

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA INC.,

Petitioner,

v.

MOLECULAR LOOP BIOSCIENCES, INC.,

Patent Owner.

Case IPR2024-01419

U.S. Patent No. 11,840,730

VIDEOTAPED DEPOSITION of STACEY GABRIEL, PH.D.,

VOLUME 1, DAY 1

Thursday, November 6, 2025

9:05 a.m.

Henderson Legal Services

202-220-4158

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IPR2024-01419

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

Molecular Loop's Exhibit 2025

EX2025, Page 1

1

2

Deposition of STACEY GABRIEL, PH.D., held

3

at the offices of:

4

5

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Job No.: 57595

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Pages: 1 - 143

12

Reported By: Michelle Keegan, RMR, CRR, CSR

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1 APPEARANCES (continued)

2

3 Also Present:

4 Bob Giannini, Videographer

5 Marcus Burch, Illumina

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1 I N D E X

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7 E X H I B I T S

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12 P R E V I O U S L Y M A R K E D

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21 * Original exhibits retained by court reporter *

22 * Documents quoted on record transcribed as read *

6

1 P R O C E E D I N G S 09:05:15

2 THE VIDEOGRAPHER: Good morning. We are 09:05:15

3 on the record. This is the videographer speaking, 09:05:27

4 Bob Giannini. I am with court reporter Michelle 09:05:30

5 Keegan with Henderson Legal Services. 09:05:33

6 Today's date is November 6th, 2025, and 09:05:36

7 the time is 9:05 a.m. We are here at Sidley 09:05:39

8 Austin, located in Boston, Massachusetts, to take 09:05:45

9 the video deposition of Dr. Stacey Gabriel in the 09:05:48

10 matter of Illumina Inc. versus Molecular Loop, 09:05:51

11 IPR2024-01419. 09:05:57

12 Will counsel please introduce themselves 09:06:02

13 for the record. 09:06:04

14 MR. BROUGHAN: Tom Broughan from Sidley 09:06:06

15 Austin on behalf of petitioner Illumina. With me 09:06:08

16 is Marcus Burch of Illumina. 09:06:11

17 MR. WUESTE: Michael Wueste from 09:06:13

18 Desmarais LLP on behalf of patent owner Molecular 09:06:14

19 Loop. And with me is Kevin Goon, also of 09:06:19

20 Desmarais LLP. 09:06:21

21 THE VIDEOGRAPHER: Thank you. 09:06:23

22 Will the court reporter please swear in 09:06:23

1 the witness. 09:06:24

2 STACEY GABRIEL, PH.D.,
3 having been satisfactorily identified and duly
4 sworn by the Notary Public, was examined and
5 testified as follows:

6 EXAMINATION BY COUNSEL FOR
7 PATENT OWNER MOLECULAR LOOP BIOSCIENCES, INC. 09:06:33

8 BY MR. WUESTE: 09:06:33

9 Q. Hi again, Dr. Gabriel. 09:06:34

10 A. Hi. 09:06:36

11 Q. I know this is the second time we've 09:06:36
12 spoken, but could you once again please state and 09:06:38
13 spell your full name for the record. 09:06:40

14 A. Yes. Stacey Gabriel. S-T-A-C-E-Y, 09:06:42
15 G-A-B-R-I-E-L. 09:06:46

16 Q. And, Dr. Gabriel, as with your previous 09:06:47
17 deposition, you understand the oath you just took 09:06:51
18 requires you to tell the truth. Correct? 09:06:54

19 A. Yes. 09:06:55

20 Q. Okay. Is there any reason you cannot 09:06:56
21 provide your best, truthful testimony today? 09:06:58

22 A. No. 09:07:01

8

1 Q. Okay. And we're not going to go over all 09:07:01
2 of the ground rules, but if I ask you a question 09:07:06
3 and you answer it, I will assume you understood 09:07:08
4 it. Fair? 09:07:10

5 **A. That's fair.** 09:07:10

6 Q. Okay. Dr. Gabriel, are you familiar with 09:07:11
7 stochastic effects in genome sequencing? 09:07:17

8 **A. Is there a reference or some context you** 09:07:20
9 **want to give for that question?** 09:07:31

10 Q. Just the concept to begin with. 09:07:32

11 Have you ever heard of a stochastic 09:07:36
12 effect? 09:07:38

13 **A. Not in that way. No. Not a stochastic** 09:07:38
14 **effect.** 09:07:47

15 Q. Have you ever -- you're familiar with 09:07:47
16 amplification in the context of a genome 09:07:51
17 sequencing workflow. Correct? 09:07:53

18 **A. Yes. There is amplification in most DNA** 09:07:55
19 **sequencing workflows.** 09:08:02

20 Q. And have you ever heard that at least in 09:08:03
21 terms of -- well, let's start with PCR 09:08:08
22 amplification, that PCR amplification is 09:08:12

1 stochastic? 09:08:16

2 MR. BROUGHAN: Object to form. 09:08:17

3 A. I'm not really familiar with that 09:08:17

4 necessarily. No. 09:08:29

5 Q. Is it fair to say that amplification in 09:08:30

6 the context of a genome sequencing workflow is 09:08:33

7 random? 09:08:44

8 MR. BROUGHAN: Object to form. 09:08:44

9 A. I think -- I'd need to know what you mean 09:08:50

10 by "random." 09:08:54

11 Q. Well, let's start with your definition, 09:08:55

12 then. Right? 09:08:57

13 If you agree that PCR amplification in the 09:08:58

14 concept of genome sequencing can be random, what 09:09:03

15 randomness would you apply to that? 09:09:06

16 MR. BROUGHAN: Object to form. 09:09:11

17 A. I don't know that I said it can be random. 09:09:11

18 I said sequencing workflows can involve 09:09:13

19 amplification. I don't know that -- I don't know 09:09:16

20 that I lumped -- I described them as random. 09:09:21

21 Q. That's fair. And I'm just trying to get, 09:09:23

22 like, a base level of common understanding here. 09:09:26

10

1 Is it the case that during PCR 09:09:29
2 amplification, you know exactly how you're going 09:09:34
3 to apply a given primer to a given molecule? 09:09:37

4 MR. BROUGHAN: Object to form. 09:09:41

5 A. I'm not sure what you mean by how you 09:09:42
6 apply. I do know that there are typically rules 09:09:54
7 and approaches for designing primers and then 09:09:57
8 using primers in a PCR reaction. There are 09:10:00
9 protocols for PCR, but I don't know what you mean 09:10:04
10 by how you apply. 09:10:07

11 Q. Well, certainly. So let's say I want to 09:10:07
12 apply a primer to a set of molecules in a sample. 09:10:10

13 A. Uh-hmm. 09:10:15

14 Q. Okay? 09:10:16

15 A. Yup. 09:10:16

16 Q. Am I able to say here is Primer A and I'm 09:10:17
17 going to make sure it attaches to Molecule A? 09:10:21

18 A. Not a given molecule in the sample. The 09:10:23
19 primer will attach to its corresponding region on 09:10:33
20 multiple molecules. 09:10:41

21 Q. Okay. And so if I've got a pool of 09:10:42
22 primers that are developed to attach to a 09:10:45

11

1 corresponding region in a pool of molecules, I 09:10:51
2 can't really know which of those primers are going 09:10:54
3 to attach to which of those molecules. Right? 09:10:57

4 MR. BROUGHAN: Object to form. 09:11:04

5 **A. Generally, I would say you don't know that** 09:11:05
6 **beforehand. I suppose there could be some special** 09:11:22
7 **case where primers were designed to match some** 09:11:28
8 **particular molecule if you already knew that** 09:11:36
9 **sequence variant was on that molecule. But again,** 09:11:40
10 **I don't know the specifics that we're getting** 09:11:43
11 **into, but --** 09:11:45

12 Q. So generally speaking, if I've got a pool 09:11:47
13 of primers and a pool of molecules and I want to 09:11:49
14 attach the primers to the molecules, right, in my 09:11:52
15 experiment, which primer is going to attach to 09:11:55
16 which molecule if they all have the same 09:11:59
17 corresponding regions is going to be random. Is 09:12:01
18 that fair to say? 09:12:03

19 MR. BROUGHAN: Object to form. 09:12:04

20 **A. I think in a generic way I would agree** 09:12:05
21 **with that. One could imagine different scenarios,** 09:12:17
22 **but yes.** 09:12:20

12

1 Q. And have you ever heard of that quality, 09:12:20
2 that dynamic, referred to as "stochastic"? 09:12:23

3 MR. BROUGHAN: Object to form. 09:12:27

4 A. I don't know that I've used that term 09:12:28
5 myself or read that term for that example you've 09:12:32
6 given. 09:12:36

7 Q. Sitting here today, you don't know if 09:12:36
8 you've ever heard "stochastic" being used in the 09:12:42
9 context of amplification during genome sequencing? 09:12:46

10 A. I can't remember a specific reference that 09:12:50
11 points to that. If you have one, feel free -- I'd 09:13:02
12 be happy to look at it. 09:13:05

13 Q. Just in your general knowledge sitting 09:13:07
14 here today, you don't know if you've ever heard 09:13:09
15 "stochastic" being used to describe amplification 09:13:13
16 during genomic sequencing? 09:13:16

17 MR. BROUGHAN: Object to form. 09:13:17

18 A. Yeah. Right now, I don't know. 09:13:18

19 Q. Okay. Are you familiar with something 09:13:23
20 called "allele dropout"? 09:13:27

21 A. I am. 09:13:31

22 Q. What is allele dropout? 09:13:32

13

1 **A. So "allele dropout" would refer to** 09:13:33
2 **something you would observe in an analysis where** 09:13:46
3 **you only detected one copy of an allele and not** 09:13:50
4 **both.** 09:13:54

5 **And that could be because both weren't** 09:13:56
6 **equally sampled or both weren't adequately** 09:13:59
7 **sampled. And so then in your analysis, you would** 09:14:05
8 **observe a dropout, so you would only observe one** 09:14:08
9 **of the alleles.** 09:14:11

10 **Q. And when in a genome sequencing workflow** 09:14:11
11 **would allele dropout occur? And then I'm going to** 09:14:19
12 **follow up -- let me set the stage first. All** 09:14:24
13 **right?** 09:14:27

14 **I want to ask both when allele dropout** 09:14:27
15 **occurs and then when it is observed. All right?** 09:14:30
16 **So I'm going to start with the first one.** 09:14:32

17 **In a genome sequencing workflow, when** 09:14:35
18 **would allele dropout typically occur?** 09:14:37

19 **MR. BROUGHAN: Object to form.** 09:14:40

20 **A. It could occur during a PCR amplification.** 09:14:45
21 **It could occur depending on how you're doing** 09:14:56
22 **your -- like, what your sequencing assay is during** 09:15:01

14

1 **some other type of enrichment of the sample, some** 09:15:05
2 **selection of a sample. So it could occur in** 09:15:10
3 **different places.** 09:15:15

4 Q. Okay. And then when would the, I guess, 09:15:15
5 consequences of the allele dropout be observed in 09:15:20
6 the genome sequencing workflow? 09:15:23

7 **A. In data analysis.** 09:15:25

8 Q. Okay. Is allele dropout a type of error? 09:15:29

9 MR. BROUGHAN: Object to form. 09:15:36

10 **A. It could be an error.** 09:15:37

11 Q. Would you call it -- so I don't know all 09:15:48
12 the categories of error. We talked about a couple 09:15:55
13 of potential categories at your first deposition. 09:15:58
14 I don't know if you recall that. 09:16:00

15 So I'm going to give you a list of 09:16:01
16 potential types, not meant to be comprehensive. I 09:16:05
17 just want to know what type allele dropout would 09:16:09
18 be. Okay? So that's, again, setting the scene 09:16:11
19 for the question. 09:16:18

20 Can allele dropout be a type of sequencing 09:16:18
21 error or amplification error, sequence error, or 09:16:21
22 quantification error? 09:16:26

15

1 MR. BROUGHAN: Object to form. 09:16:28

2 A. Well, it shows up as an error, a missed 09:16:29

3 call. It could be a quantification error. Yeah. 09:16:42

4 Q. Okay. Fair to say that allele dropout 09:16:55

5 shows up as an error. Correct? 09:17:01

6 MR. BROUGHAN: Object to form. 09:17:07

7 A. Well, if there really were two alleles in 09:17:08

8 a sample and you only detect one of them, that is 09:17:16

9 inaccurate. You can call it an error. 09:17:24

10 Q. Okay. And I think I heard you say earlier 09:17:28

11 that allele dropout could be -- strike that. 09:17:31

12 I believe I heard you say earlier that 09:17:35

13 allele dropout could arise during amplification. 09:17:37

14 Did I hear that right? 09:17:41

15 A. I believe it could. 09:17:41

16 Q. Okay. Could you call that a form of 09:17:44

17 amplification error, then, if it was dropped out 09:17:47

18 during amplification? 09:17:51

19 MR. BROUGHAN: Object to form. 09:17:54

20 A. I don't know that I've ever used that 09:17:55

21 term. I think it could happen during 09:18:09

22 amplification and it would show up as an error. 09:18:10

16

1 Q. Okay. That's fair. Are you familiar with 09:18:12
2 something called "locus dropout"? 09:18:15

3 A. No. 09:18:17

4 Q. Okay. Are you familiar with something 09:18:19
5 called "allele drop-in"? 09:18:24

6 A. No. 09:18:25

7 Q. Okay. If we have allele dropout occurring 09:18:27
8 at the beginning of a number of cycles of 09:18:48
9 amplification -- that's the scene. So let me set 09:18:53
10 up a hypothetical. 09:19:01

11 We've got our experiment. We are going to 09:19:01
12 be doing multiple rounds of amplification. In the 09:19:08
13 very first round, we've got allele dropout. And 09:19:11
14 then we continue to cycle through the next several 09:19:15
15 rounds of amplification. 09:19:19

16 What is the result of allele dropout 09:19:22
17 happening at the beginning of that amplification 09:19:26
18 cycle once we've, you know, completed all the 09:19:28
19 other rounds of amplification? 09:19:33

20 MR. BROUGHAN: Object to form. 09:19:38

21 A. The result is that the allele is not being 09:19:39
22 amplified as much as the other allele. 09:19:54

17

1 Q. Okay. So you would get a larger number of 09:19:55
2 let's call them product sequences following 09:20:02
3 amplification with the incorrect sequence compared 09:20:04
4 to the total population of a product after 09:20:08
5 amplification. Is that fair to say? 09:20:12

6 MR. BROUGHAN: Object to form. 09:20:14

7 A. There would be more copies with the allele 09:20:15
8 that was amplified more often. 09:20:26

9 Q. Got it. And again, would you call that a 09:20:29
10 sequence error, a quantification error, both? 09:20:36

11 MR. BROUGHAN: Object to form. 09:20:42

12 A. You would detect it in the sequence. But 09:20:43
13 in your hypothetical it happened during 09:20:55
14 amplification, so I don't know what I would refer 09:21:00
15 to it as in that hypothetical. 09:21:04

16 Q. It would just be an error? 09:21:06

17 MR. BROUGHAN: Object to form. 09:21:09

18 A. It would be an inaccurate representation 09:21:10
19 of what the true answer was. 09:21:14

20 Q. Right. And is it fair to call an 09:21:16
21 inaccurate representation of the true answer an 09:21:20
22 error? 09:21:23

18

1 MR. BROUGHAN: Object to form. 09:21:24

2 A. You can call it that. 09:21:25

3 Q. Okay. Have you ever heard of something 09:21:26
4 called "synthesis error"? 09:21:32

5 A. Synthesis error. In what context? 09:21:34

6 Q. In the context of genome sequencing. 09:21:42

7 A. I've heard of oligos. Oligos are 09:21:51
8 synthetic pieces of DNA. I've heard of oligos 09:21:58
9 being incorrectly synthesized. 09:22:01

10 I don't know that I've used the term 09:22:03
11 "synthesis error," then, with genome sequencing. 09:22:05
12 That's the best I can give you. 09:22:08

13 Q. That's fair. And what happens when oligos 09:22:09
14 are incorrectly synthesized? 09:22:13

15 MR. BROUGHAN: Object to form. 09:22:15

16 A. When? What happens when? 09:22:16

17 Q. Well, okay. Let's walk through the genome 09:22:22
18 sequencing workflow again. 09:22:28

19 A. Uh-hmm. 09:22:30

20 Q. Let's say we are intending to build an 09:22:31
21 oligonucleotide and let's say we want to build a 09:22:38
22 lot of them. Okay? 09:22:46

19

1 The way I understand it -- and I'll defer 09:22:50
2 to your expertise. I can set up my pool of 09:22:55
3 samples of oligos. 09:23:00

4 And what happens if I, you know, 09:23:07
5 missequence the oligo when I'm first setting up 09:23:10
6 that pool? Would that be an oligo -- would that 09:23:12
7 be incorrectly synthesizing the oligo? 09:23:16

8 MR. BROUGHAN: Object to form. 09:23:19

9 **A. You lost me there. I don't know what you 09:23:20**
10 **mean by missequence an oligo before I set up the 09:23:26**
11 **pool. 09:23:28**

12 Q. Let's say I wanted a certain sequence, 09:23:28
13 right, but in the course of constructing the 09:23:30
14 original pool before amplification I got the 09:23:32
15 sequence wrong. Is that an example of incorrectly 09:23:35
16 synthesizing it? 09:23:40

17 **A. If the user got the sequence wrong, that's 09:23:47**
18 **a user error. But the synthesis machine might get 09:23:51**
19 **an incorporation wrong, and then that could be an 09:23:55**
20 **error making the oligo. I don't know. 09:23:58**

21 Q. Okay. And then another option within the 09:24:00
22 genome sequencing workflow is in order to create 09:24:10

20

1 more, you would synthesize a complementary strand 09:24:15

2 of a genome or a sequence. Right? 09:24:17

3 MR. BROUGHAN: Object to form. 09:24:23

4 **A. I don't understand your question.** 09:24:24

5 Q. Okay. Would you agree with this: Errors 09:24:26

6 can occur when nucleotides are incorrectly 09:24:31

7 incorporated when making a copy of DNA by 09:24:34

8 synthesizing the complementary strand? 09:24:37

9 **A. Yes.** 09:24:38

10 Q. Okay. That process of synthesizing the 09:24:46

11 complementary strand, if we introduce an error 09:24:52

12 into that when we're creating an oligo, is that 09:24:54

13 different in kind from an error that is introduced 09:25:00

14 at different stages of the genome sequencing 09:25:03

15 workflow? 09:25:05

16 MR. BROUGHAN: Object to form. 09:25:06

17 **A. I don't know what you mean.** 09:25:07

18 Q. Okay. Have you ever heard of PCR error? 09:25:10

19 **A. Yes.** 09:25:18

20 Q. What is PCR error? 09:25:18

21 **A. Did you ask me what is PCR?** 09:25:21

22 Q. Yeah. No. Sorry, sorry. Let me 09:25:25

21

1 rephrase. 09:25:28

2 What is PCR error? 09:25:28

3 **A. An error that happens during PCR.** 09:25:30

4 Q. Okay. And what are the kinds of results 09:25:36

5 that can happen from PCR error, an error that 09:25:39

6 happens during PCR? 09:25:43

7 **A. Various types.** 09:25:44

8 Q. Can you give me an example? 09:25:47

9 **A. You could have amplification that is** 09:25:48

10 **nonspecific. You could have overrepresentation of** 09:25:59

11 **one area versus another. You could have incorrect** 09:26:08

12 **nucleotides being added. You could have** 09:26:15

13 **insertions or deletions.** 09:26:21

14 **There's various kinds of errors that can** 09:26:23

15 **happen during PCR.** 09:26:26

16 Q. Got it. What do you mean by 09:26:27

17 "amplification that is nonspecific"? That was the 09:26:30

18 first example that you gave. 09:26:33

19 **A. The PCR primers might bind places where** 09:26:34

20 **you don't intend them to, and then you get** 09:26:37

21 **amplification you didn't intend -- you didn't want** 09:26:40

22 **to have because the primers weren't specific** 09:26:43

22

1 **enough.** 09:26:44

2 Q. Got it. And then "overrepresentation of 09:26:45

3 one area versus another," what do you mean by 09:26:48

4 that? 09:26:50

5 **A. You could have certain sequence contexts 09:26:50**

6 **that amplify better than other areas and there 09:26:58**

7 **could be different representation of those 09:27:05**

8 **sequences.** 09:27:07

9 Q. Is that different from bias? 09:27:07

10 MR. BROUGHAN: Object to form. 09:27:21

11 **A. It's not traditionally how I think about 09:27:22**

12 **bias. It's sort of a representation problem I 09:27:42**

13 **guess I was referring to there.** 09:27:47

14 Q. Okay. So just -- 09:27:48

15 **A. From PCR.** 09:27:51

16 Q. I see. So in the instance where you have 09:27:52

17 certain sequence context that amplified better 09:28:03

18 than others, that could lead to an 09:28:05

19 overrepresentation of one set of sequences over 09:28:08

20 another set of sequences. Correct? 09:28:12

21 MR. BROUGHAN: Object to form. 09:28:17

22 **A. That can happen.** 09:28:18

23

1 Q. And when you have an overrepresentation of 09:28:19
2 one set of sequences over another set of sequences 09:28:23
3 based upon PCR amplification, that is an error 09:28:28
4 that is different from bias. Correct? 09:28:34

5 MR. BROUGHAN: Object to form. 09:28:38

6 A. I guess it depends on the context of 09:28:40
7 how -- of how you're using the terms. 09:28:50

8 I know in the report, you know, where we 09:28:53
9 considered the discussion of bias and error as 09:28:59
10 part of the -- as part of the language of the 09:29:01
11 claims, those are different things. Those are 09:29:05
12 handled differently. 09:29:09

13 But in your generic case where you're 09:29:11
14 saying -- you're asking me if overrepresentation 09:29:13
15 shows up as a bias in the sequence, I think it 09:29:17
16 can. But it's just the observation of what would 09:29:24
17 happen with the overrepresentation and a word we 09:29:27
18 can use to describe it. 09:29:32

19 Q. I'd like to pick that apart a little bit. 09:29:33
20 And before I do so, I'm actually going to go back 09:29:35
21 to something that you said a couple of questions 09:29:37
22 ago, which is, you mentioned it's not how you 09:29:39

24

1 traditionally think about bias. 09:29:46

2 So here is my question: What is your 09:29:49

3 understanding of the traditional definition of 09:29:52

4 "bias" in the context of genome sequencing? 09:29:55

5 MR. BROUGHAN: Object to form. 09:30:00

6 **A. I think, generally, a skewing of the** 09:30:01

7 **results in one context versus another, in one** 09:30:16

8 **region versus another.** 09:30:23

9 Q. And how would you define "skewing"? 09:30:24

10 **A. I would say skewing -- misrepresentation** 09:30:29

11 **of what was there originally or misrepresentation** 09:30:47

12 **of the original sequence.** 09:30:51

13 Q. Okay. So let me see if I've got this 09:30:54

14 right. The traditional definition of "bias" in 09:31:11

15 the context of genome sequencing is a skewing of 09:31:14

16 the results in one context versus another such 09:31:16

17 that there's a misrepresentation of what was 09:31:20

18 originally there or a misrepresentation of the 09:31:23

19 original sequence. Correct? 09:31:27

20 **A. That's what I said.** 09:31:33

21 Q. Okay. In the context of nonspecific 09:31:35

22 amplification that could lead to an 09:31:47

25

1 overrepresentation of one sequence context over 09:31:53
2 another that could lead to bias or -- but that is 09:31:57
3 an error that may not necessarily lead to bias? 09:32:05

4 **A. Not necessarily lead to bias. No.** 09:32:08

5 Q. Okay. I'm trying to piece out the 09:32:13
6 difference. Right? Because if I remember 09:32:16
7 correctly -- and I say "remember correctly." I'm 09:32:18
8 just going to look back at the transcript. 09:32:23

9 Your testimony was: 09:32:31

10 "ANSWER: -- you're asking me if 09:32:33
11 overrepresentation shows up as a bias in the 09:32:35
12 sequence, I think it can. It's just the 09:32:38
13 observation of what would happen with the 09:32:42
14 overrepresentation and a word we can use to 09:32:43
15 describe it." 09:32:46

16 That was correct. Right? 09:32:48

17 **A. That's what you read. Yes.** 09:32:49

18 Q. Is bias the observation of 09:32:51
19 overrepresentation whereas the overrepresentation 09:32:56
20 itself is the result of an error? 09:33:04

21 MR. BROUGHAN: Object to form. 09:33:08

22 **A. No.** 09:33:08

1 Q. Okay. So what is -- what is the 09:33:09
2 difference between nonspecific amplification that 09:33:12
3 leads to an overrepresentation and bias? 09:33:16

4 **A. First off, nonspecific amplification is 09:33:19**
5 **just a different problem. 09:33:24**

6 **Nonspecific amplification is my primers 09:33:26**
7 **aren't specific enough, so I'm amplifying multiple 09:33:30**
8 **regions that I don't necessarily want to sequence. 09:33:36**
9 **That's nonspecific amplification, not necessarily 09:33:40**
10 **a representation problem. 09:33:44**

11 Q. I see. Representation problems can arise 09:33:46
12 from a number of potential errors, including, as 09:33:49
13 one example, nonspecific amplification. Is that 09:33:53
14 fair? 09:33:56

15 **A. I'm sorry. Say that again. 09:33:56**

16 Q. Sure. An overrepresentation can arise 09:33:59
17 from a number of potential errors, including, as 09:34:04
18 one example, nonspecific amplification? 09:34:08

19 MR. BROUGHAN: Object to form. 09:34:13

20 **A. I don't think you're using it correctly, 09:34:14**
21 **actually. 09:34:16**

22 Q. Okay. Okay. Let me ask a more basic 09:34:16

27

1 question, then. What is the difference between 09:34:28
2 overrepresentation and bias in the context of 09:34:30
3 genome sequencing? 09:34:33

4 A. Those are, in a way, general terms. It 09:34:34
5 could be overrepresentation happens because you 09:35:03
6 have too much amplification in one area versus 09:35:05
7 another. 09:35:11

8 Bias could happen because -- so you could 09:35:15
9 say if that happens, I'm going to have a bias in 09:35:20
10 my results. But then again, you could also have 09:35:22
11 bias resulting from the sequencer working better 09:35:26
12 or worse in different sequencing contexts. For 09:35:32
13 example, GC bias is a thing in PCR sequencing. 09:35:35

14 So in some ways, they're general terms. 09:35:42
15 So I can't really give you a perfect definition. 09:35:45
16 Again, in the context of, again, looking at the 09:35:51
17 '730 patent, they're described in two different 09:35:54
18 ways, bias or errors -- "error or bias" I think is 09:36:03
19 what it says. So not the same. 09:36:06

20 Q. Is overrepresentation a type of error? 09:36:08

21 MR. BROUGHAN: Object to form. 09:36:13

22 A. Well, generally, anything that is not -- 09:36:14

28

1 if it's not a true representation of what your 09:36:22
2 original molecule was, then there's an inaccurate 09:36:25
3 result. 09:36:29

4 Again, just semantics. We can say an 09:36:31
5 inaccurate result is an error. But if you want to 09:36:34
6 talk about, like, how we use those words, there 09:36:38
7 are errors that are errors and then there are 09:36:44
8 biases in the result. So in the art, it can be 09:36:46
9 used in different ways. Yeah. 09:36:49

10 Q. Just to make the record clear, if 09:36:51
11 overrepresentation leads to a not-true 09:36:59
12 representation of what your original molecule was, 09:37:06
13 that's an inaccurate result and you would call 09:37:10
14 that an error. Correct? 09:37:12

15 MR. BROUGHAN: Object to form. 09:37:14

16 Go ahead. 09:37:16

17 A. Broadly, that would be an inaccurate 09:37:17
18 result. And so generically, we can call that a 09:37:22
19 type of an error. 09:37:27

20 Q. Okay. Is it your contention that the '730 09:37:29
21 patent uses the term "bias" in a way that is 09:37:36
22 different from the traditional understanding of 09:37:41

29

1 it? 09:37:43

2 **A. You have to point me to the part of the** 09:37:44

3 **'730 patent. We can talk about specifics. I** 09:37:49

4 **don't want to speak about that term generally.** 09:37:52

5 Q. Okay. I ask only because you mentioned 09:37:54

6 what the traditional understanding of bias was. 09:37:59

7 Right? 09:38:01

8 **A. Uh-hmm.** 09:38:01

9 Q. Is that traditional understanding of bias 09:38:02

10 different or the same, in your opinion, from how 09:38:09

11 you think the '730 patent uses the term "bias"? 09:38:13

12 MR. BROUGHAN: Object to form. 09:38:17

13 **A. My recollection is that there's not some** 09:38:18

14 **new kind of bias discussed in the '730 patent that** 09:38:41

15 **I haven't heard of before.** 09:38:43

16 Q. Okay. Your recollection is that the '730 09:38:44

17 patent uses "bias" in a way that conforms with the 09:38:50

18 traditional definition or understanding. Fair? 09:38:53

19 MR. BROUGHAN: Object to form. 09:38:57

20 **A. With types of bias that we understand** 09:38:58

21 **exist, yes.** 09:39:07

22 Q. Does the '730 patent, in your opinion, use 09:39:07

30

1 "error" to mean something different than an 09:39:13

2 inaccurate result? 09:39:16

3 **A. I don't know. Again, I'd rather have the 09:39:17**

4 **context of the use of the word "error" in the '730 09:39:29**

5 **patent rather than just try to answer that in a 09:39:36**

6 **generic way. 09:39:39**

7 Q. When you were rendering your opinions on 09:39:42

8 the '730 patent in the course of this inter partes 09:39:44

9 review, were you applying a different definition 09:39:49

10 of "error" than the traditional understanding of 09:39:53

11 an inaccurate result? 09:39:57

12 MR. BROUGHAN: Object to form. 09:39:59

13 **A. I don't think so. No. 09:40:00**

14 Q. Okay. I'm going to hand you a copy of 09:40:07

15 what's previously been marked as EX-1065. 09:40:46

16 (Previously marked Exhibit EX-1065) 09:40:52

17 Q. EX-1065 is the reply declaration you 09:41:15

18 submitted in this inter partes review. Correct? 09:41:19

19 **A. That's correct. 09:41:23**

20 Q. Okay. If you look at not the very last 09:41:25

21 page but page 22 of EX-1065, that's your 09:41:29

22 signature? 09:41:35

1	A. It is.	09:41:35
2	Q. Executed on October 10th, 2025?	09:41:35
3	A. Correct.	09:41:39
4	Q. Okay. I'd like to point your attention to	09:41:40
5	Paragraph 40 of EX-1065.	09:41:48
6	A. Yes.	09:41:57
7	Q. And just going forward, if I say "your	09:41:57
8	reply declaration," you'll have the understanding	09:42:03
9	it's referring to this?	09:42:07
10	A. Yes.	09:42:08
11	Q. Beginning with the second sentence in	09:42:08
12	Paragraph 40, you state, "This type of error can	09:42:23
13	occur during amplification. It can also occur	09:42:29
14	during the sequencing step, such as during	09:42:33
15	sequencing by synthesis, which also involves	09:42:37
16	copying DNA by making complementary strands."	09:42:41
17	And then you go on to say, "Sequencing	09:42:46
18	error can also occur when the nucleotide was	09:42:48
19	incorrectly incorporated in the complementary	09:42:51
20	strand subsequently misread by the sequencing	09:42:57
21	machine." Correct?	09:42:59
22	A. Yes.	09:43:01

1 MR. BROUGHAN: Object to form. 09:43:02

2 Q. In that last sentence, what did you mean 09:43:03

3 by "sequencing error"? 09:43:05

4 A. An error that occurs on the sequencer. 09:43:06

5 Q. So a sequencing error arises during the 09:43:29

6 sequencing process performed by the sequencer. Is 09:43:36

7 that fair? 09:43:38

8 A. It's a type of error. Yes. 09:43:40

9 Q. Is that different from a sequence error? 09:43:43

10 MR. BROUGHAN: Object to form. 09:43:50

11 A. It shows up the same because errors can 09:43:51

12 happen at different parts of the process, as I 09:44:02

13 articulate here. 09:44:05

14 I think traditionally if you would say 09:44:07

15 "sequencing error," you could understand that 09:44:09

16 meant on a sequencer. I suppose it could also 09:44:15

17 mean when I read my sequencing there was an error. 09:44:18

18 So really, it's a little bit, again, 09:44:20

19 semantics of how you use the term. 09:44:23

20 Q. So whether we use the term "sequence 09:44:27

21 error" or "sequencing error," the upshot is the 09:44:33

22 results -- strike that. 09:44:40

33

1 So whether we use "sequence error" or 09:44:43
2 "sequencing error," the upshot is the resulting 09:44:52
3 data analyzed by someone like yourself is 09:44:54
4 incorrect regardless of where it arose during the 09:45:02
5 sequencing process. Is that fair? 09:45:07

6 MR. BROUGHAN: Object to form. 09:45:10

7 **A. It's still an error.** 09:45:11

8 Q. Errors are errors no matter where in the 09:45:18
9 sequencing process they arose. Fair? 09:45:21

10 **A. Sure.** 09:45:23

11 Q. Okay. This comes up a lot throughout this 09:45:29
12 proceeding. You're familiar with the term 09:46:43
13 "barcode" in the context of genome sequencing in 09:46:46
14 the analysis. Correct? 09:46:48

15 **A. Yes.** 09:46:49

16 Q. If you have a barcode unique to each 09:46:50
17 target in a starting sample and you know what the 09:47:01
18 sequence is for a given target before 09:47:05
19 amplification, could you use the barcode and your 09:47:07
20 knowledge or information about the sequence itself 09:47:12
21 to determine whether or not there's an error in 09:47:14
22 the sequence after amplification? 09:47:17

1 **A. I'm sorry. You've got to -- that's a long** 09:47:18
2 **question. You got to say that again.** 09:47:24

3 Q. Yeah. Sure. If you have a barcode unique 09:47:25
4 to each target in the starting sample and you know 09:47:29
5 what the sequence is for a given target before you 09:47:33
6 begin amplification, could you use the barcode and 09:47:37
7 the information about that starting sequence to 09:47:42
8 determine whether there was a sequence error that 09:47:46
9 arose after amplification? 09:47:49

10 MR. BROUGHAN: Objection to form. 09:47:51

11 **A. I think there would be a lot of steps in** 09:48:00
12 **the process you just described, so I'm not going** 09:48:02
13 **to be able to give you a yes-or-no answer to that** 09:48:04
14 **question.** 09:48:06

15 Q. Absolutely. And I want to walk through 09:48:07
16 those steps. 09:48:10

17 **A. Sure.** 09:48:10

18 Q. So Step 1, how would you determine whether 09:48:11
19 or not there was a sequence error that arose 09:48:16
20 during amplification using a barcode and knowledge 09:48:20
21 of the starting sequence? 09:48:25

22 MR. BROUGHAN: Object to form. 09:48:33

35

1 **A. Well, some of those processes are** 09:48:34
2 **described in the prior art we considered here** 09:48:41
3 **where you use the barcode or the tag to bin** 09:48:45
4 **sequences together that share the same barcode.** 09:49:00

5 **Then you could -- you essentially compare** 09:49:07
6 **the -- all the individual sequence reads to try to** 09:49:13
7 **determine if there's any difference in any of them** 09:49:20
8 **relative to the rest of them, that deviate from** 09:49:29
9 **what the, you know, reference sequence would be.** 09:49:37

10 **Q. Okay. So given knowledge of the original** 09:49:39
11 **sequence plus a barcode, you could use those two** 09:49:47
12 **pieces of information to compare individual** 09:49:52
13 **sequence reads to determine if there's a** 09:49:57
14 **difference that deviates from what the reference** 09:50:01
15 **sequence was?** 09:50:07

16 **MR. BROUGHAN: Object to form.** 09:50:10

17 **A. I don't know what you mean by "knowledge** 09:50:10
18 **of the original sequence."** 09:50:22

19 **You could group together the reads with** 09:50:23
20 **the barcodes and then look at the sequence** 09:50:26
21 **attached to those barcodes to determine if there** 09:50:32
22 **were miscalls or bases that look like errors** 09:50:37

36

1 **relative to the rest of the reads that are grouped** 09:50:46

2 **together.** 09:50:49

3 Q. Okay. Are you familiar with the term 09:50:49

4 called "genome resequencing"? 09:51:05

5 **A. Say it again.** 09:51:08

6 Q. Sorry. Are you familiar with the term 09:51:08

7 called "genome resequencing"? 09:51:11

8 **A. Yes.** 09:51:13

9 Q. What is genome resequencing, in your 09:51:18

10 knowledge? 09:51:26

11 **A. It's a term we use to describe experiments** 09:51:26

12 **when you're sequencing genomes where you've** 09:51:38

13 **already -- where you already have a reference, as** 09:51:41

14 **opposed to de novo sequencing where -- de novo** 09:51:48

15 **sequencing is when you are, like, sequencing an** 09:51:52

16 **organism for the first time and you don't know how** 09:51:57

17 **the reads would line up to make a reference.** 09:52:00

18 **So "resequencing" is a general term of,** 09:52:03

19 **like, I'm sequencing samples that I already have a** 09:52:06

20 **reference for.** 09:52:09

21 Q. Got it. So just for the record, genome 09:52:10

22 resequencing in the traditional understanding 09:52:16

37

1 would be the process of sequencing a population of 09:52:18
2 samples in comparison to a reference genome. Is 09:52:24
3 that fair? 09:52:27

4 **A. Yes.** 09:52:30

5 Q. Okay. Can genome be -- strike that. 09:52:32

6 Can genome resequencing be used to detect 09:52:44
7 genetic variations in the population compared to 09:52:49
8 the reference genome? 09:52:52

9 **A. Yes.** 09:52:53

10 Q. In order to accurately perform genome 09:53:02
11 resequencing, you would have to sequence the 09:53:10
12 entire amplicon from the reference genome. Is 09:53:12
13 that fair? 09:53:16

14 **A. I don't know what you mean.** 09:53:16

15 Q. Okay. Strike that. 09:53:18

16 When performing genome resequencing, you 09:53:28
17 would sequence the entire amplicon and compare it 09:53:30
18 to a reference genome? 09:53:33

19 MR. BROUGHAN: Object to form. 09:53:38

20 **A. I don't know what you mean by "entire** 09:53:39
21 **amplicon," so it's kind of throwing me off. So I** 09:53:53
22 **don't know how to answer your question.** 09:53:57

1 Q. I guess what I'm trying to ask is, if you 09:53:58
2 want to compare -- let's say we're trying to 09:54:03
3 detect genetic variations, right, compared to the 09:54:07
4 reference genome. I'd want to sequence the 09:54:10
5 entirety of the equivalent of that reference 09:54:12
6 genome in my, you know -- in my samples, right, so 09:54:15
7 that I can compare all sets to all sets? 09:54:19

8 A. No. 09:54:22

9 Q. Okay. 09:54:23

10 A. That doesn't make sense, what you're 09:54:24
11 saying. 09:54:25

12 Q. Okay. 09:54:26

13 A. You wouldn't sequence the entire genome. 09:54:26
14 You can sequence a gene, right, and compare it to 09:54:30
15 the reference genome or to other samples and say 09:54:33
16 is there a difference here. 09:54:38

17 So it doesn't have to be an entire genome. 09:54:40
18 That's why your question is throwing me off. 09:54:42

19 Q. All right. It was the "you would have to" 09:54:43
20 that was incorrect there? You could, but you 09:54:47
21 don't have to. Is that fair to say? 09:54:49

22 A. You could sequence the entire genome. 09:54:51

1	Yes. We do it all the time.	09:54:53
2	Q. Apologies. Thank you for the correction.	09:54:54
3	So when performing genome resequencing,	09:54:59
4	you could sequence the entire amplicon and compare	09:55:02
5	it to the entirety of the reference genome.	09:55:04
6	Correct?	09:55:07
7	A. So there, "the entirety of the amplicon"	09:55:09
8	is throwing me off, because I don't know what you	09:55:12
9	mean by "the entirety of the amplicon."	09:55:14
10	Q. Okay.	09:55:16
11	A. You can sequence an amplicon and compare	09:55:16
12	it to the genome.	09:55:19
13	Q. Okay. Let's break it down differently,	09:55:20
14	then.	09:55:33
15	You could sequence a specific portion or	09:55:34
16	target region of a genome and compare it to the	09:55:38
17	specific corresponding region of the reference	09:55:41
18	genome. Is that a better way of putting it?	09:55:44
19	A. Yeah.	09:55:46
20	Q. Okay. In the process of making that	09:55:48
21	comparison, would a POSITA also be able to detect	09:55:53
22	any sequence errors?	09:55:56

40

1 MR. BROUGHAN: Object to form. 09:56:02

2 A. Detecting errors could be a part of your 09:56:03

3 analysis, but it's just part of the analytic 09:56:13

4 workflow. 09:56:17

5 Q. Got it. So genome resequencing is a 09:56:18

6 process by which a POSITA could detect sequence 09:56:21

7 errors if that was a part of that POSITA's 09:56:28

8 analytic workflow. Fair? 09:56:31

9 MR. BROUGHAN: Object to form. 09:56:35

10 A. I think it would be better to say that 09:56:36

11 error detection can be part of the workflow of 09:56:49

12 analyzing genome sequencing. 09:56:53

13 The way you put it kind of was the other 09:56:55

14 way around, which didn't make much sense. 09:56:57

15 Q. Okay. I'm fine with that. Let me clear 09:57:03

16 it up for the record, then. 09:57:06

17 Error detection can be part of the 09:57:06

18 workflow of -- strike that. 09:57:08

19 Error detection can be part of the 09:57:11

20 analytic workflow of genome resequencing. 09:57:14

21 Correct? 09:57:16

22 A. That's correct. 09:57:17

41

1 Q. Okay. Is there a difference between an 09:57:17
2 error and a point mutation? 09:58:14

3 A. Yes. 09:58:16

4 Q. What is that difference? 09:58:24

5 A. Well, generally, when we say "point 09:58:26
6 mutation" we're talking about a real mutation in 09:58:31
7 the DNA where there's supposed to be an A, but a 09:58:39
8 gene has a G. 09:58:45

9 And so that might just be an SNP or it 09:58:47
10 might be a -- it might be a disease-causing 09:58:50
11 mutation. But that's a point mutation, meaning it 09:58:55
12 happens at one position. 09:58:58

13 An error could happen at one position, 09:59:00
14 too, but they're not the same. 09:59:05

15 Q. Right. A mutation is not necessarily an 09:59:08
16 error. Correct? 09:59:12

17 A. A mutation can be a real biological event. 09:59:13
18 Yes. Correct. 09:59:18

19 Q. And so if you're performing an analysis 09:59:19
20 for mutation, you're not always correcting for 09:59:23
21 errors. Correct? 09:59:27

22 A. Can you say that again? 09:59:28

42

1 Q. Sure. You do not understand mutation 09:59:34

2 analysis to always be correcting for errors. 09:59:38

3 Right? 09:59:41

4 MR. BROUGHAN: Object to form. 09:59:41

5 A. I can't say "always." Should. But 09:59:43

6 someone might perform an analysis where you're not 09:59:52

7 correcting for errors. I don't know. I can't 09:59:55

8 tell you what everybody does. You can't say 09:59:57

9 "always." 10:00:00

10 Q. Right. Because not every mutation is an 10:00:00

11 error. We've already established that. Right? 10:00:03

12 A. Some mutations are real biological events. 10:00:06

13 They're not errors. 10:00:09

14 Q. So if you're performing an analysis to 10:00:10

15 detect mutation, that doesn't necessarily mean 10:00:12

16 that you are correcting for errors? 10:00:14

17 A. Ideally, you would correct for errors so 10:00:21

18 you could tell real biological events from an 10:00:23

19 error or an artifact, but those are different 10:00:27

20 concepts. 10:00:32

21 Q. Got it. 10:00:33

22 MR. WUESTE: Let's take a break. 10:00:46

43

1 THE VIDEOGRAPHER: The time is 10:00:48

2 10:00 o'clock. We're off the record. 10:00:49

3 (Recess, 10:00 a.m. to 10:14 a.m.) 10:01:54

4 THE VIDEOGRAPHER: Time is 10:14. We're 10:14:56

5 back on the record. 10:15:05

6 BY MR. WUESTE: 10:15:06

7 Q. Welcome back, Dr. Gabriel. 10:15:07

8 A. Thank you. 10:15:09

9 Q. This is kind of a rehash of stuff we've 10:15:10

10 already done, but just to be clear, agree or 10:15:16

11 disagree: Errors can be introduced in the 10:15:18

12 amplification and sequencing steps of a genomic 10:15:22

13 analysis workflow. Correct? 10:15:27

14 A. Yes. 10:15:28

15 Q. An amplification -- strike that. 10:15:31

16 During an amplification, a nucleotide 10:15:40

17 could be incorrectly incorporated in the 10:15:43

18 complementary strand, leading to error. Correct? 10:15:45

19 A. Yes. 10:15:48

20 Q. Okay. During sequencing, a nucleotide 10:15:50

21 could be incorrectly incorporated in the 10:16:00

22 complementary strand, leading to error. Correct? 10:16:02

1	A. Yes.	10:16:05
2	Q. Okay. Conversely, if the sequencing	10:16:09
3	machine misreads the sequence, that could lead to	10:16:15
4	error. Correct?	10:16:19
5	A. Yes.	10:16:19
6	Q. Okay. In both of those cases, during the	10:16:22
7	amplified -- strike that.	10:16:29
8	In both of those instances, the amplified	10:16:30
9	target nucleic acids would have sequences that are	10:16:36
10	different from the original target nucleic acid.	10:16:40
11	Correct?	10:16:43
12	MR. BROUGHAN: Object to form.	10:16:44
13	A. If errors are introduced, then yes.	10:16:45
14	Q. And those errors could be introduced	10:17:02
15	during the amplification step. Correct?	10:17:04
16	A. Yes.	10:17:06
17	Q. And those errors could be introduced	10:17:08
18	during the sequencing step. Correct?	10:17:10
19	A. Yes.	10:17:11
20	Q. Okay. I kind of want to walk through this	10:17:15
21	in a little bit more detail to better understand	10:17:22
22	it. I'm going to hand you a diagram.	10:17:25

45

1 Okay. On the left side of this diagram -- 10:17:52

2 MR. BROUGHAN: Sorry, Counsel. Is this 10:17:54

3 marked as an exhibit? 10:17:56

4 MR. WUESTE: Not yet. 10:17:57

5 MR. BROUGHAN: You're not going to mark 10:17:58

6 it? Okay. 10:17:59

7 MR. WUESTE: It will be, but after we go 10:18:00

8 through some steps, if that's okay. 10:18:02

9 MR. BROUGHAN: Okay. 10:18:03

10 Q. On the left side of the diagram I handed 10:18:06

11 you, we've got the original target nucleic acid 10:18:10

12 column. Do you see that? 10:18:13

13 **A. Yes.** 10:18:14

14 Q. In this one we've got a very, very simple 10:18:16

15 one. I have two original target nucleic acids, 10:18:22

16 one with an "A" and one with a "C." Do you see 10:18:25

17 that? 10:18:27

18 **A. I do.** 10:18:28

19 Q. I want to introduce a barcode to each of 10:18:28

20 those targets. So target Nucleic Acid A has 10:18:31

21 Barcode 1, and target Nucleic Acid C has 10:18:37

22 Barcode 2. Are you with me? 10:18:41

46

1 A. Uh-hmm. 10:18:42

2 Q. Now, I want to amplify those targets. Do 10:18:42

3 you see the amplification step? 10:18:48

4 But in this experiment, unfortunately, 10:18:50

```
5 we're going to have an error during the first 10:18:53
```

6 round of amplification. Okay? 10:18:56

A. Yes.

8 Q. And so in this amplification step, one 10:18:59

9 nucleotide in the target nucleic acid was 10:19:06

10 incorrectly incorporated in the complementary 10:19:09

```
11 strand during amplification, leading to an error. 10:19:13
```

12 Okay? 10:19:16

13 **A. Where are you referring to on the diagram?** 10:19:16

14 Q. I'm just setting up the scenario. All 10:19:25

```
15    right?                                     10:19:28
```

A. Okay.

17 Q. So in our experiment, during amplification 10:19:29

18 we incorrectly incorporate a nucleotide in the 10:19:32

19 complementary strand, leading to an error. Okay? 10:19:35

A. Okay.

21 MR. BROUGHAN: Object to form. 10:19:39

22 Q. Can I ask you to please write 10:19:40

47

1 "amplification error" underneath that 10:19:45

2 amplification arrow on the diagram? 10:19:49

3 **A. You want me to write the words** 10:19:54

4 **"amplification error"?** 10:19:56

5 Q. Yes, please. 10:19:57

6 THE WITNESS: Is that okay? 10:19:59

7 MR. BROUGHAN: Sure. 10:20:01

8 Q. All right. So in the initial round or 10:20:07

9 even in the later round of amplification, we're 10:20:10

10 going to do multiple rounds of amplification so we 10:20:13

11 get more results. Fair? 10:20:16

12 MR. BROUGHAN: Object to form. 10:20:19

13 **A. More copies -- okay. Yes.** 10:20:20

14 Q. Because of our amplification error, one of 10:20:24

15 the amplified product sequences has a "T" instead 10:20:29

16 of an "A" for the original target sequence marked 10:20:33

17 with Barcode 1. Do you see that? 10:20:37

18 **A. I do.** 10:20:40

19 Q. But because amplification can be random, 10:20:40

20 I've only got one wrong or erroneous amplified 10:20:46

21 target out of my four total amplified target 10:20:50

22 products for the sequence with Barcode 1. Do you 10:20:54

48

1 see that? 10:20:58

2 MR. BROUGHAN: Object to form. 10:20:59

3 **A. That's what your finger has.** 10:21:00

4 Q. But Barcode 1 is still applied to all four 10:21:02

5 of the amplified products because it was applied 10:21:06

6 before amplification? That's how this works. 10:21:08

7 Right? 10:21:11

8 MR. BROUGHAN: Object to form. 10:21:11

9 **A. That's what's depicted here.** 10:21:12

10 Q. Okay. So in this instance, the error 10:21:15

11 containing amplified product with a "T" would have 10:21:19

12 the correct tag but the incorrect target nucleic 10:21:22

13 acid sequence. Right? 10:21:25

14 MR. BROUGHAN: Object to form. 10:21:31

15 **A. Yes.** 10:21:34

16 Q. And that happens because the error was 10:21:35

17 introduced during amplification, right, after 10:21:39

18 we've incorporated the barcode? 10:21:41

19 MR. BROUGHAN: Object to form. 10:21:46

20 **A. Yes.** 10:21:47

21 Q. Can you please circle the amplified 10:21:47

22 product that has the erroneous "T." 10:21:50

49

1 Now, let's say I want to authenticate the 10:22:02
2 product sequences. Okay? 10:22:04

3 MR. BROUGHAN: Object to form. 10:22:07

4 **A. I don't know what you mean.** 10:22:08

5 Q. I want to make -- I want to check them 10:22:09
6 against the reference sequence. Fair? 10:22:13

7 MR. BROUGHAN: Object to form. 10:22:17

8 **A. Okay.** 10:22:18

9 Q. Because I am looking at both the sequence 10:22:25
10 itself and the barcode, then I know that that 10:22:27
11 first amplified product with the "T" is wrong 10:22:32
12 because the reference sequence had the "A." 10:22:35
13 Correct? 10:22:37

14 MR. BROUGHAN: Object to form. 10:22:43

15 **A. No, not necessarily.** 10:22:44

16 Q. Why not? 10:22:45

17 **A. Well, just by the different counts, you** 10:22:49
18 **could know that the "T" was -- and again, this is** 10:23:03
19 **just a -- this is not how a real result would be** 10:23:09
20 **with only, like, four copies.** 10:23:14

21 **But again, depending on how you analyze** 10:23:15
22 **the data, you can look at the -- you can look at** 10:23:18

1 **these reads themselves and understand that "T"** 10:23:20
2 **is -- there's one outlier "T" where you have a** 10:23:25
3 **bunch of "As".** 10:23:28

4 Q. Right. But that's because I'm looking at 10:23:29
5 both the sequence and -- I have the sequence 10:23:31
6 information in my results. Right? And that's 10:23:33
7 what I'm looking at? 10:23:35

8 **A. That's what you're looking at, yeah.** 10:23:36

9 Q. Would you mind signing that, please. 10:23:39

10 MR. WUESTE: And now if we could mark that 10:23:46
11 as EX-2026. 10:23:48

12 (Exhibit EX-2026 marked for 10:23:50
13 identification) 10:24:12

14 Q. And now I'm going to hand you a second 10:24:12
15 diagram, and we're going to go through the same 10:24:14
16 process. Okay? 10:24:36

17 We start the same way, two original target 10:24:38
18 nucleic acids, one with an "A" and one with a "T" 10:24:41
19 on the left-hand side. Do you see that? 10:24:45

20 **A. One with an "A" and one with a "C." You** 10:24:47
21 **said "T."** 10:24:50

22 Q. You're absolutely right. Thank you for 10:24:51

1 the clarification. Okay. Let me rephrase. 10:24:52

2 We start the same way, two original target 10:24:55

3 nucleic acids, one with an "A" and one with a "C." 10:24:58

4 Do you see that? 10:25:01

5 **A. Uh-hmm.** 10:25:02

6 Q. And we're still introducing a barcode to 10:25:03

7 each of those targets. So target Nucleic Acid A 10:25:05

8 has Barcode 1. Do you see that? 10:25:10

9 **A. Yes.** 10:25:12

10 Q. Target Nucleic Acid C has Barcode 2? 10:25:13

11 **A. Yes.** 10:25:16

12 Q. And then we're going to have the same 10:25:17

13 amplification error. Okay? 10:25:21

14 **A. Okay.** 10:25:24

15 MR. BROUGHAN: Object to form. 10:25:24

16 Q. So once again, can you write 10:25:25

17 "amplification" -- strike that. 10:25:28

18 All right. Can you write "amplification 10:25:34

19 error" under the amplification arrow in this 10:25:38

20 diagram. 10:25:41

21 And once again, I want to authenticate the 10:25:51

22 product sequence. I want to compare it to the 10:25:53

1 reference genome. This time I'm going to look 10:25:55

2 just at the barcode alone and not the amplified 10:25:58

3 product sequence itself. Okay? 10:26:01

4 Using just the barcode alone, can you 10:26:03

5 please circle for me which amplified product has 10:26:05

6 the error. 10:26:08

7 MR. BROUGHAN: Object to form. 10:26:10

8 **A. But you know the sequence. When you do** 10:26:11

9 **the analysis, you know the sequence in these black** 10:26:16

10 **lines. You're just showing me black lines.** 10:26:19

11 **How am I going to circle the error?** 10:26:22

12 Q. So using just the barcode alone, you 10:26:24

13 cannot circle the error in this diagram. Correct? 10:26:27

14 MR. BROUGHAN: Object to form. 10:26:30

15 **A. Not if there's just black lines. But if** 10:26:31

16 **there were As, Gs, Cs, and Ts there, I imagine I** 10:26:34

17 **could.** 10:26:37

18 Q. Right. So using the barcode alone, you 10:26:37

19 cannot circle or identify the error? If you had 10:26:39

20 the sequence itself as well, you would be able to. 10:26:44

21 Is that correct? 10:26:48

22 MR. BROUGHAN: Object to form. 10:26:49

1 **A. Well, in your cartoon there's black lines.** 10:26:50

2 **So I don't understand how I -- this is not the** 10:26:58

3 **results of an experiment. This is a cartoon. So** 10:27:04

4 **obviously I can't circle one of these.** 10:27:07

5 **Q. Okay.** 10:27:09

6 **A. That's not how analysis happens.** 10:27:12

7 **Q. Right. When the information provided to** 10:27:14

8 **you is just the barcode alone, you cannot identify** 10:27:18

9 **the error?** 10:27:21

10 **MR. BROUGHAN: Objection to form.** 10:27:22

11 **A. Oh, no. I believe you can because you** 10:27:23

12 **have the sequence. You have the As, Gs, Cs,** 10:27:27

13 **and Ts.** 10:27:32

14 **Q. When the information provided to you is** 10:27:32

15 **just the barcode alone, you cannot identify which** 10:27:33

16 **sequence has an error resulting from an** 10:27:37

17 **incorrectly incorporated nucleotide during** 10:27:40

18 **amplification?** 10:27:42

19 **MR. BROUGHAN: Objection to form.** 10:27:43

20 **A. That's not right. You never just are** 10:27:44

21 **analyzing the -- well, there's certain types of** 10:27:49

22 **experiments called "counting applications" where** 10:27:56

1 **you can analyze the barcode to understand how many** 10:27:59
2 **molecules are there. But that's aside. That's** 10:28:01
3 **not what we're talking about here.** 10:28:04

4 **The things we're talking about here,** 10:28:05
5 **you're using the barcode to make the bins to** 10:28:07
6 **make -- to line up sequences that have the same** 10:28:11
7 **barcode. And then you can look at those** 10:28:16
8 **sequences -- they're not black lines, they're** 10:28:18
9 **sequences -- to find out if there's an error.** 10:28:20

10 **Q. In the scenario where you would be using** 10:28:24
11 **just the barcode alone, such as a counting** 10:28:28
12 **application -- is that what you said?** 10:28:31

13 **A. Uh-hmm.** 10:28:33

14 **Q. So in the scenario in which you're using** 10:28:33
15 **just the barcode alone, like in a counting** 10:28:37
16 **application, you would not be able to identify** 10:28:39
17 **error. Correct?** 10:28:41

18 **A. You wouldn't be trying to.** 10:28:42

19 **MR. BROUGHAN: Objection to form.** 10:28:43

20 **A. It's a different type of experiment.** 10:28:44

21 **That's a different application. Yeah.** 10:28:46

22 **Q. Got it. Can you sign that one as well,** 10:28:47

55

1 please. 10:28:50

2 MR. WUESTE: And then, ma'am, would you 10:28:58

3 please mark this EX-2027. 10:29:00

4 (Exhibit EX-2027 marked for 10:29:11

5 identification) 10:29:31

6 Q. I'm handing you what has previously been 10:29:31

7 marked as EX-1005. 10:29:33

8 (Previously marked Exhibit EX-1005) 10:29:35

9 Q. EX-1005 is the first declaration you 10:29:38

10 submitted in this inter partes review proceeding. 10:29:48

11 Correct? 10:29:51

12 A. Correct. 10:29:52

13 Q. And then if you pull out EX-1065 as well. 10:29:52

14 It should be still in front of you. 10:29:58

15 A. Yes. 10:30:01

16 Q. EX-1065 is the reply declaration? 10:30:01

17 A. That's right. 10:30:07

18 Q. Your first and second declarations 10:30:07

19 together, EX-1005, EX-1065, include all of your 10:30:16

20 opinions in this IPR proceeding. Correct? 10:30:20

21 A. That's right. 10:30:25

22 Q. As of October 10th, 2025, the date you 10:30:25

56

1 signed your reply declaration, you had no 10:30:32
2 additional opinions that were not included in 10:30:35
3 either your first or second declarations. 10:30:38
4 Correct? 10:30:39

5 **A. No.** 10:30:40

6 Q. Okay. Do you still stand by all the 10:30:43
7 opinions in both of your declarations? 10:30:46

8 **A. I do.** 10:30:48

9 Q. What did you do to prepare for your 10:30:48
10 deposition today? 10:30:52

11 MR. BROUGHAN: I'll caution you not to 10:30:54
12 reveal the substance of communications with 10:30:56
13 counsel. Subject to that, you may answer. 10:30:58

14 **A. I reviewed my previous declarations. I** 10:30:59
15 **met with the attorneys, looked at the prior art** 10:31:10
16 **again.** 10:31:15

17 Q. When you say you met with the attorneys, 10:31:17
18 without getting into the substance, what are the 10:31:19
19 names of the attorneys you met with? 10:31:21

20 **A. Tom and Marcus.** 10:31:23

21 Q. And how long did you meet with Tom and 10:31:24
22 Marcus? 10:31:27

1 **A. A few hours over the past week.** 10:31:27

3 **A. A couple phone calls and met in person** 10:31:40

5 Q. Did you speak with anyone other than the 10:31:44

7 deposition today? 10:31:50

9 Q. And have you spoken with anyone from 10:31:52

```
11      matter?                                     10:31:57
```

13 Q. You mentioned reviewing your previous 10:31:59

15 preparation for your deposition today. Correct? 10:32:11

17 Q. Did you review any other documents? 10:32:13

18 **A. I looked at a few parts of the declaration** 10:32:20

19 of the opposing expert witness and a few parts of 10:32:28

20 the transcript of that deposition. 10:32:33

21 Q. So for clarity, in preparing for today's 10:32:38

22 deposition you reviewed your previous declaration, 10:32:40

1 the prior art, portions of Dr. Pugliese's 10:32:42
2 declaration, and portions of Dr. Pugliese's 10:32:47
3 deposition transcript. Correct? 10:32:51

4 **A. That's right.** 10:32:52

5 Q. Anything else? 10:32:53

6 **A. No.** 10:32:53

7 Q. In your work on this matter, have you 10:33:04
8 reviewed any documents other than the exhibits 10:33:06
9 that are listed as "Materials Considered" in your 10:33:07
10 declaration? Actually, I'll strike that. That's 10:33:10
11 a bad question. 10:33:17

12 In your work in this matter, have you 10:33:18
13 reviewed any documents other than the exhibits 10:33:20
14 listed as "Materials Considered" in your first 10:33:21
15 declaration and second declaration? 10:33:24

16 **A. I don't think so.** 10:33:25

17 Q. Okay. And I did not see this in your 10:33:30
18 materials considered, but just to confirm, you did 10:33:33
19 not review any emails between the inventors of the 10:33:37
20 '730 patent and their prosecution attorneys in the 10:33:41
21 preparation of the application that became the 10:33:47
22 '730 patent. Correct? 10:33:49

59

A. No.

2 Q. Okay. If you could please turn to 10:33:51

3 EX-1005 -- 10:34:02

A. Yes.

5 Q. -- your opening declaration. And I'd like 10:34:03

6 you to turn to page 34, the section titled 10:34:08

7 "Construction of Terms Using the '730 Patent 10:34:24

8 Claims." 10:34:26

9 **A. Yes.**10:34:29

10 Q. Feel free to take a look over the next 10:34:29

11 couple of pages. 10:34:32

12 My question is, that section beginning on 10:34:34

13 page 34, "Construction of Terms Used in the '730 10:34:39

14 Patent Claims," contains the entirety of the claim 10:34:42

```
15 constructions you applied -- opined on and applied 10:34:46
```

16 in your opinions mapping the prior art to the 10:34:51

17 claims of the '730 patent. Correct? 10:34:53

18 **A. Yes. That's my recollection. Again, I** 10:34:54

19 didn't review this declaration in great detail. I 10:35:30

20 in more detail reviewed the reply declaration. 10:35:40

21 I'm happy to talk about it. 10:35:43

22 Q. Sure. Just to confirm, your reply 10:35:44

60

1 declaration does not contain a claim construction 10:35:46

2 section. Correct? 10:35:50

3 **A. It does not.** 10:35:50

4 Q. Okay. In your original declaration, you 10:35:51

5 opined on applied constructions for three sets of 10:35:55

6 terms. Correct? The first one, appearing on 10:35:59

7 page 34, you opined on and applied a construction 10:36:05

8 for the terms "set of differentiator tags" and 10:36:09

9 "set of unique differentiator tags." Correct? 10:36:15

10 **A. Yes.** 10:36:18

11 Q. And then if you turn to page 37, 10:36:18

12 Subsection 2. 10:36:24

13 **A. Yes.** 10:36:26

14 Q. You opined on and applied a construction 10:36:26

15 for the term "locus of origin." Correct? 10:36:31

16 **A. Yes.** 10:36:34

17 Q. And then moving on to page 40, there you 10:36:35

18 opined on and applied a construction for 10:36:44

19 "consensus base call." Correct? 10:36:47

20 **A. Yes.** 10:36:48

21 Q. And then that section ends on page 41 -- 10:36:49

22 strike that. 10:36:55

1	That section ends on page 42. Correct?	10:36:55
2	A. It does.	10:36:59
3	Q. Okay. Those are the only three terms or	10:37:00
4	sets of terms for which you applied a	10:37:03
5	construction?	10:37:07
6	MR. BROUGHAN: Object to form.	10:37:08
7	A. That's right.	10:37:09
8	Q. You did not opine on a construction of the	10:37:10
9	term "collapsing" in the context of the '730	10:37:17
10	patent in either of your declarations. Correct?	10:37:22
11	Strike that.	10:37:25
12	You did not opine on a construction of the	10:37:26
13	term "collapsing" in the context of the '730	10:37:28
14	patent in your original declaration, EX-1005.	10:37:32
15	Correct?	10:37:38
16	MR. BROUGHAN: Object to form.	10:37:38
17	A. I don't believe I was asked to.	10:37:39
18	Q. Okay. And you did not opine on the	10:37:42
19	construction of the term "error" in the context of	10:37:45
20	the '730 patent in your original declaration,	10:37:49
21	EX-1005. Correct?	10:37:54
22	A. Again, I don't think I was asked to.	10:37:55

1 Q. And because you weren't asked to, you did 10:37:58
2 not apply a different construction for the term 10:38:01
3 "error" in mapping the prior art to the claims of 10:38:05
4 the '730 patent. Correct? 10:38:07

5 MR. BROUGHAN: Object to form. 10:38:09

6 **A. Different than what?** 10:38:10

7 Q. Fair. Because you weren't asked to, you 10:38:11
8 did not apply a construction for the term "error" 10:38:17
9 in mapping the prior art to the claims of the '730 10:38:22
10 patent. Correct? 10:38:24

11 MR. BROUGHAN: Object to form. 10:38:24

12 **A. I supplied my understanding of the word,** 10:38:25
13 **not a construction as written down there.** 10:38:32

14 Q. Your understanding of the word would be 10:38:37
15 the plain and ordinary meaning. Correct? 10:38:39

16 **A. I think so. Yeah.** 10:38:40

17 Q. Okay. You did not opine on -- strike 10:38:41
18 that. 10:38:45

19 You did not opine on a construction of the 10:38:45
20 term "bias" in the context of the '730 patent in 10:38:49
21 your original declaration, EX-1005. Correct? 10:38:53

22 **A. Yeah. Again, I wasn't asked to.** 10:38:58

1 Q. And because you weren't asked to, you did 10:38:59
2 not apply a construction of the word -- term 10:39:02
3 "bias" to the prior art in your original 10:39:08
4 declaration, EX-1005. Correct? 10:39:11

5 A. That's right. 10:39:13

6 Q. Okay. And I realize that we didn't do 10:39:13
7 this for the first one, so I'm just going to ask 10:39:17
8 that question at the end. 10:39:19

9 Because you were not asked to, you did not 10:39:28
10 apply a construction of the term "collapsing" to 10:39:31
11 the prior art in your original declaration, 10:39:35
12 EX-1005. Correct? 10:39:41

13 MR. BROUGHAN: Object to form. 10:39:43

14 A. Yes. 10:39:44

15 Q. I want to turn to Paragraph 239 of your 10:39:44
16 original declaration, EX-1005. 10:40:10

17 A. Okay. 10:40:19

18 Q. Paragraph 239 is the first paragraph in 10:40:20
19 the section titled "Overview of McCloskey." Do 10:40:29
20 you see that? 10:40:33

21 A. Yes. 10:40:33

22 Q. And I'd like to turn your attention to the 10:40:34

1 second sentence in Paragraph 239, reading 10:40:39

2 "McCloskey explains that the tags allow its method 10:40:44

3 to identify and correct errors and bias stemming 10:40:48

4 from amplification including skewing." Do you see 10:40:52

5 that? 10:40:55

6 **A. Yes.** 10:40:56

7 Q. Okay. You still agree with that opinion. 10:40:58

8 Correct? 10:41:08

9 **A. Yes.** 10:41:09

10 Q. Okay. And then at the bottom, the last 10:41:11

11 sentence of Paragraph 239 in your original 10:41:17

12 declaration beginning "Additionally" -- do you see 10:41:21

13 that? 10:41:24

14 **A. Yes.** 10:41:24

15 Q. You state, "Additionally, McCloskey 10:41:25

16 teaches that its method also" -- strike that. 10:41:30

17 You state, "Additionally, McCloskey 10:41:35

18 teaches that its method also allows for the 10:41:38

19 analysis of mutations arising during PCR 10:41:42

20 amplification," and then you cite to McCloskey, 10:41:44

21 and then you have a parenthetical stating "PCR 10:41:46

22 errors." Do you see that? 10:41:50

65

A. I do.

2 Q. Do you still agree with that? 10:41:53

A. I do.

4 Q. Mutations arising during PCR amplification 10:41:54

5 are not always errors. Correct? 10:42:01

6 A. I'm sorry. Could you say that again? I 10:42:03

```
7      didn't --
```

8 Q. Sure. Tripping over my own tongue. 10:42:05

```
9    Apologies for that.  I'll try again.                                10:42:08
```

10 Mutations arising during PCR amplification 10:42:10

```
11 are not always errors. Correct? 10:42:13
```

12 MR. BROUGHAN: Object to form. 10:42:16

13 A. Again, I didn't understand your question. 10:42:17

14 **Say that again.** 10:42:21

15 Q. A mutation that arises during PCR 10:42:22

```
16 amplification may not necessarily be an error.      10:42:27
```

17 Correct? 10:42:30

18 MR. BROUGHAN: Object to form. 10:42:31

19 A. What would it be, then? I don't 10:42:32

20 understand your question. 10:42:42

21 Q. Okay. 10:42:42

22 A. The use of the word "mutation" there is 10:42:43

1 different than the -- we talked about point 10:42:51

2 mutations earlier that are biological mutations. 10:42:54

3 And so the use of that word is different, but -- 10:42:59

4 Q. Okay. 10:43:02

5 A. If something happened during PCR that 10:43:03

6 wasn't the real representation or the real base, 10:43:05

7 it's an error. 10:43:07

8 Q. Okay. I'd like to move now to your reply 10:43:08

9 declaration, but keep the original one in front of 10:43:21

10 you, if you don't mind. 10:43:23

11 A. Okay. 10:43:24

12 Q. If you'd turn to page 2 of your reply 10:43:25

13 declaration, EX-1065. And just looking at the 10:43:35

14 subheading, it's your opinion that "McCloskey 10:43:46

15 discloses correcting for errors or bias introduced 10:43:50

16 during said workflow by collapsing 10:43:55

17 target:differentiator tag combinations observed 10:43:58

18 more than once into a single count." Correct? 10:44:01

19 A. Yes. 10:44:04

20 Q. And if you go down into that section 10:44:09

21 beginning at Paragraph 8, it's your opinion that 10:44:12

22 "McCloskey discloses collapsing the combination of 10:44:18

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1 the barcode and target nucleic acid into a single 10:44:22
2 count because McCloskey supposedly identifies 10:44:26
3 target:barcode combinations that appear more than 10:44:31
4 once in the amplified sample using the barcode 10:44:35
5 alone." Correct? 10:44:37

6 MR. BROUGHAN: Object to form. 10:44:38

7 **A. Yes. She uses the barcode to identify the 10:44:52**
8 **redundant sequences and collapses them into a 10:44:56**
9 **single count. 10:44:58**

10 Q. Okay. And just to confirm, McCloskey 10:44:59
11 identifies -- strike that. 10:45:04

12 In your opinion, McCloskey identifies 10:45:06
13 target:barcode -- strike that. 10:45:11

14 In your opinion, McCloskey identifies 10:45:15
15 target:barcode combinations using the barcode 10:45:19
16 alone. Correct? 10:45:23

17 **A. Yes. 10:45:24**

18 Q. If you go down to Paragraph 9 of your 10:45:42
19 reply declaration, the first sentence there, you 10:46:09
20 state, "McCloskey explains that when use of the 10:46:14
21 barcodes is to identify redundant copies of each 10:46:17
22 target:barcode combination to correct for 10:46:21

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1 amplification bias, which allows accurately 10:46:25
2 counting the number of nucleic acids in the 10:46:29
3 original sample." Correct? 10:46:32

4 **A. Yes.** 10:46:33

5 Q. And then you go on to quote from 10:46:40
6 McCloskey, stating that "McCloskey uses the 10:46:44
7 barcodes to identify redundant sequences and 10:46:46
8 quantify accurately the proportion of cells 10:46:50
9 carrying a particular sequence variant by counting 10:46:54
10 only distinctly tagged sequences." Correct? 10:46:57

11 **A. Yes.** 10:46:59

12 Q. And it's your opinion that when McCloskey 10:47:01
13 describes counting only distinctly tagged 10:47:07
14 sequences, that allegedly discloses the collapsing 10:47:10
15 limitation of the '730 patent. Right? 10:47:15

16 MR. BROUGHAN: Object to form. 10:47:20

17 **A. Yes.** 10:47:21

18 Q. Okay. You're being handed what's 10:47:28
19 previously been marked as EX-1012. 10:47:40

20 (Previously marked Exhibit EX-1012) 10:47:43

21 Q. EX-1012 is the reference to McCloskey. 10:47:48
22 Correct? 10:47:57

69

A. Yes.

2 Q. Now, you point to Paragraph 0093 of 10:47:58

3 McCloskey as the support for this opinion of 10:48:05

4 yours. Correct? 10:48:08

A. Yes.

6 Q. And Paragraph 0093 in McCloskey is under 10:48:12

```
7 the heading "Example 6." Is that right? 10:48:20
```

8 **A. It is.**10:48:23

9 Q. Okay. At the bottom of Paragraph 0093, 10:48:24

```
10  there's a sentence that begins, "Each genomic 10:48:42
```

```
11  fragment." Do you see that? It's the second 10:48:44
```

```
12 sentence from the bottom. 10:48:50
```

13 **A. I see that. Yes.** 10:48:57

14 Q. Okay. And that's the sentence that's the 10:48:58

15 source of your statement regarding how McCloskey 10:49:02

```
16 allegedly counts only distinctly tagged sequences. 10:49:09
```

17 Correct? 10:49:12

18 MR. BROUGHAN: Object to form. 10:49:13

19 **A. That's what's quoted in Paragraph 9 of the** 10:49:15

```
20      reply declaration.                                     10:49:19
```

21 Q. Okay. That sentence reads, "Each genomic 10:49:20

22 fragment is marked prior to amplification, 10:49:48

1 allowing us to identify contaminant and redundant 10:49:52
2 sequences and to quantify accurately the 10:49:56
3 proportion of cells carrying a particular sequence 10:49:58
4 variant by counting only distinctly tagged 10:50:01
5 sequences." Correct? 10:50:04

6 **A. That's what it says.** 10:50:05

7 Q. Okay. And was McCloskey one of the prior 10:50:07
8 art references you reviewed in preparation for 10:50:11
9 today's deposition? 10:50:13

10 **A. Yes.** 10:50:14

11 Q. Okay. When McCloskey discusses tagging, 10:50:16
12 it's describing something that it calls the second 10:50:24
13 sequence. Is that right? 10:50:28

14 MR. BROUGHAN: Object to form. 10:50:29

15 **A. Where are we?** 10:50:30

16 Q. Sure. So let's go back to Paragraph 21 of 10:50:31
17 McCloskey. 10:50:35

18 **A. I see that.** 10:50:41

19 Q. All right. And then the very first 10:50:42
20 sentence in Paragraph 21 reads, "The barcoded 10:50:47
21 oligonucleotide further comprises a second 10:50:53
22 sequence that provides a random barcode." 10:50:56

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1 Correct? 10:50:59

2 A. Yes. 10:50:59

3 Q. And then it goes on to say, "The term 10:51:00

4 'random barcode' can refer" -- strike that. 10:51:03

5 It goes on to say, "The term 'random 10:51:08

6 barcode' refers to an arbitrary sequence that can 10:51:11

7 uniquely identify a target nucleic acid in an 10:51:14

8 experiment and whose sequence is unknown at the 10:51:18

9 start of the experiment." Correct? 10:51:19

10 A. Yes. 10:51:21

11 Q. Okay. The barcode, that second sequence 10:51:21

12 in McCloskey, is what tags a distinct sequence. 10:51:29

13 Correct? 10:51:33

14 MR. BROUGHAN: Object to form. 10:51:36

15 A. Right. As stated here, the random barcode 10:51:37

16 is an arbitrary sequence that can uniquely 10:51:52

17 identify a target nucleic acid molecule -- 10:51:55

18 sorry -- a target nucleic acid in an experiment. 10:51:58

19 Q. Got it. And then if you turn to 10:52:01

20 Paragraph 32 of McCloskey. 10:52:10

21 A. Yes. 10:52:16

22 Q. Do you agree that McCloskey discloses 10:52:16

1 methods for authenticating a DNA amplification 10:52:27

2 product? 10:52:30

3 **A. That's what it says in Paragraph 32.** 10:52:30

4 Q. And then if you scroll down to -- I said 10:52:36

5 scroll. If you'd go down to about five lines up 10:52:40

6 from the bottom of Paragraph 32, the Subpoint D. 10:52:43

7 **A. Yes.** 10:52:54

8 Q. That Subpoint D reads, "Authenticating the 10:52:54

9 amplification product by detecting the presence of 10:53:00

10 the second sequence in the amplification product." 10:53:02

11 Correct? 10:53:05

12 **A. That's what it says. Yes.** 10:53:05

13 Q. When McCloskey discusses authenticating -- 10:53:08

14 strike that. 10:53:12

15 When McCloskey discusses its methods for 10:53:12

16 authenticating DNA amplification products, it 10:53:15

17 detects the second sequence, the barcode. 10:53:18

18 Correct? 10:53:22

19 MR. BROUGHAN: Object to form. 10:53:22

20 **A. That's what Step D is. Yes.** 10:53:23

21 Q. Okay. And just for confirmation, if you 10:53:29

22 go down to Paragraph 0034, the first sentence says 10:53:34

1 the same thing. Right? 10:53:38

2 In Step D of the methods, the 10:53:41

3 amplification product is authenticated by 10:53:43

4 detecting the presence of the second sequence in 10:53:45

5 the amplification product. Correct? 10:53:47

6 **A. Yes.** 10:53:49

7 Q. Okay. And that second sequence is the 10:53:51

8 barcode? 10:54:01

9 **A. Yes.** 10:54:09

10 Q. Turn to Paragraph 9 of McCloskey. 10:54:09

11 Paragraph 9 from McCloskey describes in the first 10:55:10

12 sentence, "In another aspect, the present 10:55:13

13 invention provides methods for authenticating a 10:55:15

14 DNA amplification product." Correct? 10:55:18

15 **A. Yes.** 10:55:20

16 Q. And then it goes through similar steps. 10:55:22

17 Correct? 10:55:24

18 MR. BROUGHAN: Object to form. 10:55:25

19 **A. Yes.** 10:55:26

20 Q. All right. And the last step in 10:55:33

21 Paragraph 9, Substep D, states, "Authenticated the 10:55:35

22 amplification product by detecting the presence of 10:55:40

1 the second sequence in the amplification product." 10:55:43

2 Correct? 10:55:45

3 **A. That's what it says. Yes.** 10:55:45

4 Q. And that second sentence -- strike that. 10:55:48

5 That second sequence is the barcode. 10:55:51

6 Correct? 10:55:53

7 **A. I believe so.** 10:55:53

8 Q. Okay. Would you please turn back to your 10:55:57

9 reply report now, EX-1065. 10:56:26

10 **A. I have that. Yup.** 10:56:30

11 Q. And turn to Paragraph 15. 10:56:31

12 **A. Yes.** 10:56:39

13 Q. Paragraph 15 contains your opinions 10:56:40

14 responding to Dr. Pugliese about whether or not 10:56:44

15 McCloskey discloses a method to make genotype 10:56:48

16 calls. Right? 10:56:56

17 **A. That's right.** 10:56:57

18 Q. And it's your opinion that you disagree 10:56:58

19 that McCloskey does not contain a method to make 10:57:07

20 genotype calls. Right? 10:57:11

21 **A. That's right.** 10:57:12

22 Q. I hate the double negatives in the record. 10:57:13

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1 So to make the record clear, it's your opinion 10:57:15
2 that McCloskey does disclose a method to make 10:57:17
3 genotype calls. Correct? 10:57:20

4 **A. Yes.** 10:57:21

5 Q. And once again, you pointed to 10:57:22
6 Paragraph 0093 as your support of McCloskey for 10:57:26
7 that opinion? That's in Paragraph 16 of your 10:57:31
8 reply declaration. Correct? 10:57:35

9 **A. That's right.** 10:57:36

10 Q. Okay. And what Paragraph 0093 refers to 10:57:39
11 is using the method McCloskey uses to test the 10:57:46
12 FMR1 locus. Correct? 10:57:55

13 **A. Yes.** 10:57:57

14 Q. And if you go down to -- a little bit 10:57:58
15 farther down the way in Paragraph 16 of your reply 10:58:14
16 report, the third sentence, "McCloskey explains." 10:58:17
17 Do you see that? 10:58:24

18 **A. Yes.** 10:58:24

19 Q. And it's your opinion that "McCloskey 10:58:25
20 explains that its methods are useful for 10:58:28
21 sequencing the FMR1 locus because its barcodes 10:58:31
22 allow it to 'quantify accurately the proportion of 10:58:37

1 cells carrying a particular sequence variant by 10:58:41

2 counting only distinctly tagged sequences.'" 10:58:45

3 Correct? 10:58:49

4 **A. That's right.** 10:58:49

5 Q. And then you say in the next sentence, 10:58:49

6 "This information would be used to make a genotype 10:58:53

7 call, whether the person carries two normal 10:58:55

8 alleles, two abnormal alleles, or one of each." 10:59:00

9 Correct? 10:59:03

10 **A. Yes.** 10:59:03

11 Q. What specifically is the information 10:59:04

12 disclosed in McCloskey that is used to make the 10:59:07

13 genotype call? 10:59:10

14 MR. BROUGHAN: Object to form. 10:59:18

15 **A. The sequence of the amplified products** 10:59:19

16 **makes a genotype call.** 10:59:21

17 Q. So you need the particular sequence 10:59:22

18 variant in each of the amplified products. 10:59:31

19 Correct? 10:59:33

20 MR. BROUGHAN: Object to form. 10:59:37

21 **A. Yeah. You need the sequence information** 10:59:39

22 **for the amplified product to make the call.** 10:59:43

1 Q. Got it. Do you need the barcode? 10:59:46

2 A. The barcode is used to get to the binning 10:59:49

3 and remove the redundant sequences. And then 11:00:01

4 there's another step of making a genotype call. 11:00:05

5 So you're using the barcode to make the 11:00:08

6 call, but the barcode is used in the process -- in 11:00:10

7 the data processing step. 11:00:14

8 Q. McCloskey doesn't actually disclose the 11:00:18

9 data processing step. Right? 11:00:21

10 MR. BROUGHAN: Object to form. 11:00:23

11 A. I think the analysis that is performed is 11:00:24

12 described. I don't think they're calling it "data 11:00:48

13 processing" necessarily, but a person of skill in 11:00:50

14 the art would understand what they were going to 11:00:53

15 do with that information that McCloskey says she 11:00:55

16 generates. 11:00:59

17 Q. The line for McCloskey is "to quantify 11:00:59

18 accurately the proportion of cells carrying a 11:01:03

19 particular sequence variant by counting only 11:01:07

20 distinctly tagged sequences." Correct? 11:01:09

21 A. Yes. 11:01:12

22 Q. That describes what you call the binning 11:01:12

1 step. Correct? 11:01:15

2 MR. BROUGHAN: Object to form. 11:01:19

3 A. Well, binning or putting together the 11:01:19

4 reads to carry the same barcode is a part of that. 11:01:43

5 It's a part of that step. 11:01:47

6 Q. McCloskey does not actually reference the 11:01:49

7 second step that you described, and that is making 11:01:52

8 the genotype call. Correct? 11:01:56

9 MR. BROUGHAN: Object to form. 11:01:58

10 A. Well, they're doing their whole approach 11:01:59

11 here in order to detect genotype calls. I mean, 11:02:05

12 that's the point of amplifying the FMR1 -- the 11:02:08

13 FMR1 locus for determining Fragile X status. 11:02:12

14 Q. Are you familiar with something called 11:02:20

15 "methylation analysis"? 11:02:22

16 A. I am. 11:02:23

17 Q. What is methylation analysis? 11:02:23

18 A. It is an analysis of whether or not the 11:02:25

19 DNA is -- it's sort of saying what the word is, 11:02:34

20 whether the DNA is marked by a methyl group or 11:02:40

21 not. And a methyl group can indicate whether or 11:02:43

22 not the gene can be activated or not. 11:02:46

1 Q. Is methylation analysis the same type as 11:02:52
2 making a genotype call? 11:02:56

3 MR. BROUGHAN: Object to form. 11:02:58

4 A. The state of the DNA, whether or not it's 11:02:59
5 methylated or not, could be considered its 11:03:10
6 genotype, so its form, essentially. Yeah. 11:03:15

7 Q. Okay. Paragraph 0093 in McCloskey doesn't 11:03:33
8 actually use the word "genotype," does it? 11:03:47

9 A. It does not use the word "genotype." But 11:03:51
10 it's understood that different sequences, which 11:04:06
11 are different genotypes, can lead to different 11:04:08
12 methylation status. 11:04:10

13 So it's related, but that particular word 11:04:11
14 isn't used in the paragraph. 11:04:14

15 Q. I'm going to be moving on to another 11:04:28
16 section now. I'm happy to power through that if 11:04:31
17 you want to power through, or we can take a break 11:04:34
18 if you'd prefer to take a break now. I'm leaving 11:04:37
19 it up to your -- to you, Dr. Gabriel. 11:04:39

20 A. I can go. 11:04:43

21 Q. Okay. If you could turn to Paragraph 18 11:04:49
22 of your declaration. 11:04:59

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A. The reply?

2 Q. The reply, yes. 11:05:01

A. Yes.

4 Q. Paragraph 18 is part of your opinion that 11:05:03

5 a POSA would have been motivated to combine 11:05:08

6 Bignell and McCloskey. Correct? 11:05:12

7 **A. Yes.** 11:05:13

8 Q. And just for confirmation, it's your 11:05:15

9 opinion that a POSA would have been motivated to 11:05:21

10 combine Bignell and McCloskey. Correct? 11:05:24

A. That's correct.

12 Q. And Paragraph 18 describes your 11:05:26

13 disagreement with Dr. Pugliese. Right? 11:05:39

A. Yes.

15 Q. Specifically, the first sentence of 11:05:43

16 Paragraph 18 you state, "I disagree that Bignell 11:05:44

```
17 rejects the concept of applying a tag to every 11:05:48
```

18 molecule." Correct? 11:05:51

A. Yes.

20 Q. And you don't cite it here, but in the 11:05:53

21 previous paragraph, Paragraph 17, you cite to 11:05:56

22 Column 3, lines 28 through 35 of Bignell? 11:06:00

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A. That's right. 11:06:08

2 Q. Just to make sure you have it in front of 11:06:08

3 you. 11:06:15

A. Thanks.

5 Q. Thank you. You've been handed what has 11:06:16

6 previously been marked as EX-1013. 11:06:25

7 (Previously marked Exhibit EX-1013) 11:06:29

8 Q. That's Bignell. Correct? 11:06:32

9 A. It is. 11:06:33

10 Q. And if we could turn to that section of 11:06:34

11 Bignell. 11:07:00

A. Yes.

13 Q. You'd agree that Bignell raises a problem 11:07:28

14 with a prior approach by disclosure described by 11:07:36

15 Brenner, et al. Correct? 11:07:45

16 MR. BROUGHAN: Object to form. 11:07:46

17 A. I wouldn't call it problem. I would say 11:07:47

18 **that Bignell is trying to accomplish something** 11:07:49

```
19      different.                                     11:07:51
```

20 Q. Well -- 11:07:51

21 A. So for her -- for Bignell's application, I 11:07:53

22 think it's just citing a limitation of what 11:07:58

1 Brenner was doing, but I don't think it's 11:08:01
2 necessarily -- she's trying to do something 11:08:04
3 different, is my point. 11:08:06

4 Is it a she? I'm sorry. 11:08:07

5 Q. You disagree that Bignell has a problem 11:08:08
6 with the Brenner approach? 11:08:11

7 A. For what she's trying to accomplish here, 11:08:12
8 she's saying there was a problem with the Brenner 11:08:19
9 approach. 11:08:21

10 Q. So the Brenner approach -- just to be 11:08:21
11 clear, if you look at lines 24 through 27 in 11:08:23
12 Column 3 of Bignell, Bignell describes the Brenner 11:08:29
13 approach as, "In this application, the tags are 11:08:32
14 not sequenced so the method does not provide a 11:08:35
15 method of analyzing targets from multiple samples 11:08:37
16 but rather a method of sorting a mixture of 11:08:41
17 amplified templates from a single sample." 11:08:43
18 Correct? 11:08:46

19 A. Yes. 11:08:46

20 Q. And Bignell goes on to say, "The problem 11:08:46
21 with enabling the method for individual samples 11:08:49
22 rather than individual molecules is that the tags 11:08:51

1 are synthesized in a combinatorial manner." 11:08:54

2 Correct? 11:08:58

3 **A. That's right.** 11:08:58

4 Q. And that means you get all 16,777,216 11:08:59

5 different sequences obtained in the single mixture 11:09:06

6 in the same tube? 11:09:08

7 **A. That's right.** 11:09:11

8 Q. Correct? 11:09:12

9 Okay. But you're aware that Bignell 11:09:13

10 discloses methods to sequence multiple samples 11:09:24

11 together at once, not just one sample. Correct? 11:09:27

12 **A. Yes. I believe that that's what -- that's** 11:09:29

13 **what her method is, is multiplexing samples** 11:09:35

14 **together.** 11:09:40

15 Q. That's right. And that's because the 11:09:40

16 problem Bignell is trying to solve is issues with 11:09:50

17 pooling samples. Correct? 11:09:56

18 MR. BROUGHAN: Object to form. 11:09:59

19 **A. The approach that she's describing is to** 11:10:00

20 **enable you to multiplex samples together.** 11:10:07

21 Q. If you go to Column 1, line 66 of Bignell. 11:10:11

22 **A. Oh, I'm sorry. Yup.** 11:10:23

1 Q. And -- 11:10:26

2 A. 66. Yes. 11:10:27

3 Q. Sorry. Didn't mean to speak over you. 11:10:29

4 The sentence beginning at line 66 reads, 11:10:31

5 "One disadvantage of pooling samples prior to 11:10:35

6 analysis is that information pertaining to 11:10:37

7 individual DNA samples is lost." Correct? 11:10:39

8 A. Yes. 11:10:42

9 Q. And that's one of the problems that 11:10:42

10 Bignell is trying to solve. Correct? 11:10:43

11 A. Yes. 11:10:45

12 Q. Okay. Because if you look at the line -- 11:10:45

13 sentence immediately prior, "pooling" -- and by 11:10:55

14 that she means pooling samples -- "therefore 11:10:57

15 represents an effective technique for analyzing 11:11:00

16 large quantities of samples in a facile manner." 11:11:02

17 Correct? 11:11:06

18 A. That's right. 11:11:06

19 Q. And what she is trying to do -- and I'm 11:11:07

20 sorry for skipping around like this, but it's all 11:11:09

21 in the same general area. 11:11:12

22 If you go down to Column 2 and line 3. 11:11:13

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A. Column 2 -- which line?

2 Q. Line 3, beginning "An ability." 11:11:20

A. Uh-hmm.

4 Q. So what she's trying to create is, she 11:11:24

5 states, "An ability to genotype large populations 11:11:29

6 in a small number of reactions while retaining the 11:11:33

7 information relating to the source of the 11:11:36

8 individual samples would yield the information 11:11:38

9 content of a full nonpooled population screen in 11:11:41

10 the time and at the cost of a pooled reaction." 11:11:46

11 Right? 11:11:48

A. Yes.

13 Q. Throughput and cost are two of the things 11:11:49

14 that Bignell is concerned with. Correct? 11:11:57

15 MR. BROUGHAN: Object to form. 11:12:01

16 A. Well, what she's saying is that with this 11:12:02

```
17  approach of tagging -- of having sample-specific 11:12:14
```

```
18 barcodes, you can get the same information as if 11:12:23
```

19 you just pool all the DNA together, but you can 11:12:27

```
20 get the individual information because you have 11:12:30
```

```
21 the sample-specific barcode with the same -- 11:12:31
```

22 essentially the same cost and time as if you just 11:12:36

1 mixed all the DNA together. 11:12:39

2 That's the comparison she's making. You 11:12:40

3 get better information because you have a 11:12:42

4 sample-specific barcode and it doesn't cost you 11:12:45

5 any more. It costs you a very little bit more and 11:12:47

6 it takes the same amount of time because they're 11:12:51

7 grouped together in the same tube. 11:12:54

8 Q. Right. Bignell's method is designed to 11:12:55

9 provide better information through the sample- 11:13:02

10 specific barcode at a lower relative cost. 11:13:07

11 Correct? 11:13:11

12 MR. BROUGHAN: Objection to form. 11:13:12

13 A. No. It's just better information than 11:13:13

14 pooling all the DNA together without the sample- 11:13:21

15 specific barcode. 11:13:24

16 Q. Okay. Fair distinction. So let me 11:13:25

17 rephrase that question. Bignell's method is to 11:13:28

18 provide -- strike that. 11:13:33

19 Bignell's method is designed to provide 11:13:34

20 better information using the sample-specific 11:13:38

21 barcode at a lower relative cost compared to 11:13:41

22 pooling all the DNA together without the sample- 11:13:47

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1 specific barcode. Is that fair to say? 11:13:51

2 **A. No, not a lower cost.** 11:13:52

3 Q. Okay. 11:13:54

4 **A. It would be a lower cost than sequencing** 11:14:01

5 **all of those DNAs one at a time.** 11:14:03

6 Q. I see. Okay, okay. Let me try it one 11:14:06

7 more time, then. Okay? 11:14:09

8 **A. Okay.** 11:14:10

9 Q. And apologies. I appreciate you working 11:14:11

10 with me. 11:14:14

11 Bignell's method is designed to provide 11:14:16

12 better information using the sample-specific 11:14:19

13 barcode at a lower relative cost than sequencing 11:14:22

14 all of those DNAs one at a time. Is that right? 11:14:26

15 **A. Yeah.** 11:14:28

16 Q. Okay. If you'd move to Paragraph 20 of 11:14:29

17 your reply declaration. 11:14:47

18 **A. Yes.** 11:14:57

19 Q. The third sentence down, "I have 11:14:58

20 extensive." 11:15:01

21 **A. I do. Yes.** 11:15:02

22 Q. You state in Paragraph 20 of your reply 11:15:03

1 declaration, "I have extensive experience in 11:15:08
2 managing the costs of sequencing and addressing 11:15:11
3 trade-offs between cost and quality based upon the 11:15:15
4 goals of an experiment." 11:15:19

5 That's the first clause of that sentence. 11:15:20
6 Correct? 11:15:22

7 **A. Uh-hmm. Yes.** 11:15:22

8 Q. And that's because, as you say, you run 11:15:23
9 the largest sequencing lab in the United States 11:15:27
10 and have done so for the past 13 years? 11:15:29

11 **A. That's correct.** 11:15:31

12 Q. I'll have to say, that's pretty cool. So 11:15:32
13 nicely done. 11:15:38

14 **A. Thanks.** 11:15:39

15 Q. You'd agree that when addressing the 11:15:39
16 trade-offs particularly between cost and quality, 11:15:41
17 there's a point in which the increase in quality 11:15:45
18 would be worth an increase in cost. Correct? 11:15:48

19 MR. BROUGHAN: Object to form. 11:15:52

20 **A. Yeah.** 11:15:53

21 Q. And you'd agree that when addressing 11:15:56
22 trade-offs between cost and quality, there's a 11:15:58

1 point at which the degree of increase in quality 11:16:01

2 would be not worth an increase in cost. Correct? 11:16:03

3 **A. It depends on what you want to do.** 11:16:06

4 Q. How much increased accuracy or quality do 11:16:12

5 you have to have before the increased costs become 11:16:14

6 unacceptable -- become -- strike that. 11:16:17

7 How much increased quality or accuracy do 11:16:20

8 you have to have before -- strike that once again. 11:16:27

9 Sorry. 11:16:32

10 How much increased quality do you actually 11:16:33

11 have to have for increased costs to become 11:16:36

12 acceptable? 11:16:39

13 **A. All depends on what you're trying to do.** 11:16:39

14 Q. That point at which an increase in quality 11:16:42

15 is either worth or not worth an increase in cost 11:16:46

16 might differ from experiment to experiment. You'd 11:16:49

17 agree with that. Right? 11:16:51

18 **A. Could. Yeah.** 11:16:52

19 Q. That point might differ based upon the 11:16:54

20 parameters of the experiment? 11:16:57

21 **A. I really think of it as, like, the intent** 11:16:59

22 **of the experiment or the use case. You might need** 11:17:05

1 to be more accurate sometimes than others. 11:17:09

A. Yeah.

11 MR. BROUGHAN: Object to form. 11:17:46

12 A. Say that again. I'm sorry. 11:17:47

18 MR. BROUGHAN: Object to form. 11:18:04

19	A. No. What I've stated is that a person of	11:18:05
20	skill in the art would know how to make that	11:18:11
21	trade-off based on what they're trying to	11:18:14
22	accomplish.	11:18:16

1 Q. Your reply declaration does not state what 11:18:17
2 a person of skill in the art would be trying to 11:18:23
3 accomplish. Correct? 11:18:25

4 A. Well, no. There's a lot of things you 11:18:26
5 could be trying to accomplish with sequencing. 11:18:34

6 Q. Right. And so -- 11:18:35

7 A. You would make that trade-off of cost and 11:18:39
8 accuracy depending upon what you were trying to 11:18:41
9 accomplish. 11:18:43

10 Q. And you don't list out what somebody might 11:18:43
11 be trying to accomplish in your reply declaration. 11:18:46
12 Correct? 11:18:48

13 A. I don't list that out. No. 11:18:48

14 Q. But that point -- strike that. 11:18:51

15 And the same is true of your first 11:19:00
16 declaration. Right? 11:19:02

17 MR. BROUGHAN: Object to form. 11:19:03

18 A. Not that I recall. 11:19:04

19 Q. You'd agree that your reply declaration 11:19:10
20 contains no mention of the point at which an 11:19:12
21 increase in quality is worth an increase in cost 11:19:17
22 based upon the intent of an experiment in the 11:19:20

1 McCloskey-Bignell combination. Correct? 11:19:22

2 A. The only thing -- I've made the point here 11:19:25

3 that if very high accuracy is required, that can 11:19:36

4 warrant additional costs. They haven't given what 11:19:42

5 that cost is or an example of what that could be. 11:19:47

6 We can talk about that, but that's not 11:19:50

7 what I've given here in this paragraph. 11:19:51

8 Q. And if very high accuracy was not the 11:19:53

9 intent of the experiment using the McCloskey- 11:19:56

10 Bignell combination, then the cost would not be 11:19:59

11 worth it. Correct? 11:20:01

12 MR. BROUGHAN: Object to form. 11:20:03

13 A. It may or may not be, depending upon what 11:20:04

14 a person was trying to do. 11:20:10

15 Q. You don't have any of that kind of 11:20:12

16 analysis in your reply declaration. Correct? 11:20:13

17 A. I mean, the analysis I offered is that, 11:20:15

18 first of all, adding those random barcodes doesn't 11:20:22

19 really significantly increase the cost of the 11:20:25

20 sequencing approach. 11:20:28

21 But in that it might increase the cost, if 11:20:31

22 you really required high accuracy you would make 11:20:34

1 **that trade-off. And we could debate what "high** 11:20:36
2 **accuracy" means. It can be different in different** 11:20:41
3 **settings.** 11:20:44

4 Q. That's fair. 11:20:44

5 **A. Depends what you're trying to do.** 11:20:45

6 Q. Because you might need to be more accurate 11:20:46
7 sometimes than others. Correct? That's what you 11:20:49
8 said? 11:20:50

9 **A. That's true.** 11:20:51

10 Q. Okay. And the same is true of your first 11:20:51
11 declaration. Correct? 11:21:04

12 **A. Yes. That's what I recall. Yes.** 11:21:05

13 MR. WUESTE: Okay. Let's take another 11:21:13
14 break. 11:21:15

15 THE VIDEOGRAPHER: The time is 11:21. 11:21:16
16 We're off the record. 11:21:18

17 (Recess, 11:21 a.m. to 11:34 a.m.) 11:21:20

18 THE VIDEOGRAPHER: Okay. The time is 11:34:50
19 11:34. We're back on the record. 11:34:58

20 BY MR. WUESTE: 11:35:00

21 Q. Welcome back, Dr. Gabriel. 11:35:01

22 **A. Thank you.** 11:35:02

1 Q. We're going to turn back to your original 11:35:03
2 declaration, EX-1005. And if you could turn to 11:35:05
3 Paragraph 176. 11:35:12

4 All right. Just for confirmation, 11:35:20
5 Paragraph 176 is part of the section of your 11:35:26
6 original declaration mapping Chee to the 11:35:31
7 correcting for error or bias limitation of Claim 1 11:35:37
8 of the '730 patent. Correct? 11:35:40

9 A. Yes. 11:35:42

10 Q. And it's your opinion that Chee describes 11:35:42
11 how its methods can identify and correct errors in 11:35:58
12 several places? That's what you state in 11:36:00
13 Paragraph 176 of your original declaration. 11:36:02
14 Correct? 11:36:05

15 A. Yes. 11:36:05

16 Q. Okay. You opine "Chee observes that 11:36:06
17 errors can be introduced when synthesizing copies 11:36:13
18 of nucleic acids." Correct? 11:36:16

19 A. That's right. 11:36:17

20 Q. Okay. And that's specifically the portion 11:36:20
21 of a nucleic acid or a genome sequencing workflow 11:36:23
22 when you're actually synthesizing before 11:36:28

1 sequencing. Correct? 11:36:31

2 **A. It just says synthesizing copies of 11:36:32**

3 **nucleic acid. So that can be in different 11:36:41**

4 **scenarios, but that's what the sentence says. 11:36:43**

5 Q. I see. So the synthesizing can happen 11:36:45

6 during amplification. Is that right? 11:36:49

7 **A. Yeah. You can consider that. Sure. 11:36:50**

8 Q. The synthesizing can happen during 11:36:58

9 sequencing? 11:37:00

10 **A. I'm not sure I would use that word, but 11:37:05**

11 **you are making copies when you're sequencing. 11:37:15**

12 **Yes. 11:37:18**

13 Q. You quote from Chee in Paragraph 176 of 11:37:18

14 your original declaration. Correct? 11:37:24

15 **A. Yes. 11:37:26**

16 Q. Okay. And then the second sentence in 11:37:27

17 Chee, the one beginning "In addition." Do you see 11:37:31

18 where that starts? 11:37:35

19 **A. Yes. 11:37:36**

20 Q. "In addition, error can be introduced as a 11:37:36

21 result of sequencing error." Do you see that? 11:37:39

22 **A. Yes. 11:37:41**

1 Q. What is sequencing error, as you 11:37:41

2 understand it? 11:37:45

3 A. Error that's the result of sequencing. It 11:37:45

4 happens during sequencing. 11:37:53

5 Q. Okay. Is error that happens during 11:37:55

6 sequencing a category of error that can be 11:37:58

7 introduced when synthesizing copies of nucleic 11:38:01

8 acids, as you describe in Paragraph 176? 11:38:04

9 A. I think it can include that. 11:38:06

10 Q. And then if you'd turn to Paragraph 189 of 11:38:18

11 your original declaration. 11:38:41

12 A. Yes. 11:38:46

13 Q. Paragraph 189 of your original 11:38:46

14 declaration, EX-1005, contains your opinions 11:38:53

15 mapping Chee to Claim 3 of the '730 patent. 11:38:58

16 Correct? 11:39:01

17 A. Yes. 11:39:01

18 Q. All right. And your opinion is that Chee 11:39:05

19 teaches that amplification can introduce errors 11:39:11

20 and bias. Correct? 11:39:14

21 A. Yes. 11:39:15

22 Q. If you go down to the beginning of the 11:39:22

1 last sentence in Paragraph 189, "This means that." 11:39:38

2 Do you see that? 11:39:44

3 **A. Yes.** 11:39:44

4 Q. Okay. There you state -- and it continues 11:39:45

5 on to the next page. There you state, "This means 11:39:48

6 that after amplification, the number of different 11:39:51

7 unique identifiers associated with each ROI can be 11:39:54

8 counted to provide information on the number of 11:39:59

9 each ROI that was present in the original sample." 11:40:03

10 Do you see that? 11:40:06

11 Oh, "initial sample." Correct? 11:40:07

12 **A. I see that.** 11:40:10

13 Q. And you say, "A person of ordinary skill 11:40:11

14 in the art would have understood that this method 11:40:13

15 corrects for amplification error." Right? 11:40:15

16 **A. That's what it says.** 11:40:18

17 Q. Okay. If you go on to the next paragraph, 11:40:22

18 Paragraph 190, you state, "Similarly, Chee 11:40:35

19 explains that if a nucleic acid is either 11:40:38

20 overrepresented or underrepresented due to 11:40:41

21 amplification bias." Correct? 11:40:45

22 **A. Uh-hmm. Yes.** 11:40:48

1 Q. Is amplification bias the only way -- 11:40:49

2 strike that. Let me ask it a different way. 11:40:58

3 Does an overrepresentation of a nucleic 11:41:08

4 acid result only from amplification bias? 11:41:11

5 **A. Not necessarily.** 11:41:13

6 Q. Okay. Amplification error could lead to 11:41:23

7 overrepresentation as well. Correct? 11:41:27

8 MR. BROUGHAN: Object to form. 11:41:30

9 **A. I think those are two different things.** 11:41:31

10 **I'm sorry. Could you say them again.** 11:41:41

11 Q. Sure. What are some of -- let me ask it a 11:41:43

12 different way. What are some of the other ways 11:41:46

13 that overrepresentation could result other than 11:41:48

14 due to amplification bias? 11:41:53

15 **A. There could be an artifact. There could** 11:41:54

16 **be preferential sequencing of certain regions on** 11:42:11

17 **the sequencer, maybe, that's not amplification.** 11:42:17

18 **There could be different -- I suppose there could** 11:42:23

19 **be different sample preparation methods that** 11:42:25

20 **might -- for example, could select for longer or** 11:42:33

21 **shorter fragments that could lead to some** 11:42:36

22 **representation bias.** 11:42:38

1 **There's different -- I don't want to say** 11:42:39
2 **that it's only amplification bias or amplification** 11:42:42
3 **errors.** 11:42:45

4 Q. I don't think you're saying anything 11:42:48
5 differently, but I just want to confirm. In your 11:42:51
6 mind, is there a difference between amplification 11:42:53
7 error and amplification bias? 11:42:55

8 MR. BROUGHAN: Object to form. 11:42:58

9 **A. Yes.** 11:42:58

10 Q. And Chee's method of counting up the 11:43:00
11 number of unique identifiers associated with each 11:43:10
12 ROI, in your opinion, would correct for both 11:43:13
13 amplification bias and amplification error? 11:43:16

14 MR. BROUGHAN: Object to form. 11:43:22

15 **A. Again, using the unique identifiers is** 11:43:24
16 **part of the process that can correct -- that can** 11:43:28
17 **correct for bias or error.** 11:43:33

18 Q. Okay. We've been talking about Chee a 11:43:38
19 lot. I just want to make sure you have it in 11:43:48
20 front of you. 11:43:50

21 You've been handed what's been previously 11:44:00
22 marked as EX-1010. 11:44:02

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1 (Previously marked Exhibit EX-1010) 11:44:04

2 Q. EX-1010 is the Chee reference. Correct? 11:44:09

3 A. Yes. 11:44:12

4 Q. Okay. And we've discussed how -- sorry 11:44:12

5 for flipping around here. Let's go to your reply 11:44:53

6 declaration at page 11. 11:44:56

7 A. Yes. 11:45:00

8 Q. And we've seen this before. Well, strike 11:45:01

9 that. 11:45:04

10 The title of Subsection A on page 11 of 11:45:04

11 your reply declaration, "Chee Discloses Correcting 11:45:09

12 Amplification Bias." Right? 11:45:12

13 A. Yes. 11:45:14

14 Q. And then you've got a footnote, Footnote 11:45:15

15 3? 11:45:21

16 A. Yes. 11:45:21

17 Q. And you state, "In my first declaration, I 11:45:22

18 explained how Chee's technique for correcting 11:45:26

19 sequencing errors met this limitation as well." 11:45:28

20 Correct? 11:45:31

21 A. That's right. 11:45:31

22 Q. And is it your opinion that disclosure of 11:45:32

1 a method for correcting sequencing errors 11:45:36

2 discloses correcting for amplification bias? 11:45:40

3 **A. No, not necessarily.** 11:45:42

4 Q. Okay. 11:45:48

5 **A. It might.** 11:45:50

6 Q. Okay. Now, you refer to your first 11:45:52

7 declaration in your reply declaration in that 11:46:00

8 Footnote 3. So let's go back to the first 11:46:02

9 declaration and at page 67 and 68, the 11:46:05

10 Paragraph 176 that we were looking at earlier. 11:46:14

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

12 Q. Paragraph 176 describes the kinds of 11:46:23

13 errors that you opine Chee can identify. Correct? 11:46:26

14 **A. Yes.** 11:46:30

15 Q. And then you say in Paragraph 177, "Chee 11:46:36

16 explains that those errors can be corrected by 11:46:44

17 sequencing multiple copies of the same original 11:46:46

18 molecule and comparing them." Correct? 11:46:49

19 **A. Yes.** 11:46:51

20 Q. And at the bottom of that sentence, you 11:46:52

21 describe -- strike that. 11:47:05

22 Two sentences down, "Chee describes." Do 11:47:06

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1 you see that? 11:47:10

2 **A. Yes.** 11:47:10

3 Q. "Chee describes the well-known concept of 11:47:12

4 a consensus sequence or consensus base call to 11:47:15

5 correct any such errors"? 11:47:17

6 **A. Yes.** 11:47:19

7 Q. Do you still agree with that opinion? 11:47:20

8 **A. Yes.** 11:47:22

9 Q. It's your opinion that a consensus base 11:47:22
10 call corrects sequencing errors? 11:47:27

11 MR. BROUGHAN: Object to form. 11:47:33

12 **A. It's part of a process you could use to 11:47:34**
13 **identify errors.** 11:47:51

14 Q. If you go on to 178, I think this is where 11:47:51
15 you describe that process. Let me make sure. 11:48:03

16 If you go down to 178, you opine, "It was 11:48:06

17 well known to those in the art that deriving a 11:48:10

18 consensus sequence involved considering sequencing 11:48:14

19 reads from multiple overlapping copies of a DNA 11:48:17

20 sequence to come up with a single sequence for the 11:48:21

21 DNA segment." Correct? 11:48:23

22 **A. Yes.** 11:48:26

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1 Q. And that's deriving a consensus sequence. 11:48:26

2 Correct? 11:48:35

3 A. That's what it says. It says "deriving a 11:48:36

4 consensus sequence." Yes. 11:48:37

5 Q. You go on to say, two sentences down, "For 11:48:39

6 a particular base, if one sequencing read is 11:48:42

7 different than the other reads for that base, the 11:48:43

8 errant read is likely an error." Correct? 11:48:47

9 A. Yes. 11:48:49

10 Q. And so when performing a -- strike that. 11:48:49

11 When performing the process for deriving a 11:48:55

12 consensus sequence, if you can establish that one 11:48:57

13 sequencing read is different than the other reads 11:49:02

14 for that base, it's your opinion that a POSITA 11:49:04

15 would have known that that's an error? 11:49:09

16 MR. BROUGHAN: Object to form. 11:49:11

17 A. Well, that would, I mean, depend on the 11:49:12

18 set of results you're looking at. So how many 11:49:21

19 copies are you analyzing and how many differences 11:49:24

20 are there at a position. 11:49:32

21 So it really -- you need to have a set of 11:49:36

22 results to be able to answer that question. 11:49:38

1 Q. Okay. It's your opinion that when 11:49:42
2 performing the process for deriving a consensus 11:49:50
3 sequence based upon a set of results and how many 11:49:54
4 differences there are at a given position, if you 11:50:00
5 can establish that one sequencing read is 11:50:03
6 different from the other reads for that base 11:50:07
7 within that set, a POSITA would have known that 11:50:09
8 that's an error? 11:50:13

9 MR. BROUGHAN: Object to form. 11:50:15

10 **A. There are other parameters that a POSITA 11:50:16**
11 **would want to know. It would want to know the 11:50:21**
12 **quality of the base, would want to know, again, 11:50:25**
13 **the depth of sequencing that you have available. 11:50:28**
14 **Those are all parameters that would be taken into 11:50:33**
15 **account in your process of determining error. 11:50:40**

16 Q. Do you have to know the depth of 11:50:47
17 sequencing or the quality of the base in order to 11:50:49
18 determine error? 11:50:53

19 **A. I think that's helpful. And it depends, 11:50:54**
20 **again, on the -- it depends on the analysis that 11:50:59**
21 **you're doing, of what you -- it depends on the 11:51:03**
22 **process you're using, of the analysis you're 11:51:08**

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1 **using. But I think a person would understand how** 11:51:10
2 **to do that.** 11:51:12

3 Q. Okay. So setting that aside, it's your 11:51:13
4 opinion that a POSITA would have known how to 11:51:18
5 determine error from the process for deriving a 11:51:24
6 consensus sequence based upon a set of results and 11:51:33
7 how many differences there are at a given 11:51:36
8 position. Correct? 11:51:39

9 **A. Yes.** 11:51:40

10 Q. Okay. I'm going to hand you another 11:51:40
11 document. 11:52:17

12 You were handed a document that's 11:52:18
13 previously been marked as EX-1011. 11:52:19

14 (Previously marked Exhibit EX-1011) 11:52:22

15 Q. EX-1011 is the provisional application for 11:52:32
16 the Chee reference, EX-1010. Correct? 11:52:36

17 **A. It looks like it. Yeah.** 11:52:40

18 Q. And did you review EX-1011 in preparation 11:52:41
19 for your deposition today? 11:52:48

20 **A. No.** 11:52:48

21 Q. But certainly you considered it in the 11:52:53
22 context of forming your opinions in this case. 11:52:55

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1 Correct? 11:52:57

2 **A. In a previous -- yes. In an original.** 11:52:58

3 Q. Okay. Well, just make sure I'm not 11:53:03

4 misunderstanding. In your reply declaration as 11:53:06

5 well. Right? 11:53:08

6 Let's turn to your reply declaration. If 11:53:09

7 you look at Paragraph 31, for example. 11:53:13

8 Actually -- yes, the section beginning on page 15. 11:53:21

9 **A. Yes.** 11:53:25

10 Q. Okay. 11:53:26

11 **A. Oh, this section? Yes.** 11:53:28

12 Q. And just to be sure, in your reply 11:53:29

13 declaration, EX-1065, Subsection C contains your 11:53:36

14 opinions that Chee's provisional discloses its 11:53:42

15 methods applied to biological samples from natural 11:53:46

16 sources and naturally occurring nucleic acids. 11:53:51

17 Correct? 11:53:53

18 **A. Yes.** 11:53:54

19 Q. Okay. So you did not review EX-1011, the 11:53:54

20 Chee provisional, in preparation for today's 11:53:59

21 deposition, but you did consider it in the course 11:54:01

22 of forming your opinions in -- as set forth in 11:54:03

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1 your reply declaration. Correct? 11:54:06

2 **A. Oh, yes. For sure. Yes.** 11:54:08

3 Q. All right. If you'd turn to Paragraph 1 11:54:10

4 of the Chee provisional, EX-1011. It's a single 11:54:21

5 sentence. 11:54:34

6 You'd agree that the Chee provisional 11:54:35

7 discloses that -- the field of the invention, and 11:54:37

8 states, "This invention relates to the field of 11:54:41

9 oligonucleotide selection and synthetic biology"? 11:54:44

10 **A. I see that. Yes.** 11:54:48

11 Q. And then if you'd go down to 11:54:49

12 Paragraph 0003. 11:54:54

13 **A. Yup.** 11:54:57

14 Q. The first sentence, "Synthetic biology is 11:54:58

15 a promising new field at the interface of 11:55:00

16 engineering and biology." Correct? 11:55:03

17 **A. Yes.** 11:55:05

18 Q. Okay. The third sentence reads, "Recently 11:55:05

19 parallel methods have been used to synthesize many 11:55:17

20 different DNA sequences simultaneously and to 11:55:20

21 provide them as a pool of oligonucleotides." 11:55:23

22 Correct? 11:55:26

1	A. Correct.	11:55:26
2	Q. And then if you go to the next paragraph,	11:55:26
3	0004.	11:55:32
4	A. Uh-hmm.	11:55:34
5	Q. The problem that Chee is trying to	11:55:35
6	solve -- strike that.	11:55:38
7	Chee establishes a problem with DNA	11:55:39
8	synthesis. Right?	11:55:43
9	A. Yes.	11:55:44
10	Q. So the first sentence of Paragraph 0004,	11:55:47
11	"Despite these advances, construction of	11:55:52
12	multikilo-based scale DNA molecules remains	11:55:56
13	difficult and costly, largely because that de novo	11:55:59
14	chemical synthesis of the DNA building blocks is	11:56:03
15	quite error-prone." Correct?	11:56:06
16	A. That's -- yes.	11:56:08
17	Q. And then the last section, 0005, states,	11:56:10
18	"There remains a need to select error-free	11:56:23
19	synthesized oligonucleotides for use in synthetic	11:56:26
20	biology and other analytical methods." Correct?	11:56:31
21	A. Yes.	11:56:34
22	Q. Fair to say this Chee provisional in both	11:56:34

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1 the field of the invention and the background of 11:56:39

2 the invention is talking about errors and problems 11:56:41

3 in de novo chemical synthesis. Correct? 11:56:45

4 **A. That's what he was describing here. Yes.** 11:56:47

5 Q. Right. Okay. I'm handing you a document 11:56:57

6 previously marked as EX-1001. 11:58:41

7 (Previously marked Exhibit EX-1001) 11:58:44

8 Q. Do you recognize EX-1001 as the '730 11:58:46

9 patent to Gregory Porreca and Uri Laserson. 11:58:52

10 Correct? 11:58:57

11 **A. I do.** 11:58:57

12 Q. And I'd like you to turn to the very last 11:58:57

13 page of EX-1001 where the claims are. 11:59:02

14 **A. Yes.** 11:59:08

15 Q. All right. And just have that in front of 11:59:08

16 you. 11:59:11

17 I'm also handing you a document that's 11:59:38

18 previously been marked EX-2006. 11:59:39

19 (Previously marked Exhibit EX-2006) 11:59:43

20 Q. EX-2006 is the March 6th, 2009 11:59:53

21 application -- draft application. Correct? 11:59:59

22 **A. Yes.** 12:00:02

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1 Q. And you've reviewed this document. 12:00:02

2 Correct? 12:00:04

3 A. Yes. 12:00:05

4 Q. Did you review this document in 12:00:05

5 preparation for today's deposition? 12:00:09

6 A. Yes. 12:00:10

7 Q. Okay. Now, your opinion is that EX-2006 12:00:13

8 does not disclose correcting for errors as claimed 12:00:23

9 by the '730 patent. Correct? 12:00:27

10 A. That's correct. 12:00:29

11 Q. Okay. And just to confirm, if you look at 12:00:31

12 Paragraph 38 of your reply declaration. 12:00:39

13 A. Yes. 12:00:45

14 Q. That's the only limitation in the '730 12:00:45

15 patent that you opine is not disclosed in the 12:00:53

16 March 6th application. Correct? 12:00:56

17 A. Yes. 12:00:58

18 Q. Okay. You do not dispute that EX-2006 12:01:02

19 discloses correcting for bias. Correct? 12:01:10

20 A. That's right. 12:01:12

21 Q. Okay. And this is one of those instances 12:01:16

22 in which we're just going to run through the claim 12:01:19

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1 limitations of the '730 patent. So that's why I 12:01:22

2 had you put it in front of you. 12:01:25

3 **A. Okay.** 12:01:26

4 Q. Okay. You do not dispute that the 12:01:26

5 March 6th, 2009 application, EX-2006, discloses 12:01:38

6 correcting for bias introduced during nucleic acid 12:01:44

7 analysis workflow. Correct? 12:01:48

8 MR. BROUGHAN: Object to form. 12:01:50

9 MR. WUESTE: Thank you for that, Tom. Let 12:01:57

10 me rephrase that question. 12:01:59

11 Q. You do not dispute that the March 6th, 12:02:00

12 2009 application, EX-2006, discloses correcting 12:02:06

13 for bias introduced during nucleic acid analysis 12:02:10

14 workflow. Correct? 12:02:14

15 MR. BROUGHAN: Object to form. 12:02:16

16 **A. That's right.** 12:02:23

17 Q. You do not dispute that the March 6th, 12:02:23

18 2009 draft application discloses obtaining a 12:02:30

19 biological sample comprising a plurality of target 12:02:31

20 nucleic acid molecules from more than one locus of 12:02:37

21 origin. Correct? 12:02:41

22 **A. I don't think I gave an opinion on that.** 12:02:55

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1 **I was asked to consider if error was -- that's** 12:03:06
2 **what I had considered. But I could -- but I** 12:03:11
3 **don't -- I haven't disputed that limitation.** 12:03:16

4 Q. Sitting here today, neither of the 12:03:18
5 declarations you submitted in this case dispute 12:03:23
6 that the March 6th, 2009 draft application 12:03:26
7 discloses the obtaining of biological sample 12:03:29
8 limitation of Claim 1 of the '730 patent. 12:03:32
9 Correct? 12:03:35

10 MR. BROUGHAN: Object to form. 12:03:36

11 **A. I have not given that opinion.** 12:03:38

12 Q. Sitting here today, you have not given an 12:03:39
13 opinion nor do you dispute that the March 6th, 12:03:45
14 2009 draft application, EX-2006, discloses 12:03:47
15 introducing a set of differentiator tags, the 12:03:55
16 entirety of that limitation. Correct? 12:04:00

17 **A. That's correct.** 12:04:02

18 Q. And sitting here today, you have not 12:04:04
19 given -- strike that. 12:04:08

20 Sitting here today, you do not dispute 12:04:09
21 that the March 6th, 2009 draft application, 12:04:11
22 EX-2006, discloses amplifying each of the 12:04:15

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1 plurality of tagged target nucleic acid molecules 12:04:19

2 to generate amplicons. Correct? 12:04:23

3 MR. BROUGHAN: Object to form. 12:04:26

4 **A. I have not given that opinion. Correct.** 12:04:27

5 Q. Sitting here today, you do not dispute 12:04:29

6 that the March 6th, 2009 draft application, 12:04:32

7 EX-2006, discloses the sequencing the amplicons 12:04:36

8 obtained at said amplifying step limitation. 12:04:41

9 Correct? 12:04:44

10 **A. Correct.** 12:04:44

11 Q. And sitting here today, you do not dispute 12:04:48

12 that the March 6th, 2009 draft application, 12:04:52

13 EX-2006, discloses correcting for bias introduced 12:04:55

14 during said workflow by collapsing 12:05:00

15 target:differentiator tag combinations observed 12:05:06

16 more than once into a single count. Correct? 12:05:08

17 **A. That's correct.** 12:05:10

18 Q. So the only dispute you have with the 12:05:10

19 March 6th, 2009 draft application, at least as 12:05:14

20 presented in your declaration to date, is that you 12:05:18

21 allege it fails to disclose correcting for error. 12:05:23

22 Correct? 12:05:25

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A. That's right. 12:05:26

2 Q. Okay. In Paragraph 40 -- strike that. 12:05:26

3	Let's start at Paragraph 39. The last	12:05:44
4	sentence of Paragraph 39 of your draft -- strike	12:05:48
5	that.	12:05:51

6	The last sentence of Paragraph 39 of your	12:05:51
7	reply declaration states, "The claims separately	12:05:54
8	recite error and bias, which I interpret as	12:05:57
9	meaning that an error is something distinct from	12:05:59
10	bias." Correct?	12:06:01

A. Correct.

12 Q. And then in Paragraph 40, you describe 12:06:03

13 when errors can occur. Right? 12:06:12

A. That's right.

15 Q. That's not the only time errors can occur 12:06:15

16 during nucleic acid analysis workflow. Right? 12:06:18

17 MR. BROUGHAN: Object to form. 12:06:22

18 Q. You know what, I'll clean that up. 12:06:32

19	You opine that "errors can occur when	12:06:34
20	nucleotides are incorrectly incorporated when	12:06:37
21	making a copy of DNA by synthesizing a	12:06:40
22	complementary strand." Correct?	12:06:42

1	A. Yes.	12:06:44
2	Q. And you state that "this type of error can	12:06:44
3	occur during amplification"?	12:06:46
4	A. Yes.	12:06:47
5	Q. Is amplification the only time that type	12:06:48
6	of error can occur?	12:06:51
7	A. Well, if you're making a copy of DNA,	12:06:51
8	you're amplifying it. So there's kind of two	12:07:03
9	similar words there. But yeah.	12:07:06
10	Q. An error can also occur during the	12:07:09
11	sequencing step. Correct?	12:07:13
12	A. Yes.	12:07:14
13	Q. Okay. An error can also occur when the	12:07:15
14	nucleotide was correctly incorporated but	12:07:24
15	subsequently misread by the sequencing machine.	12:07:27
16	Right?	12:07:29
17	A. That's right.	12:07:30
18	Q. And you say a POSA would consider these to	12:07:30
19	be errors, not bias. Correct?	12:07:35
20	A. Yes.	12:07:36
21	Q. In your opinion, is error limited to the	12:07:36
22	sequence of the amplicon instead of an error to	12:07:45

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1 the quantities of amplicons? 12:07:49

2 MR. BROUGHAN: Object to form. 12:07:54

3 A. What do you mean by the quantity of the -- 12:07:55

4 I guess it's not clear to me how you stated that. 12:08:03

5 Q. So the examples you gave here in 12:08:05

6 Paragraph 40 are errors to the sequence itself, 12:08:09

7 whether through incorrect incorporation or through 12:08:17

8 misreads by the sequencing machine. Correct? 12:08:21

9 A. Uh-hmm. Yes. 12:08:23

10 Q. If during amplification you get an 12:08:24

11 overrepresentation of certain molecules, is that a 12:08:28

12 different kind of error than what you're 12:08:34

13 considering here? 12:08:36

14 A. So that would be bias in your result. 12:08:36

15 Q. Okay. So in your opinion, 12:08:43

16 overrepresentation is bias? 12:08:45

17 A. Yes. 12:08:49

18 Q. If you can turn to EX-2006. 12:08:52

19 A. Yes. 12:09:18

20 Q. And in EX-2006, if you'd turn to the third 12:09:18

21 paragraph down. 12:09:41

22 A. Yup. 12:09:44

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1 Q. "A common problem to overcome." Do you 12:09:44

2 see that? 12:09:48

3 A. Yes. 12:09:49

4 Q. That first sentence reads, "A common 12:09:49

5 problem to overcome is that these techniques 12:09:55

6 commonly introduced biases into the sequencing 12:09:58

7 libraries generally due to biases in enzyme 12:10:01

8 function or to the exponential and stochastic 12:10:05

9 nature of amplification methods like PCR." Do you 12:10:09

10 see that? 12:10:12

11 A. I do. 12:10:12

12 Q. What's your understanding of what "biases 12:10:12

13 in enzyme function" refers to? 12:10:15

14 A. I would read that to mean the enzyme might 12:10:17

15 be acting unequally in different regions or 12:10:30

16 different sequence contexts. 12:10:37

17 Q. And what does that lead to? 12:10:39

18 A. That could lead to bias. 12:10:43

19 Q. Okay. 12:10:45

20 A. Over- or underrepresentation. 12:10:46

21 Q. Right. But over- or underrepresentation 12:10:49

22 is not error, in your opinion? 12:10:54

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1 **A. Well, in this context and, again, in the** 12:10:55
2 **context of the claims where they're using the two** 12:10:58
3 **words differently, I would say this -- I would** 12:11:01
4 **count that as the bias category.** 12:11:03

5 Q. Okay. And so "error," in your mind, means 12:11:07
6 something other than overrepresentation. Correct? 12:11:10

7 **A. Again, in the context of the claims where** 12:11:13
8 **they use the two words, "error" and "bias," I'm** 12:11:18
9 **going to lump over- and underrepresentation into** 12:11:21
10 **the bias word and errors as something different.** 12:11:24

11 Q. Okay. The latter half of the first 12:11:28
12 sentence in the third paragraph of the EX-2006 12:11:34
13 reads "the exponential and stochastic nature of 12:11:41
14 amplification methods like PCR." Do you see that? 12:11:44

15 **A. I do.** 12:11:47

16 Q. What is stochastic? 12:11:47

17 **A. I think the general word "stochastic"** 12:11:50
18 **means sort of random or by chance.** 12:11:57

19 Q. Okay. And how do -- what makes PCR 12:11:58
20 amplification stochastic? 12:12:08

21 MR. BROUGHAN: Objection to form. 12:12:14

22 **A. I suppose the molecular biology of PCR,** 12:12:15

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1 **you may -- different molecules may be amplified at** 12:12:33
2 **different cycles or at different rates in the** 12:12:38
3 **process. I think that could lead to the** 12:12:41
4 **stochasticity or randomness.** 12:12:43

5 **I suppose I haven't considered that really** 12:12:46
6 **deeply recently.** 12:12:51

7 **Q. We've established already that you can** 12:12:52
8 **incorrectly incorporate a nucleotide during** 12:12:55
9 **amplification. Right?** 12:12:58

10 **A. You can. Yeah.** 12:12:59

11 **Q. Is that an example of stochastic effects** 12:13:03
12 **of PCR amplification?** 12:13:06

13 **A. I don't think that's quite the same thing** 12:13:17
14 **as I was just talking about in terms of, like,** 12:13:19
15 **which molecules are getting amplified. I think of** 12:13:24
16 **that as a mistake that happens in PCR** 12:13:26
17 **amplification.** 12:13:30

18 **I don't know. Is the error process itself** 12:13:31
19 **stochastic? I think the error -- like, where** 12:13:34
20 **errors land can be stochastic and they can also be** 12:13:37
21 **systematic. It depends on what you're talking** 12:13:40
22 **about.** 12:13:43

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1 Q. Right, right. There's a category of error 12:13:43
2 that can arise during amplification that would be 12:13:46
3 a systematic error where there was a mistake made. 12:13:48
4 Correct? 12:13:52

5 A. That's not always a systematic error. 12:13:52
6 There is systematic error and then there's random 12:13:56
7 error. There's both types of errors. 12:13:59

8 Q. And there's another type of error, just 12:14:01
9 for the record's sake -- so strike that. 12:14:04

10 There's another type of error where you 12:14:05
11 could have a nucleotide incorrectly incorporated 12:14:08
12 during PCR amplification because it would be 12:14:13
13 stochastic as opposed to systematic. Is that 12:14:16
14 fair? 12:14:19

15 MR. BROUGHAN: Objection to form. 12:14:20

16 A. You could have a wrong base incorporated 12:14:21
17 for -- as random error or as systematic error. 12:14:27

18 Q. Got it. If you'd return to your reply 12:14:30
19 declaration at Paragraph 41. 12:14:42

20 A. Yes. 12:14:48

21 Q. The last two sentences of Paragraph 41, 12:14:48
22 the one beginning "Noticeably." Do you see that? 12:14:52

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A. Yes.

2 Q. You state, "Noticeably absent from the 12:14:56

3 March 6th, 2009 application, however, is any 12:14:59

4 disclosure of error." The word "error" does not 12:15:01

5 appear. Correct? 12:15:05

A. Yes.

7 Q. That's your opinion? 12:15:07

A. Yes.

9 Q. You stand by that opinion? 12:15:11

A. Yes.

11 Q. Let's turn to page 5 of Exhibit 2006 in 12:15:17

12 the last paragraph. 12:15:21

A. Yes.

14 Q. If you look down to the second sentence in 12:15:28

15 the last paragraph, the one starting "Most 12:15:31

```
16 oligonucleotide synthesis methods are error- 12:15:35
```

17 prone." Do you see that? 12:15:39

A. Yes.

19 Q. The next sentence reads, "The fraction of 12:15:40

20 oligos with errors depends upon the length of the 12:15:42

21 oligonucleotide and the synthesis method 12:15:45

22 employed." Do you see that? 12:15:47

A. Yes.

A. Yes.

A. Yes.

14 **A. Yeah.** 12:16:17

18 A. Yeah. What I meant there was not in the 12:16:29

19 context of the type of errors that are referred to 12:16:32
20 in Claim 1. It's really talking about errors in 12:16:33
21 making primers, which is just a different -- just 12:16:37
22 a different context and usage of "error." 12:16:40

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1 Q. I see. So when you are defining "error" 12:16:43

2 as -- strike that. 12:16:49

3 In the context of Claim 1 of the '730 12:16:57

4 patent, you are not using "error" in its plain and 12:17:01

5 ordinary meaning. Correct? 12:17:07

6 MR. BROUGHAN: Object to form. 12:17:09

7 A. I don't know what you mean by that. 12:17:09

8 Q. So you would agree that EX-2006 in the 12:17:13

9 last paragraph of the draft application mentions 12:17:22

10 the word "error" multiple times. Correct? 12:17:25

11 A. Synthesis errors in oligonucleotides is 12:17:29

12 what they're talking about here, whereas, you 12:17:34

13 know, in the claims you're talking about errors 12:17:36

14 that arise when you're doing sort of this workflow 12:17:41

15 of amplifying a target and you want to understand, 12:17:48

16 you know, the sequence of that target. The 12:17:53

17 context of the word "error" is just different. 12:17:55

18 Q. I see. 12:17:58

19 A. This is not sequencing error. This is 12:18:01

20 error in making an oligo. 12:18:04

21 Q. I see. 12:18:06

22 A. Which also they think is quite favorable 12:18:07

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1 **because they might be like barcodes, which is** 12:18:10
2 **interesting.** 12:18:15

3 Q. So what EX-2006, the March 9, 2009 draft 12:18:15
4 application, discloses is errors in making -- 12:18:19
5 errors in making oligos. Correct? 12:18:22

6 **A. That's what I'm reading here.** 12:18:24

7 Q. Right. And it's your opinion that it does 12:18:27
8 not disclose a sequencing error. Correct? 12:18:29

9 **A. That's correct.** 12:18:31

10 Q. And when you look at the claims 12:18:35
11 limitations for Claim 1 of the '730 patent, it's 12:18:38
12 your opinion that "error" means sequencing error. 12:18:43
13 Correct? 12:18:47

14 MR. BROUGHAN: Objection to form. 12:18:48

15 **A. Not just sequencing error. "Error" means** 12:18:49
16 **error that is -- the error that is detected by** 12:18:52
17 **sequencing. And that error could be incorporated** 12:18:55
18 **on the sequencer or before, like we talked about** 12:18:58
19 **earlier.** 12:19:00

20 Q. In your opinion, "error," as claimed by 12:19:01
21 the '730 patent, is limited to error that is 12:19:21
22 detected by sequencing. Correct? 12:19:24

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1 MR. BROUGHAN: Object to form. 12:19:27

2 A. That's what they're -- that's how 12:19:37

3 they're -- that's how they're reading it out is by 12:19:40

4 sequencing. I don't know what else we would be 12:19:42

5 talking about. 12:19:47

6 Q. Okay. One way to sequence is sequencing 12:19:48

7 by synthesis. Right? 12:20:09

8 A. That's what happens on an Illumina 12:20:10

9 sequencer. 12:20:17

10 Q. Illumina sequencers are next-generation 12:20:17

11 sequencers. Correct? 12:20:22

12 A. They've been called that. Yes. 12:20:23

13 Q. And Illumina next-generation sequencers 12:20:24

14 use sequencing by synthesis. Correct? 12:20:27

15 A. They do. 12:20:29

16 Q. Let's turn to page 3 of EX-2006, if you 12:20:30

17 don't mind. The last paragraph on that page, the 12:21:12

18 very first sentence, "The actual incorporation." 12:21:27

19 Do you see that? 12:21:32

20 A. Yes. 12:21:32

21 Q. That reads, "The actual incorporation of 12:21:34

22 the random barcodes can be performed through 12:21:40

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1 various methods." Right? 12:21:44

2 A. Yup. 12:21:46

3 Q. And then if you move three sentences down, 12:21:46

4 "The sequencing primers." Do you see that? 12:21:49

5 A. Yes. 12:21:53

6 Q. That sentence in the March 6th, 2009 draft 12:21:53

7 application, EX-2006, states, "The sequencing 12:21:59

8 primers must be incorporated afterwards such as 12:22:04

9 they sequence both the barcode and the molecule of 12:22:06

10 interest." Correct? 12:22:09

11 A. I do. 12:22:10

12 Q. The March 6th, 2009 draft application, 12:22:11

13 EX-2006, discloses sequencing both the barcode 12:22:14

14 sequence and the sequence of the molecule of 12:22:19

15 interest. Correct? 12:22:21

16 A. Yes. 12:22:22

17 Q. And then turn the page to page 4. And 12:22:24

18 we're going to go the last paragraph there, the 12:22:33

19 "One example." 12:22:38

20 A. Oh, yes. 12:22:42

21 Q. That paragraph begins, "One example of the 12:22:42

22 use of the barcodes is in genome resequencing." 12:22:47

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1 Correct? 12:22:51

2 A. Uh-hmm. 12:22:51

3 Q. And then it goes on to say, "Considering 12:22:51

4 the accuracy of most next-generation sequencing 12:22:57

5 instruments is relatively low, it is crucial to 12:22:59

6 oversample the genomic loci of interest." 12:23:02

7 Correct? 12:23:07

8 A. Yes. 12:23:07

9 Q. And specifically, it is important to 12:23:07

10 sample enough to ensure that both alleles have 12:23:10

11 been observed a sufficient number of times to 12:23:13

12 confidently determine whether the sample is 12:23:16

13 homozygous or heterozygous. Correct? 12:23:21

14 A. Yes. 12:23:24

15 Q. And that process, determining whether a 12:23:24

16 sample is homozygous or heterozygous, is one form 12:23:28

17 of data analysis arising from genome resequencing. 12:23:32

18 Correct? 12:23:36

19 A. Yes. 12:23:36

20 Q. And you would perform the same process in 12:23:41

21 order to do -- in order to make a consensus base 12:23:45

22 call or sequence determination. Correct? 12:23:49

A. What do you mean?

3 a sample is homozygous or heterozygous involves 12:24:02

5 established that in genome resequencing. Correct? 12:24:11

⁷ A. Generally, it includes aligning to a 12:24:17

9 Q. You don't dispute that the March 6th, 2009 12:24:25

```
11 consensus base call. Correct? 12:25:05
```

13 A. I'm not sure I've given that opinion. 12:25:12

14 Q. Okay. Well -- 12:25:23

15 A. I don't think I've given that opinion. 12:25:24

16 Q. Sure. You don't dispute -- let me put it 12:25:26

17 this way: You don't dispute that the March 6, 12:25:31

18 2009 draft application discloses making a genotype 12:25:34

19 call. Correct? 12:25:37

20 **A. They describe making a genotype call.** 12:25:38

21 Q. Okay. And if you look at -- turn the page 12:25:50

22 again to page 5, the last sentence of the first 12:25:54

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1 paragraph, the one that begins "Therefore, the 12:26:00
2 sequences." 12:26:03

3 **A. Yes.** 12:26:04

4 Q. And it states, "Therefore, the sequences 12:26:04
5 and corresponding distribution of random barcodes 12:26:06
6 can be used as an additional input to the genotype 12:26:08
7 calling algorithm to significantly improve the 12:26:12
8 accuracy and confidence of the genotype calls." 12:26:14

9 **A. I see that.** 12:26:19

10 Q. You don't dispute that the March 6th, 2009 12:26:20
11 draft application discloses using both the 12:26:23
12 molecule of interest and the barcode in order to 12:26:26
13 improve the accuracy of making genotype calls. 12:26:28
14 Correct? 12:26:31

15 MR. BROUGHAN: Object to form. 12:26:31

16 **A. They are proposing here that that's what 12:26:32
17 they're doing -- 12:26:39**

18 Q. Okay. 12:26:39

19 **A. -- through correcting for bias.** 12:26:40

20 Q. Right. All right. Can you turn back to 12:26:41
21 EX-1001. And that's the '730 patent. 12:26:57

22 **A. Yes.** 12:27:03

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1 Q. We went over this in your last deposition. 12:27:03

2 The '730 patent has a "References Cited" section 12:27:13

3 on its face. Correct? 12:27:17

4 A. Yes. 12:27:18

5 Q. And you know that the "References Cited" 12:27:18

6 section lists both all the patents and, where 12:27:22

7 available, nonpatent publications presented to the 12:27:25

8 PTO during prosecution. Correct? 12:27:29

9 A. That's my understanding. Yes. 12:27:32

10 Q. And so the "References Cited" section for 12:27:33

11 the '730 patent would also just list or identify 12:27:37

12 all of the patents and nonpatent publications 12:27:41

13 presented to the Patent and Trademark Office 12:27:44

14 during prosecution of the '730 patent. Right? 12:27:47

15 A. Yes. 12:27:49

16 Q. So this list on the '730 patent contains 12:27:50

17 all the prior art available to the examiner during 12:27:55

18 prosecution? 12:27:57

19 MR. BROUGHAN: Object to form. 12:28:00

20 A. Well, I suppose any prior art is available 12:28:02

21 to the examiner. I mean, this is what they cite. 12:28:06

22 I don't know how to answer your question. 12:28:08

1 Q. Okay. The "References Cited" section of 12:28:10
2 the '730 patent includes all of the references 12:28:18
3 presented and identified to the examiner during 12:28:21
4 prosecution of this patent. Correct? 12:28:24

5 A. I assume so. Again, I'm not an attorney, 12:28:25
6 so I don't know the whole process here. But let's 12:28:33
7 just say I assume that these are the references 12:28:35
8 cited somewhere in this document. Yes. 12:28:38

9 Q. Sure. Okay. If you'd turn to page 4 of 12:28:39
10 the "References Cited" section. So that would be 12:28:49
11 actually page 4 of EX-1001 at the bottom. 12:28:52

12 A. Yeah. 12:28:58

13 Q. At the very top of the right-hand column, 12:28:58
14 there's an entry to "Turner, 2009." Do you see 12:29:01
15 that? 12:29:05

16 A. I do. 12:29:05

17 Q. That's "Turner, 2009, Massively parallel 12:29:05
18 exon capture and library-free resequencing across 12:29:10
19 16 genomes." Do you see that? 12:29:14

20 A. I do. 12:29:16

21 Q. "Massively parallel" is often a term used 12:29:16
22 to describe NGS or next-gen sequencing techniques. 12:29:22

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1 Correct? 12:29:26

2 A. Yes. 12:29:27

3 Q. Okay. Are you familiar with this Turner 12:29:27
4 reference? 12:29:32

5 A. I can't recall. 12:29:32

6 Q. Okay. But no reason to believe that the 12:29:34
7 Turner reference listed in the "Other 12:29:36
8 Publications" portion of the "References Cited" 12:29:39
9 section of the '730 patent does not address 12:29:41
10 technologies in next-generation sequencing? 12:29:46

11 MR. BROUGHAN: Object to form, relevance. 12:29:49

12 A. I don't know. I will say that the title 12:29:53
13 of the Turner is "Massively parallel exon 12:29:58
14 capture," which might just mean that they're 12:30:02
15 capturing exons in a massively parallel way. 12:30:05
16 Maybe they aren't using massively parallel 12:30:09
17 sequencing. 12:30:11

18 You had asked if massively parallel 12:30:12
19 sequencing is referred to sometimes as "NGS." I 12:30:15
20 agreed to that. But I honestly don't remember 12:30:17
21 this publication, off the top of my head. 12:30:20

22 Q. Sure. That's fine. Turn to page 6. And 12:30:22

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1 in the left-hand column, about halfway down 12:30:29

2 there's a Bau reference. 12:30:31

3 I'll give you some time to find it. It 12:30:35

4 says "Bau, 2008." 12:30:41

5 **A. Yes.** 12:30:41

6 Q. And the "Bau, 2008" reference is titled, 12:30:42

7 "Targeted next-generation sequencing by specific 12:30:44

8 capture of multiple genomic loci using low-volume 12:30:47

9 microfluidic DNA arrays." Correct? 12:30:53

10 **A. Yeah.** 12:30:55

11 Q. Are you familiar with that Bau reference? 12:30:55

12 **A. I don't recall it. No.** 12:30:57

13 Q. No reason to believe it doesn't address 12:30:58

14 next-generation sequencing? 12:31:01

15 **A. It says "Next-generation sequencing" in 12:31:03**

16 **the title, so I will assume it does.** 12:31:06

17 Q. And this would have been available to the 12:31:07

18 examiner during prosecution of the '730 patent? 12:31:09

19 **A. Yes. It looks like it.** 12:31:11

20 MR. WUESTE: All right. I will pass the 12:31:22

21 witness. 12:31:23

22 MR. BROUGHAN: We should probably take a 12:31:31

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1 break so I can . . . 12:31:32

2 THE VIDEOGRAPHER: The time is 12:31. 12:31:36

3 We're off the record. 12:31:38

4 (Recess, 12:31 p.m. to 12:43 p.m.) 12:31:39

5 THE VIDEOGRAPHER: Okay. The time is 12:43:12

6 12:43. We're back on the record. 12:43:19

7 EXAMINATION BY COUNSEL FOR 12:43:21

8 PETITIONER ILLUMINA INC. 12:43:21

9 BY MR. BROUGHAN: 12:43:21

10 Q. Dr. Gabriel, I have a few followup 12:43:22

11 questions for you. 12:43:24

12 In the pile of exhibits, would you please 12:43:25

13 pull out Exhibit 2026, which is one of the images 12:43:27

14 from Counsel. 12:43:30

15 A. Yes. 12:43:31

16 Q. And Counsel asked you a number of 12:43:31

17 questions about this figure. Do you recall that? 12:43:36

18 A. Yes. 12:43:37

19 Q. On the left of the figure there's what 12:43:37

20 Counsel has labeled "Original Target Nucleic 12:43:42

21 Acids." 12:43:45

22 A. Yes. 12:43:45

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1 Q. And there are two target -- original 12:43:46

2 target nucleic acids? 12:43:49

3 A. Yes. 12:43:51

4 Q. And then on the right, Counsel has labeled 12:43:51

5 the label saying "Amplified Product." Do you see 12:43:57

6 that? 12:43:59

7 A. Yes. 12:43:59

8 Q. On the right, are those amplicons? 12:44:00

9 A. On the right --

10 Q. Sorry. Under "Amplified Product" -- is 12:44:12

11 another word for an amplified product an 12:44:14

12 "amplicon"? 12:44:17

13 A. Sure. 12:44:17

14 Q. There are four amplicons with Barcode 1. 12:44:18

15 Do you see that? 12:44:23

16 A. Yes. 12:44:23

17 Q. Each amplicon consists of the barcode and 12:44:24

18 a copy of the target nucleic acid? 12:44:28

19 A. That's right. 12:44:32

20 Q. And Counsel had you circle one of the 12:44:32

21 amplicons where the target has a mutation in the 12:44:34

22 first position? 12:44:40

1 MR. BROUGHAN: Object to form.

2 Q. Or a different letter in the first 12:44:42

3 position? 12:44:46

4 A. That's correct. 12:44:46

5 Q. Do you recall if Counsel called that a 12:44:46

6 mutation or an error or . . . 12:44:48

7 A. I don't recall. It's a difference. 12:44:49

8 Q. Three of the amplicons had an "A" in the 12:44:58

9 first position of the target and one has a "T" in 12:45:01

10 the first position. Correct? 12:45:03

11 A. Yes. 12:45:04

12 Q. Is the one with the "T" in the first 12:45:05

13 position the same target nucleic acid as the three 12:45:07

14 with the "A" in the first position? 12:45:10

15 MR. WUESTE: Object to form. 12:45:14

16 A. It's a copy of the original. 12:45:15

17 Q. The four amplicons with Barcode 1 have a 12:45:22

18 copy of the same target nucleic acid? 12:45:26

19 MR. WUESTE: Object to form, leading. 12:45:29

20 A. They're copies. They're amplicons, all 12:45:30

21 four of them. 12:45:33

22 Q. With respect to the four amplicons with 12:45:34

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1 Barcode 1, is it four different nucleic acids or 12:45:48
2 is it one target nucleic acid? 12:45:51

3 MR. WUESTE: Object to form. 12:45:53

4 **A. Barcode 1 -- all of the Barcode 1 lines 12:45:54**
5 **are tagging copies of the same original target 12:46:07**
6 **nucleic acid. 12:46:12**

7 Q. You can put that exhibit aside. And if 12:46:15
8 you could get your reply declaration, which is 12:46:19
9 Exhibit 1065. 12:46:21

10 **A. Yes. 12:46:37**

11 Q. Would you turn to Paragraph 20, please. 12:46:37

12 **A. 20? 12:46:41**

13 Q. Yes. 12:46:42

14 Do you recall that Counsel asked you a 12:46:45
15 number of questions about Paragraph 20 of your 12:46:46
16 reply declaration? 12:46:49

17 **A. Yes. 12:46:50**

18 Q. Counsel asked about the scenarios in which 12:46:51
19 you might make a cost-accuracy trade-off? 12:46:57

20 **A. I do. 12:47:01**

21 Q. What are some scenarios when you would 12:47:01
22 want to have higher accuracy in your sequencing? 12:47:04

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1 **A. In diagnostics, you'd like to have high** 12:47:07
2 **accuracy.** 12:47:12

3 **If you're trying to detect a very rare** 12:47:13
4 **event where you might be worried you're going to** 12:47:16
5 **confuse an error with attribution, you might** 12:47:19
6 **want to have very high accuracy.** 12:47:24

7 **Yeah. I would say particularly in** 12:47:30
8 **diagnostics. In diagnostics, it can include that** 12:47:33
9 **example where you might have a rare event that you** 12:47:35
10 **want to make sure you don't confuse with some** 12:47:37
11 **noise or error.** 12:47:41

12 **Q. Is it common to perform tests where you** 12:47:41
13 **would want your sequencing to detect -- sorry.** 12:47:55
14 **Strike that.** 12:47:59

15 **Is it common to run diagnostic tests where** 12:47:59
16 **you would want to have high accuracy?** 12:48:07

17 **MR. WUESTE: Object to form, leading.** 12:48:09

18 **A. Absolutely. I mean, the diagnostic tests** 12:48:11
19 **you're giving a result back to an individual, so** 12:48:18
20 **you'd want to have high accuracy. Yes.** 12:48:20

21 **Q. You can set that aside. Would you get** 12:48:31
22 **Exhibit 2006, which is the conception document.** 12:48:37

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1 Would you turn to the last paragraph of the 12:48:55
2 document. 12:48:57

3 **A. Yes.** 12:48:59

4 Q. Counsel had asked you a number of 12:48:59
5 questions about the last paragraph of 12:49:05
6 Exhibit 2006. Do you recall that? 12:49:08

7 **A. I do.** 12:49:09

8 Q. What type of error does this paragraph of 12:49:09
9 Exhibit 2006 describe? 12:49:17

10 **A. Errors in the PCR primers.** 12:49:19

11 Q. Those are errors in the -- in an 12:49:32
12 oligonucleotide sequence? 12:49:35

13 **A. Yes.** 12:49:37

14 Q. Does the last paragraph of Exhibit 2006 12:49:38
15 disclose correcting for errors? 12:49:44

16 **A. It does not.** 12:49:45

17 MR. BROUGHAN: We have no further 12:49:53
18 questions. 12:49:54

19 FURTHER EXAMINATION BY COUNSEL FOR

20 PATENT OWNER MOLECULAR LOOP BIOSCIENCES, INC. 12:50:04

21 BY MR. WUESTE: 12:50:04

22 Q. Dr. Gabriel, is it your opinion that 12:50:04

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1 "error," as claimed in the '730 patent, does not 12:50:07
2 cover errors in PCR primers? 12:50:12

3 MR. BROUGHAN: Object to form. 12:50:16

4 **A. Not the errors that are described here in 12:50:16**
5 **the conception document in the PCR primers. No. 12:50:30**

6 Q. Okay. Errors in PCR primers are a type of 12:50:33
7 error. Correct? 12:50:36

8 MR. BROUGHAN: Object to form. 12:50:38

9 **A. It's an oligonucleotide synthesis error in 12:50:40**
10 **the PCR primer itself. Yes. 12:50:43**

11 Q. All right. 12:50:45

12 **A. That's not the same error that I read in 12:50:46**
13 **the context of the '730 claims. No. 12:50:49**

14 Q. And an oligonucleotide synthesis error in 12:50:54
15 the PCR primer itself arises from the synthesis 12:50:57
16 process. Right? 12:51:02

17 MR. BROUGHAN: Object to form. 12:51:04

18 **A. Yes. 12:51:05**

19 Q. Okay. And it's your opinion that the term 12:51:06
20 "error" as claimed by the '730 patent does not 12:51:10
21 cover errors arising from the synthesis process 12:51:14
22 like oligonucleotide synthesis errors in the PCR 12:51:18

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1 primer? 12:51:21

2 MR. BROUGHAN: Object to form. 12:51:22

3 A. That's not the context of how I read 12:51:23

4 "error" in Claim 1 of the '730 patent. 12:51:41

5 The errors that are described here in the 12:51:45

6 2006 -- in Exhibit 2006 in the PCR primers, 12:51:49

7 they're just saying they're a way that you might 12:51:53

8 further correct bias, actually. They're not used 12:51:55

9 for error correction. 12:51:58

10 Q. All right. And it's your opinion that 12:51:59

11 error correction -- strike that. 12:52:02

12 It's your opinion that correcting for 12:52:05

13 errors as claimed by the '730 patent is narrower 12:52:06

14 than identifying errors generally? 12:52:12

15 MR. BROUGHAN: Object to form. 12:52:19

16 A. I think, again, if you look at the claim 12:52:20

17 language, to me it's errors -- it's what they say 12:52:24

18 here, errors that are introduced during this 12:52:36

19 workflow of taking a sample, introducing tags, 12:52:38

20 amplifying the sample, and sequencing it. 12:52:43

21 That's the errors that I'm talking -- that 12:52:45

22 I consider errors in the '730 patent. 12:52:48

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1 Q. Does an error in a PCR primer that arose 12:52:52
2 during synthesis occur during a nucleic acid 12:52:58
3 analysis workflow? 12:53:02

4 A. It would have occurred before that, when 12:53:03
5 you're making the primer, which is not happening 12:53:09
6 here. 12:53:11

7 Q. Okay. So again, you are reading "error" 12:53:13
8 to be narrower -- strike that. 12:53:16

9 You are reading "error," as claimed by the 12:53:18
10 '730 patent, to be narrower than errors generally? 12:53:20

11 MR. BROUGHAN: Object to form. 12:53:29

12 A. Again, I'm reading "errors" to be errors 12:53:30
13 that occur during this workflow because that's 12:53:32
14 what I was asked to consider when I was -- when I 12:53:35
15 was asked my opinion on errors in the context of 12:53:39
16 the '730 patent. 12:53:43

17 MR. WUESTE: Okay. No further questions. 12:53:47

18 THE VIDEOGRAPHER: Okay. The time is 12:53:52
19 12:53. We're off the record. 12:53:55

20 (Off the record at 12:53 p.m.) 12:53:59

21

22

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2 I, Michelle Keegan, Registered Merit
3 Reporter and Notary Public within and for the
4 Commonwealth of Massachusetts, do hereby certify:

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

11 I further certify that the adverse party
12 was represented by counsel at the deposition.

13 I further certify that the deposition of
14 STACEY GABRIEL, PH.D. occurred at the offices of
15 Sidley Austin LLP, 60 State Street, Boston,
16 Massachusetts 02109, on Thursday,
17 November 6, 2025, commencing at 9:05 a.m. to
18 12:54 p.m.

19 I further certify that I am not related to
20 any of the parties to this action by blood or
21 marriage, I am not employed by or an attorney to
22 any of the parties in this action, and that I am
in no way interested, financially or otherwise, in
the outcome of this matter.

I declare under penalty of perjury that
the foregoing is true and correct. Executed on
the 6th day of November, 2025.

Michelle Keegan

My commission expires: May 15, 2026
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22

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