couple of years 11:32:26

1 **for some individuals with the T2T reference genomes.** 11:32:29
2 **So the gaps that they're talking about are these** 11:32:35
3 **very complicated medium-complexity repeat sequences.** 11:32:38
4 Q. Okay. So at the time of Campbell, there 11:32:43
5 were gaps in the human reference genome around very 11:32:50
6 large repetitive sequences, right? 11:32:53
7 **A. Correct. They would not normally be** 11:32:57
8 **around repeats that were 100 base pairs in length,** 11:32:59
9 **but, you know, if they stretched beyond 10,000 base** 11:33:03
10 **pairs, then certainly 100,000 base pairs of highly** 11:33:08
11 **repetitive sequences. there would have certainly** 11:33:13
12 **been gaps there.** 11:33:16
13 Q. Okay. Those highly repetitive sequences 11:33:16
14 were difficult to map at the time of Campbell 11:33:20
15 because of some limitations in the sequencing 11:33:27
16 technology at the time? 11:33:29
17 **A. No, you could map to them. That's not the** 11:33:34
18 **problem. The problem is the -- you didn't know** 11:33:36
19 **which part of the repeat you were looking at. So** 11:33:46
20 **you didn't know if you were looking at the first** 11:33:48
21 **base or the 100th base or the 1,000th base or** 11:33:50
22 **100,000 base because they're all very, very similar** 11:33:55

1 **to one another.** 11:33:59
2 Q. Right. So in these highly repetitive 11:33:59
3 sequences, you have maybe the same sequence of bases 11:34:01
4 over and over and over and over and over again, 11:34:05
5 right? 11:34:08
6 **A. The same or nearly the same, yes.** 11:34:10
7 Q. And so if you get one of those sequences, 11:34:13
8 you don't know whether to map it to the first 11:34:17
9 instance, the second instance, the fifth instance, 11:34:19
10 the tenth instance of that sequence in this sort of 11:34:22
11 repetitive section of the genome, right? 11:34:25
12 **A. Broadly speaking, that's correct. I mean,** 11:34:28
13 **the mapping algorithms makes some assumptions about** 11:34:29
14 **this and have a process for doing it, so it's a** 11:34:34
15 **little -- and there's some logic to it that's** 11:34:38
16 **probably correct, but overall I would say your** 11:34:41
17 **assessment is accurate.** 11:34:44
18 Q. At the time of Campbell, at least, it was 11:34:47
19 still a difficult thing to do, that's why he says, 11:34:50
20 "that generated many mapping errors," right? 11:34:52
21 **A. I would say it's still a problem today.** 11:34:56
22 Q. Okay. In that sentence he mentions that 11:35:00

"repetitive DNA in these regions is often similar to 11:35:03
heterochromatic sequence in the reference genome 11:35:07
build." Do you see that? 11:35:11
A. **Yes.** 11:35:12
Q. Can you explain to me what the 11:35:13
heterochromatic sequence there means? 11:35:15
A. **Heterochromatin, the way they're using it,** 11:35:19
I believe, is probably talking about sequences near 11:35:22
the centromeres and potentially near the telomeres. 11:35:26
You see that in the following sentence. "These 11:35:33
sequences manifested as substantial increases in 11:35:35
copy number near centrometers and telometers." 11:35:35
So, sometimes you can have these repeats 11:35:39
that are long enough that they look unique-ish. 11:35:46
Right? It is not just A's all over, right, so that 11:35:49
you don't know what to do with it, but it's 11:35:52
something that looks like it could be a unique 11:35:54
sequence, but it's just repeated a lot. And 11:35:56
sometimes those sequences have moved in the human 11:35:59
genome from where they were -- from one place to 11:36:03
another in human evolution or even during the 11:36:08
development of this cell line. And so you could 11:36:11

1 **have movement of these sequences in genetic** 11:36:14
2 **evolution that make it -- you can map to them even** 11:36:20
3 **if they're not necessarily in the reference because** 11:36:26
4 **they're in the telomeres or in the centromeres and,** 11:36:30
5 **therefore, you can map to them uniquely.** 11:36:35
6 Q. Okay. So, going on, Campbell talks about 11:36:49
7 the centromeres and telomeres and then says that 11:36:53
8 they "excluded regions within one mega-base of a 11:36:56
9 telomeric or centromeric sequence gap from copy 11:37:02
10 number analysis or rearrangement screens." 11:37:07
11 Do you see that? 11:37:08
12 **A. Yes.** 11:37:10
13 Q. And he says that was about 1.2 million 11:37:10
14 reads, right? 11:37:13
15 **A. Yes.** 11:37:13
16 Q. Is that the same 1.2 million reads that 11:37:14
17 you're talking about elsewhere with the possible 11:37:18
18 rearrangements? 11:37:20
19 **A. I would have to do a very careful** 11:37:28
20 **analysis. If you would like me to do that, I can** 11:37:29
21 **read it very, very carefully.** 11:37:32
22 Q. I think the 1.2 million reads number comes 11:37:33

1 up quite a bit in your reply declaration, and I'm 11:37:36
2 just trying to understand if the 1.2 million number 11:37:39
3 is that -- if the 1.2 million reads that you are 11:37:42
4 referring to are the 1.2 million that Campbell is 11:37:46
5 talking about here when he's talking about telomeres 11:37:50
6 and centromeres. That's my question. 11:37:53
7 **A. That's a good question. Let me read and** 11:37:56
8 **then I can give you an answer.** 11:37:59
9 **(Document reviewed.)** 11:38:00
10 **I actually don't think so, and the reason** 11:38:12
11 **for that is that in the second sentence under** 11:38:14
12 **rearrangements, "most of these were presumably due** 11:38:20
13 **to incorrect mapping induced by sequencing errors,"** 11:38:23
14 **so if it was mapping to telomeric regions, they** 11:38:26
15 **wouldn't have written it that way.** 11:38:30
16 Q. Okay. Okay. That's helpful. Let's go 11:38:31
17 back. 11:38:34
18 We had 11.6 million reads that got past 11:38:34
19 Campbell's quality screen and PCR duplicate screen, 11:38:40
20 right? 11:38:46
21 **A. I'm not keeping track. If you would like** 11:38:46
22 **me to, I can.** 11:38:48

Q. So let's keep track. 11:38:50

A. Can I have a pen, please? 11:38:51

Q. Sure. Why don't we do this. I'll give 11:39:13
you a fresh piece of paper. 11:39:16

A. Okay. 11:39:17

Q. So just to go back to some of the numbers 11:39:22
that we started with. In the 2171 cell line, 11:39:25
Campbell got 36.2 million total paired-end reads, 11:39:30
right? 11:39:38

A. Yes. 11:39:38

Q. Let's make that our starting number. 11:39:40

And then Campbell applied a quality filter 11:39:54
with ends mapping back to the reference genome and 11:39:56
got that down to 18.8 million reads, right? 11:40:00

A. Yes. 11:40:03

Q. So 18.8 million reads get past Campbell's 11:40:05
quality screen, right? 11:40:09

A. Yes. 11:40:10

Q. All right. Then Campbell excluded another 11:40:14
7.2 million reads with his PCR duplicate screen, 11:40:18
right? 11:40:23

A. Yes. 11:40:25

1 Q. So that gets us down to 11.6 million reads 11:40:26
2 got past Campbell's quality screen and his duplicate 11:40:33
3 screen, right? 11:40:37
4 **A. Correct.** 11:40:39
5 Q. Then Campbell excluded an additional 1.2 11:40:43
6 million reads because they were within one mega-base 11:40:47
7 of a telomeric or a centromeric sequence gap, right? 11:40:51
8 **A. I believe that's correct.** 11:40:56
9 Q. Okay. So that gets us down to 10.4 11:40:59
10 million reads that get past Campbell's quality 11:41:02
11 screen, his duplicate screen, and his telomeric or 11:41:08
12 centromeric sequence gap screen, right? 11:41:12
13 **A. I think that's correct.** 11:41:17
14 Q. So from the original 36.2 million reads, 11:41:18
15 we are down to 10.4 million reads before we do 11:41:22
16 analysis to try to identify rearrangements in 11:41:27
17 Campbell. Right? 11:41:30
18 **A. I believe that's correct.** 11:41:31
19 Q. Again, for all these numbers, these are 11:41:42
20 just for the 2171 cell line, right? 11:41:45
21 **A. Correct.** 11:41:48
22 Q. Then in the rearrangement analysis, from 11:42:40

1 those 10.4 million reads in the 2171 cell line, 11:42:43
2 there were 1.2 million reads that you say suggest 11:42:51
3 chimeric sequences created by the sequencing 11:42:58
4 workflow, right? 11:43:02
5 **A. That is the sentence that is in Campbell,** 11:43:03
6 **yes.** 11:43:06
7 Q. Well, what Campbell says is a little 11:43:17
8 different, so I want to know in your interpretation, 11:43:19
9 when Campbell says under rearrangements refers to 11:43:22
10 1.2 million reads, your interpretation of Campbell 11:43:26
11 is that it is saying from its 10.4 million reads in 11:43:33
12 the 2171 cell line, there were 1.2 million that you 11:43:36
13 say suggest chimeric sequences created by the 11:43:42
14 sequencing workflow, right? 11:43:46
15 **A. I think I would fall back to exactly what** 11:43:50
16 **is written there, which is that 1.2 million reads** 11:43:52
17 **from NCI-H2171 suggested that -- had mapping of the** 11:43:55
18 **two ends of the genome suggested a possible** 11:44:04
19 **rearrangement. And I think chimera and** 11:44:07
20 **rearrangement in this context are close to** 11:44:09
21 **equivalent statements. So, yes, I am comfortable** 11:44:11
22 **with that. So suggesting a possible chimera.** 11:44:14

1 Q. And you say those are chimeras that were 11:44:26
2 created during the sequencing workflow, right? 11:44:28
3 **A. Can you point me to text in the -- in my** 11:44:36
4 **reply declaration?** 11:44:38
5 Q. I'm asking for your interpretation of the 11:44:40
6 paper. 11:44:42
7 **A. Reading this, I would interpret that** 11:44:49
8 **sentence to mean that these -- the 1.2 million reads** 11:44:52
9 **are sequences generated from a sequencing workflow,** 11:45:03
10 **and some of those started before -- some of those** 11:45:08
11 **were real things that happened prior to the** 11:45:18
12 **sequencing workflow and some of those things** 11:45:21
13 **happened in the sequencing workflow. Those things** 11:45:24
14 **that happened before the sequencing workflow** 11:45:27
15 **presumably would be real, the things they are** 11:45:30
16 **actually looking for. And everything after that** 11:45:34
17 **happened in the sequencing workflow from the point** 11:45:35
18 **of constructing a library, putting it on the** 11:45:38
19 **sequencer and sequencing it and infomatically** 11:45:41
20 **analyzing it.** 11:45:45
21 Q. Okay. So in Campbell, of the 1.2 million 11:45:46
22 reads that you say are possible chimeras, how many 11:45:48

of those are -- would a person of ordinary skill 11:45:54
understand were what you say are true chimeras 11:45:57
versus chimeras that were created by the sequencing 11:46:01
workflow? 11:46:03
A. Campbell is silent on that. 11:46:04
Q. Do you have an understanding? 11:46:06
A. So Campbell tries to validate this but 11:46:10
cannot possibly evaluate 1.2 million. I think that 11:46:15
if they thought that most of them, they were real, 11:46:19
they would not have engaged in any further 11:46:25
assessment. They would have just directly tested 11:46:27
them. So I think they felt that they were not real 11:46:30
and were some artifact of the sequencing, given that 11:46:35
they go through an entire process to whittle this 11:46:38
down to a possible set. So, no, I don't think a 11:46:42
POSA would read this and think that there were 1.2 11:46:46
million real rearrangements. I think they would 11:46:49
read this and think there were a small number of 11:46:51
real rearrangements in a background of high noise. 11:46:54
Q. Is it your opinion that a person of 11:47:00
ordinary skill would understand that the great 11:47:01
majority of those 1.2 million possible chimeras were 11:47:04

artifacts created by the sequencing? 11:47:08

A. I think that is correct, yes. 11:47:11

Q. Okay. And I won't make you do this live, 11:47:23
but we said 10.4 million reads were used for the 11:47:25
rearrangement analysis. These 1.2 million reads are 11:47:29
about 11.5 percent of those reads that got past all 11:47:33
the screens and were used for rearrangement 11:47:38
analysis. Does that sounds about right, one out of 11:47:40
ten? 11:47:43

**A. 1.2 is about one tenth of 10.4, yes, 11:47:44
that's about right.** 11:47:47

Q. So it's your opinion that someone of 11:47:49
ordinary skill reading Campbell would understand 11:47:52
that more than 10 percent of the chimeric sequences 11:47:55
that got past all of its quality filtering were 11:48:02
actually false artifacts made up by the Illumina 11:48:06
machine? 11:48:09

**A. The sequencing workflow includes 11:48:12
everything from the creation of the library through 11:48:14
the sequencer to the analysis. And in this 11:48:18
particular case, I think that a POSA would 11:48:23
understand that this is a very hard problem with** 11:48:28

1 **this technology and that this is a challenging thing** 11:48:30
2 **to do.** 11:48:37
3 Q. And that even with quality screens and 11:48:38
4 duplicate screens, one out of ten of your reads are 11:48:40
5 going to be false chimeras that are made up by the 11:48:45
6 machine? 11:48:48
7 **A. Partly this is because of the quite short** 11:48:49
8 **sequence lengths in this paper, but quite frankly,** 11:48:51
9 **yes, when we do this, it is a very hard technical** 11:48:56
10 **problem, even when we do it today with sequences** 11:49:00
11 **that are not 36 base pairs in length but are 20,000** 11:49:03
12 **base pairs in length. I have a graduate student** 11:49:07
13 **whose whole thesis is on that topic of using 20 kb** 11:49:11
14 **fragments to do rearrangement detection. It's a** 11:49:15
15 **really hard problem.** 11:49:19
16 Q. And we talked about this before, but from 11:49:20
17 your work in this case, you're not aware of anything 11:49:22
18 from Illumina in 2008 saying, hey, when you use our 11:49:24
19 machines, one in ten of your sequence reads might be 11:49:29
20 false artifacts made up by chimeras that the machine 11:49:32
21 created. You're not aware of anything like that, 11:49:35
22 right? 11:49:40

A. I think you're speaking a little too abstractly. There's a couple things that are relevant here. Number one -- 11:49:40 11:49:42 11:49:45

Q. I just want an answer to my question so let me ask it directly. 11:49:48 11:49:50

Are you aware of anything from 2008 where Illumina was telling people one in ten of the sequence reads that you get from our machine might be a chimera that was made up by the sequencing machine, a false artifact? 11:49:51 11:49:54 11:49:58 11:50:00 11:50:04

Are you aware of anything like that? 11:50:07

MR. RAICH: I'm going to object. Incomplete hypothetical. 11:50:10 11:50:11

A. I think you're being overly prescriptive on how a POSA would read this sentence that this is a very hard problem technically for lots of reasons, and, one, a person of ordinary skill in the art should be deeply aware that when doing this sort of work, one can have incredible challenges finding accurate sequences that are true sequences. And you will see that tons of processes were put in place, both heuristic methods and screens, and just tons of 11:50:12 11:50:17 11:50:23 11:50:29 11:50:33 11:50:36 11:50:40 11:50:47 11:50:50

1 **secondary confirmation because this is a very hard** 11:50:57
2 **problem.** 11:51:00
3 Q. And in your reply declaration, all the 11:51:01
4 materials you considered, all the materials you 11:51:04
5 cited, you haven't shown a single document where 11:51:06
6 Illumina prior to December 2010 said, hey, our 11:51:11
7 machines might cause false chimeric sequence 11:51:17
8 artifacts? You don't have any documents like that, 11:51:24
9 right? 11:51:26
10 **A. I don't believe I cited to any, no. But I** 11:51:27
11 **think that Campbell and Stratton are one of the** 11:51:29
12 **global world-class sequencing centers in the world.** 11:51:31
13 **Like people look to these folks for the -- you know,** 11:51:34
14 **between them, the Broad and WashU at the time, this** 11:51:37
15 **is one of the premier sequencing groups in the** 11:51:43
16 **entire world, one of the few that could actually do** 11:51:46
17 **this work.** 11:51:48
18 Q. And you say that it was one of the premier 11:51:48
19 sequencing groups in the world put this paper out in 11:51:51
20 June of 2008, right? 11:51:54
21 **A. Yes.** 11:51:55
22 Q. And from June 2008 to December 2010, you 11:51:57

1 don't have a single document where Illumina tells 11:52:01
2 anyone that their sequencers might cause false 11:52:06
3 chimeric sequence artifacts, right? 11:52:11
4 **A. I don't see the relevance.** 11:52:13
5 Q. I'm just asking if you have any document 11:52:15
6 like that. 11:52:16
7 So, here is my question. From June 2008 11:52:17
8 when Campbell published to December 2010, you don't 11:52:19
9 have a single document where Illumina tells anyone 11:52:24
10 that their sequencers might create false chimeric 11:52:29
11 sequence artifacts. That's true, right? 11:52:33
12 **A. Yes.** 11:52:35
13 Q. Okay. Do you know the difference between 11:52:48
14 the 2171 cell line and the 1770 cell line that was 11:52:50
15 used in the Campbell paper? 11:52:57
16 **A. I would have to look it up if you want me** 11:53:00
17 **to read about them.** 11:53:03
18 Q. Do you understand -- are you aware of any 11:53:05
19 differences between them? 11:53:08
20 **A. 2171 is a small cell lung cancer. H1770** 11:53:12
21 **is a neuroendocrine cell -- lung cell cancer line.** 11:53:16
22 **I'm sure there are more differences between them** 11:53:21

1 **than that.** 11:53:23
2 Q. When you said Campbell was one of the 11:53:56
3 premier sequencing groups in the world, were you 11:53:58
4 referring to these authors specifically or to the 11:54:01
5 Wellcome Trust Sanger Institute? 11:54:05
6 **A. Both.** 11:54:08
7 MR. RAICH: Counsel, it's been a 11:55:16
8 little over an hour. 11:55:17
9 MR. MATTY: We can take a break. 11:55:19
10 VIDEO TECHNICIAN: The time is 11:55 11:55:21
11 a.m. This ends Unit 2. We are off the record. 11:55:23
12 (A brief recess was taken.) 11:55:27
13 VIDEO TECHNICIAN: The time is 12:11 12:11:11
14 p.m. This begins Unit number 3. On the record. 12:11:13
15 BY MR. MATTY: 12:11:16
16 Q. Okay. We were talking about Campbell and 12:11:17
17 a few of the numbers that he discusses for 12:11:23
18 sequencing reads from the 2171 cell line that he 12:11:26
19 studied. Right? 12:11:31
20 **A. Yes.** 12:11:34
21 Q. And the 1.2 million reads that suggested a 12:11:34
22 possible rearrangement, those 1.2 million reads came 12:11:39

from a single sample of the 2171 cell line, right? 12:11:43

A. Probably. We don't -- I would have to read the methods. It's very likely, yes. 12:11:49 12:11:51

(Exhibit 1004 was previously marked and referred to.) 12:11:54 12:11:54

Q. Okay. I'll hand you Exhibit 1004, which is the Parameswaran reference. 12:11:54 12:12:16

A. Yes. 12:12:19

Q. Now, in some of your analysis, you've looked at the supplemental methods and data at the back of the Parameswaran reference, right? 12:12:46 12:12:47 12:12:52

A. Yes. 12:12:54

Q. And that includes the supplementary methods that Parameswaran describes at page 11 of the exhibit, right? 12:12:57 12:13:03 12:13:07

A. Yes. 12:13:08

Q. And you've reviewed some of the supplementary tables of data that Parameswaran shows at the back starting at page 20 of the exhibit, right? 12:13:10 12:13:13 12:13:17 12:13:20

A. Yes. 12:13:20

Q. Let's look at page 29 of Parameswaran. 12:14:05

1 You see there there's supplementary Table 5D. 12:14:09
2 **A. Yes.** 12:14:19
3 Q. And up at the top it says, this is data 12:14:20
4 where they analyzed their barcode, which was 10 12:14:22
5 nucleotide plus the cloning linker, which is 3 12:14:26
6 nucleotides, right? 12:14:31
7 **A. Yes.** 12:14:32
8 Q. And you understand that 10 plus 3 is the 12:14:32
9 search motif that Parameswaran decided to use for -- 12:14:35
10 ultimately use for its analysis of its data, right? 12:14:38
11 **A. I believe that's correct, yes.** 12:14:42
12 Q. Keep a pen in Table 5D. I want to look at 12:15:31
13 some of the discussion on page 8 of Parameswaran. 12:15:36
14 It's the last page of the main text before the 12:15:39
15 supplements. 12:15:42
16 **A. Yes, page 8.** 12:15:47
17 Q. On the left side, you see there's a 12:15:51
18 sentence towards the bottom of that first paragraph 12:15:57
19 that talks about run I, 0.13 percent and run II, 12:16:02
20 0.17 percent. Do you see that? 12:16:08
21 **A. Yes.** 12:16:10
22 Q. It says, "Run I, (0.13 percent) and run 12:16:10

1 II, (.17 percent) of sequences had no perfect 12:16:16
2 matches to any of the sequence motifs (forward or 12:16:23
3 reverse) and were discarded." 12:16:28
4 Do you see that? 12:16:30
5 **A. I do.** 12:16:31
6 Q. Going back to Table 5D, can you show me, 12:16:32
7 are there any cells or columns or rows in that table 12:16:38
8 that correspond to the sequences that had no perfect 12:16:43
9 matches to any of the sequence motifs? 12:16:46
10 **A. I don't believe there are.** 12:16:53
11 Q. Do you see the bottom row in Table 5D, it 12:17:03
12 says, "no match"? 12:17:08
13 **A. Yes.** 12:17:10
14 Q. And do you see the last column on the 12:17:10
15 right in Table 5D says, "no match"? 12:17:12
16 **A. Yes.** 12:17:15
17 Q. What's your understanding of what that 12:17:16
18 bottom row and far right column, what those reflect? 12:17:19
19 **A. My understanding is that the values in** 12:17:24
20 **each cell are the number of reads that contained a** 12:17:28
21 **barcode. And so if one looks at the last row, the** 12:17:34
22 **no match row there in the first column, there were** 12:17:39

1 **26 reads that contained the barcode 454-66 and no** 12:17:44
2 **match to any barcode on the other barcode.** 12:17:50
3 Q. Okay. And down at the bottom right corner 12:17:56
4 where that column -- the last row and the last 12:18:01
5 column intersect, there's a box that's empty, right? 12:18:07
6 **A. Yes.** 12:18:10
7 Q. And so if we think back to page 8, when it 12:18:12
8 talks about sequences that had no perfect matches to 12:18:17
9 any of the sequence motifs, in Table 5D, those 12:18:21
10 sequences would be represented by that box way down 12:18:30
11 in the bottom right corner, which is empty, right? 12:18:33
12 **A. I think that's correct, yes.** 12:18:36
13 Q. In the bottom right corner, there's four 12:18:40
14 boxes that are empty, right? 12:18:42
15 **A. Correct.** 12:18:43
16 Q. What's your understanding of what the -- 12:18:48
17 I'm focusing just on those four boxes down in the 12:18:51
18 bottom right corner. Do you have that in mind? 12:18:54
19 **A. Yes.** 12:18:57
20 Q. I'll start with the top left one, which is 12:18:57
21 a row that says "close," a column that says "close." 12:19:01
22 That box is empty, but do you have an understanding 12:19:05

of what type of sequences would fall into that box 12:19:08
if there was to be a number put to it? 12:19:11
A. It would be sequences in which the 12:19:15
barcodes attached to that sequence were close to one 12:19:19
of the row column box -- IDs and column IDs, but not 12:19:24
-- not either of them exactly. 12:19:33
Q. So both barcodes would be close but not a 12:19:35
perfect match to any of the sequence motifs, right? 12:19:41
A. That is my interpretation, yes. 12:19:45
Q. Okay. Going back to Table 5D, those four 12:19:47
empty boxes in the corner, the one that's in the top 12:19:52
right of those four, which is the row says "close," 12:19:56
the column says "no match," what types of sequences 12:20:00
would that represent? 12:20:05
A. The top right would be ones in which the 12:20:06
-- let me think about this. One of the sequences 12:20:12
doesn't match and the other one is close, and I'll 12:20:15
have to think about logically which one. Do you 12:20:18
mind if I figure out whether or not its row and 12:20:21
column? 12:20:24
Q. No, I think that is close enough. 12:20:25
So the top right of those boxes is one 12:20:26

1 sequence is close but not a perfect match. The 12:20:28
2 other sequence is not a perfect match and not even 12:20:30
3 close. 12:20:33
4 **A. Correct.** 12:20:34
5 Q. Okay. Now, the same is true looking back 12:20:35
6 at those four for the bottom left box. That 12:20:37
7 represents one sequence is close but not a perfect 12:20:40
8 match; the other sequence is not a perfect match, 12:20:44
9 not even close, right? 12:20:47
10 **A. Correct.** 12:20:49
11 Q. And then the bottom right, the one all the 12:20:49
12 way in the corner, that box as we said is both 12:20:51
13 barcodes don't match and they're not even close to 12:20:56
14 any sequence, right? 12:20:58
15 **A. Correct.** 12:21:00
16 Q. And those four boxes are the only boxes in 12:21:00
17 the entire chart that don't have a number in them, 12:21:04
18 right? 12:21:06
19 **A. That's correct, yes.** 12:21:08
20 Q. Let's go to page 1 of Parameswaran. 12:22:12
21 **A. Page 1, yes.** 12:22:18
22 Q. I'm sorry, I had the wrong quote. Back to 12:22:47

page 8 is where I want to be. 12:22:50

A. Page 8, yes. 12:22:57

Q. So a little bit above the run I and run II 12:22:59
sentence that we looked at before, there's a 12:23:01
sentence that starts with "The low false discovery 12:23:04
rate." Do you see that? 12:23:08

A. Yes. 12:23:09

Q. And it says, "The low false discovery rate 12:23:10
for perfect matches strengthens the argument that 12:23:13
any sequence with both 5' and 3' barcode motifs will 12:23:17
be placed with reasonable accuracy into the correct 12:23:23
bin." Do you see that? 12:23:27

A. I do. 12:23:28

Q. Do you have an understanding of what 12:23:29
Parameswaran means by reasonable accuracy? 12:23:31

**A. When one is performing experiments, one is 12:23:36
-- often has some sensitivity that you're trying to 12:23:44
deal with, and sometimes that sensitivity is 12:23:48
extremely low. You just want a ballpark 12:23:51
measurement. And sometimes that sensitivity is 12:23:54
outrageously high. You're measuring something to 20 12:23:57
decimal places. And so reasonable accuracy is 12:24:01**

1 **effectively an experimental criteria for the** 12:24:07
2 **experiment that's being done. If you wanted to** 12:24:10
3 **measure something at one part in a million, your** 12:24:14
4 **accuracy is one part in 10,000, that's not going to** 12:24:16
5 **work. If you want to measure something at one part** 12:24:18
6 **in 10 and your accuracy is at one part in 10,000,** 12:24:20
7 **you are in great shape.** 12:24:24
8 Q. And what constitutes reasonable accuracy 12:24:25
9 for a particular experiment depends on that 12:24:28
10 experiment, its methods, its purpose, right? 12:24:31
11 **A. Absolutely.** 12:24:34
12 Q. Okay. Let's go back to Table 5D on page 12:24:50
13 29. 12:24:54
14 **A. Table 5D. I'm sorry, I was looking at** 12:24:56
15 **page -- I was looking at F. My apologies. 5D.** 12:24:59
16 Q. D as in David. 12:25:05
17 **A. Yes, 5D.** 12:25:06
18 Q. And you see in Table 5D certain cells that 12:25:44
19 are shaded grey, right? 12:25:55
20 **A. Yes.** 12:25:57
21 Q. Now, in your review of Parameswaran, you 12:25:58
22 didn't see any explanation from Parameswaran stating 12:26:03

1 why those cells were greyed out, right? 12:26:08
2 **A. I don't think they're greyed out. I think** 12:26:12
3 **they're grey.** 12:26:14
4 Q. Okay. So that's fine. 12:26:15
5 In your review of Parameswaran, you didn't 12:26:17
6 see any explanation from Parameswaran stating why 12:26:20
7 those cells were grey, right? 12:26:24
8 **A. As a practitioner of the art looking at** 12:26:27
9 **this table, I think the reason for it is obvious.** 12:26:29
10 Q. And you're saying that you understand that 12:26:45
11 as a practitioner of the art looking at this table 12:26:47
12 because Parameswaran itself doesn't say, right? 12:26:51
13 **A. Parameswaran doesn't need to say all of** 12:27:00
14 **the things that a practitioner of the art would** 12:27:02
15 **understand. In this particular case, if a** 12:27:05
16 **practitioner of the art looks at this table, it is** 12:27:08
17 **immediately obvious that they have shaded the cells** 12:27:11
18 **in this table that are not the diagonal cells and** 12:27:16
19 **are not the close/don't match column rows but are in** 12:27:20
20 **the rest of the table and are off-diagonal and are** 12:27:26
21 **non-zero. They are explicitly drawing the reader's** 12:27:29
22 **attention to the values in this table that are not** 12:27:33

1 **zero. That is their clear intent.** 12:27:35
2 Q. Right. 12:27:40
3 For the four boxes in the bottom right 12:27:41
4 that we talked about, Parameswaran explicitly 12:27:45
5 mentions those sequence combinations and says they 12:27:49
6 were discarded, right? 12:27:53
7 **A. Correct.** 12:27:54
8 Q. In the text of Parameswaran, in its text 12:27:56
9 it never mentions the grey boxes. Can you agree 12:28:01
10 with that? 12:28:04
11 **A. I could carefully read it if you would** 12:28:05
12 **like me to.** 12:28:07
13 Q. You've studied it for months now. Are you 12:28:10
14 aware of any discussion in Parameswaran talking 12:28:11
15 about its grey boxes? You can review it if you need 12:28:15
16 to. 12:28:19
17 **A. I think you perhaps misunderstand how** 12:28:19
18 **experts read papers. If you think I studied this** 12:28:23
19 **paper for months, just to be clear, I've -- in my** 12:28:26
20 **opinion, as a practitioner of the art looking at** 12:28:29
21 **this table, it is immediately obvious what this** 12:28:34
22 **table means, so I -- I wouldn't necessarily go back** 12:28:37

1 **and ask the paper to tell me because I immediately** 12:28:41
2 **understood.** 12:28:44
3 Q. We know exactly why the four boxes in the 12:28:45
4 bottom right are empty, because Parameswaran tells 12:28:47
5 us, right? 12:28:51
6 **A. We can track that back, yes.** 12:28:54
7 Q. Okay. And there is no discussion in 12:28:58
8 Parameswaran, in the paper, in the text of the 12:28:59
9 reference, there is no discussion talking about grey 12:29:02
10 boxes, right? 12:29:06
11 **A. I think you are misreading this paper as** 12:29:08
12 **--** 12:29:11
13 Q. Can you show me where it talks about grey 12:29:12
14 boxes? 12:29:14
15 **A. I will point you to the abstract, the very** 12:29:15
16 **last sentence, "The false discovery rate as measured** 12:29:17
17 **by the percentage of sequences with unexpected** 12:29:19
18 **perfect pairings on unmatched forward/reverse** 12:29:22
19 **barcodes was estimated to be less than 0.005** 12:29:25
20 **percent." That is exactly the grey cells in this** 12:29:30
21 **table. Supplementary tables are often not detailed** 12:29:32
22 **in the same way as the primary figures. This is** 12:29:35

1 **just the standard in the field. You're just wrong.** 12:29:41
2 Q. That sentence that you read to me doesn't 12:29:49
3 talk about table -- any of the supplemental tables, 12:29:52
4 right? 12:29:55
5 **A. I think you'll notice that in the** 12:29:55
6 **abstract, none of the abstract refers to any actual** 12:29:57
7 **data. You are reading the paper wrong.** 12:30:00
8 Q. The sentence we looked at on page 8 that 12:30:16
9 says "sequences that had no perfect matches to any 12:30:18
10 of the sequence motifs (forward or reverse) were 12:30:23
11 discarded," do you remember that sentence? 12:30:27
12 **A. Can you help me find it again?** 12:30:42
13 Q. Yes, just to make sure we're on the same 12:30:44
14 page. You are on page 8, right? 12:30:46
15 **A. Page 8.** 12:30:48
16 Q. The paragraph says -- let me start that 12:30:50
17 over. 12:30:54
18 In Parameswaran's texts, it says, 12:30:54
19 "Sequences that had no perfect matches to any of the 12:30:58
20 sequence motifs (forward or reverse) were 12:31:04
21 discarded," right? 12:31:06
22 **A. Yes.** 12:31:08

1 Q. These sequences that had no perfect 12:31:10
2 matches to any of the sequence motifs, those are not 12:31:13
3 the grey boxes, right? 12:31:16
4 **A. Correct.** 12:31:18
5 Q. Could you go to page 2 of Parameswaran? 12:34:19
6 **A. Page 2, yes.** 12:34:28
7 Q. In the bottom right do you see there it 12:34:35
8 has -- Parameswaran has its blueprint for barcodes? 12:34:37
9 **A. Yes.** 12:34:41
10 Q. And it uses letters H through O for its 12:34:44
11 barcode formats? 12:34:49
12 **A. Yes.** 12:34:55
13 Q. Do you see that? 12:34:55
14 And it says that those letters, at least 12:34:58
15 the quartets, H to K and L to O, each independently 12:35:01
16 map to the four nucleotides H, C, T and G, right? 12:35:07
17 **A. Correct.** 12:35:12
18 Q. And the forward and reverse barcode format 12:35:13
19 that's in that section blueprint for barcodes you 12:35:16
20 understand was used to design all of the barcodes 12:35:20
21 that Parameswaran used in their study, right? 12:35:24
22 **A. That is my understanding.** 12:35:26

1 Q. And the -- in the format for the forward, 12:35:30
2 the letter J is repeated, the letter L is repeated. 12:35:35
3 Right? 12:35:38
4 **A. Correct.** 12:35:38
5 Q. In the reverse format, the letter K is 12:35:39
6 repeated and the letter M is repeated, right? 12:35:43
7 **A. Correct.** 12:35:45
8 Q. You understand that each forward barcode 12:35:46
9 in Parameswaran was designed to repeat whichever 12:35:49
10 nucleotide corresponded to J, right? 12:35:54
11 **A. Yes.** 12:35:57
12 Q. And you understand that each forward 12:35:58
13 barcode in Parameswaran was designed to repeat 12:36:01
14 whichever nucleotide corresponded to L, right? 12:36:04
15 **A. That is correct.** 12:36:08
16 Q. You understand that each reverse barcode 12:36:09
17 in Parameswaran was designed to repeat whichever 12:36:11
18 nucleotide corresponds to K, right? 12:36:16
19 **A. Correct.** 12:36:18
20 Q. You understand that each reverse barcode 12:36:19
21 in Parameswaran was designed to repeat whichever 12:36:21
22 nucleotide corresponds to M, right? 12:36:26

1 **A. Correct.** 12:36:28
2 Q. Then you saw in Table 2 it has a list -- 12:36:48
3 I'm sorry, this is on page 5. In Table 2 of 12:36:53
4 Parameswaran, it has a list of all the barcodes that 12:36:57
5 it used following its design, right? 12:37:01
6 **A. Correct.** 12:37:03
7 Q. And each of the barcodes Parameswaran 12:37:05
8 designed in Table 2 includes two instances of a 12:37:07
9 repeated nucleotide consistent with the blueprint 12:37:12
10 that we just looked at, right? 12:37:15
11 **A. Correct.** 12:37:16
12 Q. In your review of Parameswaran, did you 12:38:57
13 study the description of how its Barsort program 12:38:59
14 works? 12:39:06
15 **A. I'm sure I read it. I'm not sure I could** 12:39:08
16 **give you an accurate summary without looking at it.** 12:39:11
17 Q. If you go to page 11, that's where it 12:39:17
18 starts. 12:39:21
19 **A. Yes.** 12:39:26
20 Q. And do you see there it says the Barsort 12:39:35
21 takes two input files? Do you see that? 12:39:38
22 **A. Yes.** 12:39:41

1 Q. And the two input files are a list of 12:39:42
2 experiments with their specific 5' and 3' search 12:39:44
3 motifs and then the set of raw reads from the 12:39:49
4 sequencer given in FASTA format. Do you see that? 12:39:52
5 **A. I do.** 12:39:55
6 Q. Are you familiar with what FASTA format 12:39:55
7 is? 12:39:58
8 **A. Yes.** 12:39:58
9 Q. What is that? 12:39:59
10 **A. FASTA format is an unusually compressed** 12:39:59
11 **format that contains sequences that's a standard** 12:40:06
12 **sequence structure. It's got specific** 12:40:10
13 **characteristics to it. I don't think I could give** 12:40:12
14 **you the format of the FASTA, but I could tell you --** 12:40:14
15 **I could probably accurately tell if you something** 12:40:17
16 **wasn't FASTA.** 12:40:20
17 Q. And then in the sentence spanning page 11 12:40:25
18 and 12 it says, "The program assigns each sequence 12:40:27
19 to an experiment based on whether it contains an 12:40:30
20 exact match to the 5' and/or 3' motifs." 12:40:34
21 Do you see that? 12:40:38
22 **A. Yes.** 12:40:39

1 Q. And then it says, "Sequences that contain 12:40:39
2 both 5' and 3' motifs are given first priority." Do 12:40:42
3 you see that? 12:40:46
4 **A. Yes.** 12:40:46
5 Q. Do you have an understanding of what that 12:40:47
6 means, first priority? And if you need to read the 12:40:48
7 full description, go ahead. 12:40:52
8 **A. (Document review.)** 12:40:59
9 **It's a little unclear what it means** 12:41:07
10 **exactly. The way I would read it -- actually, I** 12:41:11
11 **don't know what first priority means, to be honest.** 12:41:27
12 Q. Okay. 12:41:31
13 **A. And how it would distinguish from followed** 12:41:32
14 **by sequencing, containing the 5' or the 3' motif.** 12:41:35
15 Q. Okay. It goes on to say that sequences 12:41:44
16 that do not contain perfect matches to any motifs 12:41:46
17 are put into an unassigned bin for further analysis. 12:41:49
18 Do you see that? 12:41:52
19 **A. Yes.** 12:41:53
20 Q. That sentence that refers to those 12:41:54
21 sequences that do not contain perfect matches to any 12:41:57
22 motifs, those are the discarded sequences that 12:42:00

1 correspond to the four boxes on the bottom right of 12:42:04
2 the supplementary data charts, right? 12:42:07
3 **A. I believe that's consistent with what's** 12:42:09
4 **written here, yes.** 12:42:12
5 Q. Okay. And those are put into an 12:42:13
6 unassigned bin, right? 12:42:14
7 **A. I believe that's correct, yes.** 12:42:18
8 Q. And it says, "Unassigned". That means 12:42:20
9 it's not assigned to any sample in the experiment, 12:42:22
10 right? 12:42:26
11 **A. I believe that's correct, yes.** 12:42:27
12 Q. Okay. Then in the few sentences that 12:42:43
13 follow, it talks about a raw bin and a trimmed bin. 12:42:45
14 You could take some time to read it and orient 12:42:52
15 yourself. I'm wondering if you have an 12:42:55
16 understanding of what the raw bin and the trimmed 12:42:57
17 bin are. 12:42:59
18 **A. It's certainly not practicable today, but** 12:43:04
19 **at the time it was quite common to process data and** 12:43:07
20 **keep it in this format because they were of moderate** 12:43:12
21 **size and they -- I think that interpretation is that** 12:43:16
22 **if it had a valid motif, it went into a raw bin and** 12:43:23

1 **kept the information attached to it. And then they** 12:43:29
2 **also trimmed it off and put it into this is our** 12:43:33
3 **analysis bucket.** 12:43:38
4 Q. And what they're trimming off is the 12:43:39
5 motifs, right? 12:43:43
6 **A. In the trim bin, yes.** 12:43:44
7 Q. Okay. So at the end of the Barsort 12:43:46
8 program, we have three bins, right? 12:43:49
9 **A. Yes.** 12:43:52
10 Q. There's the unassigned bin, and that 12:43:53
11 unassigned bin includes all the sequences that do 12:43:58
12 not contain perfect matches to any motifs, right? 12:44:02
13 **A. I believe that's correct, yes.** 12:44:07
14 Q. The rest of the sequences are put into the 12:44:08
15 raw bin first, right? 12:44:10
16 **A. Whether or not it happens first or in** 12:44:17
17 **parallel, it's unclear.** 12:44:19
18 Q. Okay. So the unassigned bin contains all 12:44:21
19 sequences that don't have any perfect match to any 12:44:24
20 motif, right? 12:44:27
21 **A. We agree with that, yes.** 12:44:28
22 Q. The rest of the sequences go in the raw 12:44:29

1 bin, right? 12:44:32
2 **A. Yes.** 12:44:35
3 Q. And then all the sequences that are in the 12:44:36
4 raw bin have their barcode motifs stripped and 12:44:39
5 they're placed into the trimmed bin, right? 12:44:43
6 **A. So we are making a little bit -- there are** 12:44:46
7 **more than three bins here. There's the unassigned** 12:44:49
8 **bin. There's a raw bin for each experiment. So if** 12:44:53
9 **there were 20 experiments, there would be 20 raw** 12:44:58
10 **bins. And there's a trim bin for each experiment,** 12:45:03
11 **so there would be 20 trim bins.** 12:45:08
12 Q. Okay. That's helpful. So the unassigned 12:45:10
13 bin contains all sequences that don't have any 12:45:16
14 perfect match to any motif. We talked about that, 12:45:20
15 right? 12:45:23
16 **A. Yes.** 12:45:24
17 Q. The rest of the sequences go into one or 12:45:24
18 more raw bins, depending on how many experiments, 12:45:27
19 right? 12:45:31
20 **A. Yes.** 12:45:32
21 Q. And then all the sequences that are in the 12:45:33
22 one or more raw bins have their motifs stripped and 12:45:35

they're placed into one or more trimmed bins, right? 12:45:39

A. Correct. 12:45:42

MR. MATTY: All right. I'm going to 12:46:13

switch gears. Why don't we take a break for lunch. 12:46:14

VIDEO TECHNICIAN: The time is 12:46 12:46:17

p.m. This ends Unit 3. We are off the record. 12:46:19

(A lunch recess was taken.) 12:46:25

VIDEO TECHNICIAN: The time is 1:33 13:33:29

p.m. This begins Unit number 4. We are on the 13:33:31

record. 13:33:33

(Exhibit 1061 was previously marked 13:33:34

and referred to.) 13:33:34

BY MR. MATTY: 13:33:35

Q. I'll hand you Exhibit 1061. Do you have 13:33:55

that in front of you? 13:33:59

A. Yes. 13:34:00

Q. And this is an exhibit that you reviewed 13:34:00

in preparing your reply declaration, right? 13:34:02

A. Yes. 13:34:05

Q. Were you familiar with this exhibit before 13:34:08

you were working on your reply declaration or was 13:34:09

this one new to you? 13:34:11

1 **A. I'm nearly certain I was familiar with** 13:34:13
2 **this one. We had a long-term collaboration -- I may** 13:34:15
3 **have already said this -- with Mr. Xian Chen from** 13:34:20
4 **Stand Up to Cancer and Dr. Catherine Grasso was a --** 13:34:21
5 **in my laboratory for a couple years, working on** 13:34:27
6 **projects like this. I have known Dr. Schroth for a** 13:34:33
7 **long time, and I am moderately aware of Dr. Chris** 13:34:37
8 **Maher. So, I know this group well.** 13:34:41
9 Q. Okay. When you were preparing your 13:34:44
10 opening declaration in this case, did you review or 13:34:46
11 consider Exhibit 1061? 13:34:48
12 **A. Beyond my knowledge of the field and that** 13:34:53
13 **this is -- you know, this is the kind of document** 13:34:55
14 **that informed my opinion of the field, no.** 13:34:57
15 Q. I want to go to the supporting information 13:35:33
16 section of the Maher paper at page 8, if you could 13:35:37
17 go there, please. 13:35:43
18 **A. Page 8.** 13:35:48
19 Q. Yes. 13:35:50
20 Do you see on the right-hand side there's 13:36:00
21 a section labeled, "Establishment of mate-pair 13:36:03
22 filtering steps"? 13:36:08

1 **A. Yes.** 13:36:10
2 Q. Do you have an understanding of what the 13:36:11
3 mate-pair filtering in the Maher paper was? 13:36:12
4 **A. Mate pair is another term for pair density** 13:36:15
5 **sequency. So if you have two reads from the same** 13:36:17
6 **cluster on an Illumina instrument, those are often** 13:36:17
7 **called mate pairs.** 13:36:22
8 Q. Do you see in the bottom right towards the 13:36:30
9 end, there's a sentence that starts, "Next, we 13:36:31
10 observed"? 13:36:34
11 **A. Yes.** 13:36:37
12 Q. It says, "We observed that some candidates 13:36:37
13 had identical mate-pair reads that were in close 13:36:39
14 proximity of the flow-cell." Do you see that? 13:36:42
15 **A. I do.** 13:36:45
16 Q. What are identical mate-pair reads as it's 13:36:46
17 used in that sentence? 13:36:49
18 **A. Identical mate-pair reads could be a lot** 13:36:52
19 **of things. They are also referred to in the -- we** 13:36:54
20 **talked about them in the Campbell reference as** 13:36:58
21 **well -- places where the read started and ended in** 13:37:00
22 **the same place on the genome or have identical** 13:37:05

1 **sequences. Usually they are not found directly.** 13:37:13
2 **It's -- it is very uncommon, if not unheard of, to** 13:37:16
3 **take the reads that you've generated and compare** 13:37:24
4 **them to all the other reads you've generated. Some** 13:37:30
5 **people do it in specific examples, but almost** 13:37:32
6 **everyone first takes the reads they generated and** 13:37:35
7 **map them to the genome and then determines where** 13:37:39
8 **they map in the genome, and then ask do we see that** 13:37:42
9 **somewhere else. So in Campbell, we saw this same** 13:37:47
10 **thing, identical mate-pair reads.** 13:37:50
11 **Here they are seeing them, I believe, on** 13:37:53
12 **the same -- in the same -- often in physical** 13:37:55
13 **proximity. There -- in Campbell, they just rejected** 13:38:01
14 **them outright. Here they are doing something a** 13:38:04
15 **little more complicated.** 13:38:06
16 Q. So in -- earlier we talked about optical 13:38:08
17 duplicates that are situations where one molecule 13:38:14
18 seeds and at the read stage there's some separation 13:38:19
19 and it's read as two different clusters, right? 13:38:23
20 **A. Yes. I mean, guess that is a term that** 13:38:29
21 **people use in the art. I don't really like it, but** 13:38:31
22 **yes.** 13:38:34

1 Q. Okay. In the case of optical duplicates, 13:38:34
2 those are identical mate-pair reads that are in 13:38:40
3 close proximity on a flow-cell, right? 13:38:44
4 **A. That is a reasonable interpretation. I** 13:38:46
5 **think that's the likely reading of this section,** 13:38:49
6 **yes.** 13:38:51
7 Q. Right. So when you have identical 13:38:52
8 mate-pair reads that are in close proximity, that's 13:38:56
9 a sign that one molecule through some mechanism got 13:38:59
10 separated into two identical reads at the analysis 13:39:05
11 stage, right? 13:39:08
12 **A. It's more complicated than that. So** 13:39:12
13 **Campbell gets rid of these as well, irregardless of** 13:39:15
14 **whether they are near -- I think whether or not they** 13:39:19
15 **are near each other on the flow-cell or not. And** 13:39:22
16 **the presumption is that in a large sequencing space,** 13:39:24
17 **one does not have mate-pair reads that start and end** 13:39:30
18 **at the same place randomly. So if one sees the same** 13:39:33
19 **start and stop coordinates, one thinks perhaps those** 13:39:38
20 **are copies of each other. In the Campbell space,** 13:39:43
21 **you saw that that was a very high number. And it** 13:39:48
22 **indicates that the PCR process that was used created** 13:39:52

1 **lots of duplicate molecules and the complexity of** 13:39:55
2 **the library was much lower than they sequenced. Here** 13:39:58
3 **they specifically observed them nearby, but they're** 13:40:03
4 **probably not getting rid of duplicate mate-pair** 13:40:07
5 **reads entirely in this paper because the -- I think** 13:40:12
6 **because the reduction in information space between** 13:40:18
7 **RNA and DNA is so large that there's a higher** 13:40:23
8 **likelihood of getting two molecules independently** 13:40:29
9 **that actually have the same start and stop end** 13:40:32
10 **points in the genome and map the same. So I think** 13:40:36
11 **there's more possibility for independent mate-pairs** 13:40:39
12 **to be truly independent molecules rather than copies** 13:40:42
13 **of each other like they are in Campbell. But here** 13:40:45
14 **they observed them locally and thus suggest that** 13:40:48
15 **those are likely, as you're describing them, optical** 13:40:50
16 **duplicates.** 13:40:54
17 Q. On that point, observing them locally in 13:40:55
18 Maher on page 8 that we're looking at, what is the 13:40:58
19 significance of noting that the identical mate-pair 13:41:03
20 reads were in close proximity on the flow-cell? 13:41:06
21 What's the significance of that piece? 13:41:09
22 **A. Well, if you had seen identical mate-pair** 13:41:12

1 **reads somewhere else, they would have been created** 13:41:12
2 **earlier in the pipeline, not on the flow-cell. Here** 13:41:14
3 **this suggests they are created on the flow-cell** 13:41:17
4 **because they're in physical proximity to one** 13:41:21
5 **another.** 13:41:23
6 Q. And that's what we were talking earlier 13:41:24
7 where you have one molecule seeding that ends up 13:41:25
8 being read as two mate pairs, right? 13:41:29
9 MR. RAICH: Objection, foundation. 13:41:32
10 **A. I think that's correct, yes.** 13:41:34
11 Q. And they're identical mate-pair reads 13:41:39
12 because the sequence doesn't change from that of the 13:41:41
13 original molecule? It's just through some 13:41:44
14 phenomenon it gets read as two instances of that 13:41:48
15 same original sequence in close proximity on the 13:41:50
16 flow-cell, right? 13:41:54
17 **A. Presumably. They don't say what the --** 13:41:58
18 **they don't actually describe how they decide in this** 13:41:59
19 **section here -- maybe it's somewhere else -- what an** 13:42:02
20 **identical mate-pair read really is. I would guess** 13:42:05
21 **that the sequences could have some differences** 13:42:09
22 **between them, given the error rate on the sequencer,** 13:42:11

1 **but they map to the same location in the genome and,** 13:42:13
2 **therefore, are presumed to be duplicate molecules.** 13:42:17
3 Q. In the general context that we talked 13:42:24
4 about of optical duplicates or PCR duplicates, 13:42:25
5 whichever term you prefer, those aren't a situation 13:42:32
6 where the original seeding molecule changes into two 13:42:34
7 different molecules? It's a situation where one 13:42:38
8 original seeding molecule gets duplicated to be read 13:42:40
9 as two different copies of the same starting 13:42:44
10 sequence, right? 13:42:49
11 **A. I think that's fair, yes.** 13:42:50
12 Q. Okay. I should have asked, the term mixed 13:43:47
13 cluster that we've been talking about, was that a 13:43:50
14 term that you knew before your work on this case, 13:43:53
15 just from your work in the field? 13:43:56
16 **A. If you had said the phrase, I think I** 13:43:59
17 **would have understood it.** 13:44:01
18 Q. How about optical duplicate? 13:44:03
19 **A. If you had given me more context than just** 13:44:06
20 **optical duplicate, yes, I think I would have** 13:44:10
21 **understood it.** 13:44:15
22 Q. We talked earlier about purity filtering 13:44:33

1 being used to weed out mixed clusters. Do you 13:44:35
2 remember that? 13:44:40
3 **A. Yes.** 13:44:41
4 Q. Can purity filtering be used to identify 13:44:41
5 optical duplicates or PCR duplicates? 13:44:45
6 **A. I could imagine that software could do** 13:44:52
7 **that. I'm not certain.** 13:44:55
8 Q. In doing some of your obviousness analysis 13:46:44
9 in this case, you address something called the 13:46:47
10 reasonable expectation of success. You're familiar 13:46:49
11 with that, right? 13:46:51
12 **A. Yes.** 13:46:53
13 Q. And what's your understanding of what 13:46:54
14 reasonable expectation of success means in the 13:46:56
15 context of an obviousness analysis? 13:46:59
16 **A. Can I have my initial declaration, please?** 13:47:19
17 **Either one of them; or point me to the section -- if** 13:47:22
18 **it's in the reply declaration, point me to the reply** 13:47:25
19 **declaration where I discuss it.** 13:47:28
20 Q. I think you have all of your declarations. 13:47:29
21 I thought I gave those to you. 13:47:32
22 **A. I just have replies that I brought with** 13:47:33

1 **me. I don't have copies of the declarations** 13:47:35
2 **themselves.** 13:47:37
3 MR. RAICH: You handed it to me 13:47:38
4 earlier in the deposition, counsel. 13:47:39
5 Q. I thought I handed them to you at the same 13:47:48
6 time. Here we go. Thanks. Here's copies of both 13:47:50
7 of your original declarations. 13:48:00
8 **A. On page 13 of this case, the 964, I have** 13:48:33
9 **that obviousness requires a reasonableness** 13:48:37
10 **expectation of success in combined prior art. I** 13:48:40
11 **understand that obviousness requires a reasonable** 13:48:43
12 **expectation of success. It does not require an** 13:48:45
13 **absolute predictability of success.** 13:48:46
14 Q. What is your understanding of what it 13:48:51
15 means to have a reasonable expectation of success in 13:48:51
16 combining the prior art to achieve the claimed 13:48:54
17 subject matter? 13:48:57
18 **A. That if I was trying to solve a problem** 13:49:03
19 **and I put two pieces of prior art together, they** 13:49:05
20 **would solve that problem with a reasonable chance of** 13:49:09
21 **success.** 13:49:16
22 Q. In these cases, there's two different 13:49:17

1 patents. That's the '200 patent and the '852 13:49:21
2 patent, right? 13:49:24
3 **A. Yes.** 13:49:24
4 Q. You know there are some differences 13:49:25
5 between the claims in those patents, right? 13:49:26
6 **A. Yes.** 13:49:28
7 Q. How did you factor in the differences 13:49:30
8 between the claims in these two patents in your 13:49:32
9 reasonable expectation of success analysis in this 13:49:34
10 case? 13:49:36
11 MR. RAICH: Object to the form of the 13:49:39
12 question. 13:49:40
13 **A. I read the claims. I read the description** 13:49:40
14 **of the invention. I read the summary of the** 13:49:42
15 **invention. I read the specification. And I read** 13:49:44
16 **the prior art, evaluated it in each case, and** 13:49:48
17 **evaluated them collectively for each case.** 13:49:53
18 Q. Okay. The specific differences between 13:49:55
19 the claim in the '200 patent and the claim in the 13:49:58
20 '852 patent, did any of those particular differences 13:50:02
21 factor in specifically to your reasonable 13:50:07
22 expectation of success analysis? 13:50:09

1 MR. RAICH: Objection to form. 13:50:13
2 **A. Can you point me to a specific place, a** 13:50:15
3 **specific claim? I evaluate each claim on its own,** 13:50:18
4 **not in comparison to one another.** 13:50:22
5 Q. Okay. Are there any differences between 13:50:24
6 the claims in the '200 patent and the claims in the 13:50:29
7 '852 patent that were important to your reasonable 13:50:32
8 expectation of success analysis? 13:50:36
9 MR. RAICH: Object to the form of the 13:50:38
10 question. 13:50:40
11 **A. I think I answered this already. I** 13:50:40
12 **evaluated each set of claims on their own. There** 13:50:42
13 **are some shared elements and the specification is** 13:50:45
14 **shared, but the claims are quite different.** 13:50:50
15 Q. How did the differences between the claims 13:50:56
16 in the '200 patent and the claims in the '852 patent 13:50:59
17 factor into your reasonable expectation of success 13:51:03
18 analysis? 13:51:05
19 MR. RAICH: Object to the form of the 13:51:08
20 question? 13:51:09
21 **A. Again, you keep asking me about the** 13:51:10
22 **differences between the claims. I evaluated each** 13:51:12

1 **set of claims on its own. I didn't compare them** 13:51:13
2 **against one another.** 13:51:16
3 Q. Is it your understanding that a person of 13:51:40
4 ordinary skill in the art in order to show 13:51:42
5 obviousness here would have to have a reasonable 13:51:45
6 expectation of successfully reducing cross-over 13:51:48
7 error in combining prior art to achieve the 13:51:52
8 invention of the '852 patent? 13:51:56
9 **A. Can I have the '852 patent, please?** 13:51:58
10 Q. That one I am certain I gave you. 13:52:03
11 **A. I don't believe I have a copy of the '852** 13:52:14
12 **patent in front of me. Maybe it's right here. Yes,** 13:52:16
13 **here it is. It was buried in my stack. My** 13:52:19
14 **apologies.** 13:52:22
15 Q. No problem. 13:52:23
16 Do you want me to repeat the question? 13:52:23
17 **A. Yes, please.** 13:52:25
18 Q. Is it your understanding that a person of 13:52:26
19 ordinary skill in the art in order to show 13:52:28
20 obviousness here would have to have a reasonable 13:52:30
21 expectation of successfully reducing cross-over 13:52:33
22 error in combining prior art to achieve the 13:52:36

1 invention in the '852 patent? 13:52:39
2 MR. RAICH: Object to the form of the 13:52:43
3 question. 13:52:44
4 **A. I'm going to have you repeat the question** 13:53:03
5 **one more time. My apologies.** 13:53:05
6 Q. Yes. 13:53:07
7 Is it your understanding that in order to 13:53:08
8 show obviousness here, a person of ordinary skill in 13:53:11
9 the art would have to have a reasonable expectation 13:53:14
10 of successfully reducing cross-over error in 13:53:16
11 combining prior art to achieve the invention in the 13:53:20
12 '852 patent? 13:53:23
13 **A. The requirement of the '852 -- well,** 13:53:29
14 **what's claimed is a method for reducing cross-over** 13:53:33
15 **error between templates, between different samples.** 13:53:36
16 **And therefore any method that would do so would --** 13:53:46
17 **would be -- I'm sorry. I'm going to need you to** 13:54:01
18 **repeat the question one more time.** 13:54:03
19 Q. No problem. 13:54:05
20 Is it your understanding that in order to 13:54:06
21 show obviousness here, a person of ordinary skill in 13:54:08
22 the art would have to have a reasonable expectation 13:54:12

of successfully reducing cross-over error in 13:54:15
combining prior art to achieve the invention in the 13:54:18
'852 patent? 13:54:21
MR. RAICH: Same objection. 13:54:25
A. I believe that that is correct, yes. 13:54:32
MR. MATTY: Okay. Thanks for your 13:54:35
time. Those are all the questions I have today. 13:54:36
MR. RAICH: Let's go ahead and go off 13:54:39
the record. 13:54:41
VIDEO TECHNICIAN: The time is 1:55 13:54:42
p.m. We are off the record. 13:54:44
(A brief recess was taken.) 13:54:47
VIDEO TECHNICIAN: The time is 2:09 14:08:49
p.m. We're on the record. 14:08:51
MR. RAICH: We have no questions for 14:08:53
Dr. Spellman. Thank you very much. 14:08:54
VIDEO TECHNICIAN: The time is 2:09 14:08:56
p.m. This concludes today's deposition. Off the 14:08:58
record. 14:09:01
(Signature having not been waived, 14:09:01
the deposition of Paul Spellman, Ph.D. was concluded 14:09:01
at 2:09 p.m.) 14:09:01

CERTIFICATE OF SHORTHAND REPORTER

I, Michele E. Eddy, Registered Professional Reporter and Certified Realtime Reporter, the court reporter before whom the foregoing deposition was taken, do hereby certify that the foregoing transcript is a true and correct record of the testimony given; that said testimony was taken by me stenographically and thereafter reduced to typewriting under my supervision; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 5th day of August, 2025.

My commission expires July 31, 2027

Michele Eddy

MICHELE EDDY
NOTARY PUBLIC IN AND FOR
THE DISTRICT OF COLUMBIA

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