

UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,

Petitioner,

vs.

TECAN GENOMICS, INC.

Patent Owner.

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Case IPR2024-01504

U.S. Patent No. 11,098,357

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Case IPR2025-00015

Case IPR2025-00016

U.S. Patent Nos. 10,036,012 and 10,876,108

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CONTINUED DEPOSITION OF  
DR. CARLOS BUSTAMANTE, VOL II

New York, New York

Thursday, October 23, 2025

Reported By:

CATHI IRISH, RPR, CRR, CLVS

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October 23, 2025

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8:15 a.m.

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Continued deposition of DR.

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CARLOS BUSTAMANTE, Vol II, held at the offices

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of Goodwin Procter, 620 Eighth Avenue,

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New York, New York, before Cathi

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Irish, a Registered Professional

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Reporter, Certified Realtime Reporter,

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and Notary Public of the State of

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New York.

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1     A P P E A R A N C E S:

2

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10

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13             Attorneys for Patent Owner

14             and the Witness

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18             BY: LINNEA P. CIPRIANO, ESQ.

19                     TIMOTHY J. BEAVERS, ESQ.

20                     (via Zoom)

21

22

23     ALSO PRESENT:

24             Andreas Schild

25

## 1 ----- I N D E X -----

2 WITNESS EXAMINATION BY PAGE

3 CARLOS BUSTAMANTE MR. HOAGLAND-HANSON 248

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## 6 ----- EXHIBITS -----

7 EXHIBIT NUMBER DESCRIPTION PAGE

8 IDT Exhibit 1123, library 324

9 preparation method

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1 D R. C A R L O S B U S T A M A N T E,  
2 recalled as a witness, having been  
3 previously sworn by a Notary Public,  
4 was examined and testified as follows:

5 CONTINUED EXAMINATION

6 BY MR. HOAGLAND-HANSON:

7 Q. You understand you're under oath?

8 A. I do.

9 Q. Good morning, Dr. Bustamante.

10 A. Good morning.

11 Q. Do you still have a copy of your  
12 declaration, Exhibit 2038 in front of you?

13 A. I do.

14 Q. Do you have still have a copy of  
15 the '012 patent, Exhibit 1001?

16 A. I do.

17 Q. I want to talk about claim 22 of  
18 the '012 patent.

19 A. Okay.

20 Q. And your opinions on that start  
21 at paragraph 294 of Exhibit 2038.

22 A. You said 200 and --

23 Q. 94.

24 A. Okay.

25 Q. And claim 22 requires that each

1 end of the nucleic acid fragment is  
2 ligated to a partial duplex adaptor. Do  
3 you recall that?

4 A. I do. Let me turn to the claim  
5 language so I have it in front of me.

6 Q. And in paragraph 297 you say,  
7 "While it is possible that some CAP  
8 primers are damaged by fragmentation, a  
9 POSA would have understood that it was not  
10 a guaranteed outcome."

11 Do you recall that?

12 A. I do.

13 Q. You agree that it can happen that  
14 the cap primer is damaged in an adaptor  
15 ligates on both ends of the frag; right?

16 A. It can happen.

17 Q. And you agree that the  
18 fragmentation process that Meyer uses  
19 breaks the cDNA strands randomly without  
20 regard to sequence; right?

21 A. They consider a series of  
22 different fragmentation conditions, if we  
23 want to say that, and actually describe  
24 more than one protocol but yes, it should  
25 sheer randomly.

1           Q.    And you agree that the  
2   fragmentation protocol that Meyer uses  
3   doesn't exclude the ends of the strands in  
4   some way?

5           A.    I would agree that it fragments  
6   randomly as we were discussing.

7           Q.    And you agree in the data that  
8   Meyer deposited that it did, in fact,  
9   happen?

10          A.    In about 1 percent or something  
11   like that.  It was a very minuscule  
12   number.

13          Q.    And that data was the data that  
14   the Meyer authors considered  
15   representative of the use of the method;  
16   right?

17          A.    It was the data from the first  
18   method, not the -- from the only method  
19   they presented data on which is the method  
20   in Figure 1 as I recall.

21          Q.    You're not aware of any other  
22   data that's publicly available from the  
23   use of this method?

24          A.    Well, there's the data that  
25   Dr. Sims described in his report.

1 Q. That's the same data; right?

2 A. I wasn't sure what you were --  
3 you were referencing. Do you mean if  
4 somebody else has implemented the Meyer  
5 protocol?

6 Q. Yeah.

7 A. I'm not aware that other data has  
8 been analyzed in this proceeding aside  
9 from the Meyer data that was deposited.

10 Q. So in the only time that this --  
11 that you're aware of that this method was  
12 used for which data was available there  
13 was fragmentation in the cap sequences?

14 A. In a very small fraction.

15 Q. Do you understand claim 22 to  
16 impose a threshold requirement as to how  
17 many adaptors have to be ligated to the  
18 other end of the strand?

19 MS. CIPRIANO: Objection, form.

20 THE WITNESS: Sorry, would you  
21 repeat the question?

22 BY MR. HOAGLAND-HANSON:

23 Q. Sure. Do you understand claim 22  
24 to impose some threshold requirement for  
25 how many fragments have to get adaptors on

1 both ends of the strand?

2 MS. CIPRIANO: Objection.

3 THE WITNESS: Well, the claim  
4 language doesn't pose a threshold but  
5 you would be hesitant to implement a  
6 method where the vast majority of the  
7 molecules won't be accessible to the  
8 protocol; right? So if there are  
9 no -- the cap by definition is a cap.  
10 That's why they can't ligate to it so  
11 you need to suppose that there are  
12 sufficient molecules available to  
13 create a library of sufficient  
14 complexity to sequence in order to  
15 want to implement such a method.

16 BY MR. HOAGLAND-HANSON:

17 Q. You agree with me that if one  
18 fragment has adaptors ligated to both ends  
19 and meets the other limitations of the  
20 method, it goes all the way through,  
21 right, has an oligo anneal, gets amplified  
22 and then gets sequenced at the end, that  
23 you practice claim 22; right?

24 A. It would be a almost  
25 unsequenceable library because you have no

1 complexity. The entire sequencing process  
2 for massive parallel sequencing requires a  
3 complexity in the library. So if you only  
4 have one fragment, that's not going to  
5 work on the sequencing side and this is a  
6 method for sequencing.

7 Q. I'm asking you so what exactly  
8 does claim 22 require in your view? Is it  
9 your view that claim 22 requires every  
10 fragment in the sample to get an adaptor  
11 on both ends?

12 MS. CIPRIANO: Objection to form.

13 THE WITNESS: My understanding of  
14 claim 22 is that it would require for  
15 a POSA to design and experiment and  
16 expect a reasonable fraction of  
17 molecules to have adaptors ligated at  
18 both ends so that you could create a  
19 library of complexity so that it could  
20 be sequenced by next generation or  
21 other massive parallel. So looking at  
22 the Meyer data, you would not have an  
23 expectation of success that it would  
24 work. The whole design of Meyer is  
25 those caps can't be ligated on the

1           other side. That's the whole reason  
2           they designed the system in that way.

3   BY MR. HOAGLAND-HANSON:

4           Q.    I guess, Dr. Bustamante, before  
5   we get to what Meyer is trying to do, I'm  
6   just trying to figure out what you think  
7   claim 22 requires, right, because you  
8   understand your analysis sort of starts  
9   from what the claims are; right?

10          A.    I do. I think claim 22 requires  
11   ligation of the duplex adaptor on both  
12   ends of the nucleic acid fragment.

13          Q.    And so that's fragment singular;  
14   right?

15          A.    Each end of the nucleic acid  
16   fragment in the pool of fragments that  
17   we're considering; right?

18          Q.    Okay. Claim 1 also talks about a  
19   fragment, right, singular?

20          A.    We can go back to claim 1.  
21                  (Witness perusing document.)  
22                  It does focus on a fragment with  
23   a partial duplex adaptor being ligated.

24          Q.    So both claim 1 and claim 22,  
25   which depends from claim 1, are talking

1 about things that have to happen to a  
2 single fragment; right?

3 A. I would agree that the language  
4 here is focused on a fragment to which you  
5 were appending the adaptors.

6 Q. Okay. And what I'm just trying  
7 to understand is if I have a reaction  
8 where just one fragment gets the adaptor  
9 ligated on both sides, have I practiced  
10 claim 22 or not?

11 MS. CIPRIANO: Objection to form.

12 THE WITNESS: Again, I would find  
13 it difficult to understand the logic  
14 behind applying this to a pool where  
15 you have purposely blunt ended one end  
16 of the molecule so that you prevent  
17 ligation. So, you know, from a  
18 thermodynamic point of view, you're  
19 going to get some fragments that have  
20 ligation but the vast majority won't  
21 and so you won't be able to proceed in  
22 producing a usable library.

23 BY MR. HOAGLAND-HANSON:

24 Q. Okay. I want to go back to  
25 something else that you said.

1           Your lawyers gave you some  
2 instructions on the legal standards that  
3 are applicable to your analysis. Do you  
4 recall that?

5           A.    I do.

6           Q.    And you recall that there are two  
7 different legal issues and I'm not trying  
8 to hide the ball. You can look at  
9 paragraph 33 and 34 of your declaration,  
10 Exhibit 2038.

11           And you understand per paragraph  
12 33 that there's an anticipation issue and  
13 in paragraph 34 you talk about  
14 obviousness; is that right?

15           A.    That's correct.

16           Q.    Is it your understanding that in  
17 your analysis of the anticipation issue  
18 that the POSA has to have a reasonable  
19 expectation of success for there to be an  
20 anticipation?

21           A.    My understanding of anticipation  
22 is that every claim element must be  
23 present in the prior art in the same way  
24 and order as it is illustrated in the --  
25 in the claims.

1           Q.    Okay.  So earlier you just  
2   misspoke when you talk about a reasonable  
3   expectation of success with respect to  
4   anticipation, that's not part of your  
5   analysis; right?

6                   MS. CIPRIANO:  Objection to form.

7                   THE WITNESS:  You asked me about  
8           anticipation, I've answered about  
9           anticipation because there are also  
10          obviousness issues at the end and you  
11          were asking me about whether claim 22  
12          would require a threshold.  And my  
13          answer was meant to convey the fact  
14          that in the Meyer experiment you  
15          purposely built the library so that  
16          you couldn't ligate adaptors on it.  
17          So I think it is quite unreasonable to  
18          suppose that somebody would want to  
19          take that and view it as a way to  
20          ligate the two ends of the molecule  
21          with an adaptor, given the design of  
22          Meyer.

23          BY MR. HOAGLAND-HANSON:

24                Q.    Okay.  And I just want to follow  
25   up on this to make sure I understand.

1                   For purposes of your anticipation  
2   opinions, does it matter whether or not  
3   the Meyer authors intended for something  
4   to happen if it did, in fact, happen? Let  
5   me try to ask a better question.

6                   Dr. Bustamante, if, in fact, all  
7   of the limitations of claim 22 are met by  
8   the Meyer process, does it matter if the  
9   Meyer authors intended for that to happen?

10                  MS. CIPRIANO: Objection, form.

11                  THE WITNESS: It is my  
12   understanding that for the prior art  
13   to anticipate, the POSA would need to  
14   read the prior art in such a way that  
15   the claims could be practiced as they  
16   were in the prior art. Meyer makes no  
17   real attempt to use the broken cap  
18   sequence to derive any biological  
19   insight beyond the fact that the cap's  
20   pretty much capped. It wasn't an  
21   alternative method to say oh now,  
22   because our caps don't work well, in  
23   fact, we're ligating to both ends. So  
24   there's nothing in my reading of Meyer  
25   that would say clearly they are

1           ligating two adaptors to both ends  
2           because the cap sequence is not really  
3           capping. It's capping very well and  
4           that's the whole purpose of Meyer.

5   BY MR. HOAGLAND-HANSON:

6           Q.    But in fact, the data shows they  
7           didn't successfully cap every fragment.

8           A.    99 percent. I mean it's about as  
9           successful as the experiment can be and  
10          this is part of their design. Their whole  
11          goal was to do an unbiased transcriptome  
12          sequencing from the internal molecule;  
13          right? They wanted to stay away from the  
14          cap all together; right? They don't want  
15          to sequence the cap, they don't want real  
16          estate on cap. So the fact that you have  
17          a minuscule amount of this happening, it's  
18          an off product. It's the same way primer  
19          dimers, it is part of the thermodynamics  
20          of the reaction, you would not use that to  
21          then logically conclude this is an  
22          efficient and great way to do the  
23          sequencing because you're getting adaptors  
24          on both ends.

25          Q.    Is it your opinion that it

1 doesn't anticipate because those 1 percent  
2 fragments were undesired?

3 MS. CIPRIANO: Objection, form.

4 THE WITNESS: No, because it's a  
5 by-product and not in any way, shape  
6 or form part of the design and you're  
7 not guaranteed to get it again.  
8 Right? You could rerun the experiment  
9 and find that instead of 1 percent you  
10 didn't see any. If you'd sequenced  
11 less you wouldn't have seen any.  
12 There are all kinds of things that end  
13 up in the library that don't get  
14 sequenced. They are not part of  
15 what's in the claims.

16 BY MR. HOAGLAND-HANSON:

17 Q. So two follow-ups on that.  
18 First, what's your evidence if you  
19 repeated this you wouldn't get the same  
20 data?

21 A. Because of stochasticity. You  
22 change the parameters on the  
23 fragmentation, you'll get less  
24 fragmentation. You may not get a broken  
25 cap. And enough broken cap to have

1    ligated to be sequenced given the depth of  
2    sequencing that they did. So the fact  
3    they found some broken cap at a very  
4    minuscule amount in this experiment is no  
5    guarantee that were you to repeat it you  
6    would see it again. It's stochastic  
7    sampling.

8           Q.    You agree with me that the Meyer  
9    authors reported and deposited data that  
10   they considered to be representative of  
11   the use of their method; right?

12          A.    They --

13                MS. CIPRIANO:  Objection, form.

14                THE WITNESS:  They deposited the  
15   data from their paper as is standard  
16   in the field, you deposit your data.  
17   And other folks can do reanalysis of  
18   the data.

19   BY MR. HOAGLAND-HANSON:

20          Q.    One of the purposes of the Meyer  
21   publication was as a proof of concept for  
22   this method of library preparation; right?

23                MS. CIPRIANO:  Objection, form.

24                THE WITNESS:  For the intended  
25   purpose of full transcriptome

1 sequencing and to demonstrate that  
2 they could solve a lot of the problems  
3 with getting cDNA sequencing from a  
4 non-model organism.

5 BY MR. HOAGLAND-HANSON:

6 Q. Claim 22 just says each end of  
7 the nucleic acid fragment is ligated to  
8 the partial duplex adaptor; right?

9 A. That's what it says.

10 Q. It doesn't say wherein more than  
11 1 percent of the total fragments in the  
12 sample are also so ligated; right?

13 A. It does not say that.

14 Q. In other words, that claim 22  
15 doesn't exclude a situation in which only  
16 a single fragment is ligated; right?

17 MS. CIPRIANO: Objection, form.

18 THE WITNESS: The claim says what  
19 it says. I will leave it to the court  
20 to decide. In my opinion I don't feel  
21 someone would look at the Meyer data  
22 and derive from that an understanding  
23 that you're getting meaningful  
24 ligation of the partial duplex adaptor  
25 to both ends.

1 BY MR. HOAGLAND-HANSON:

2 Q. Okay.

3 A. Because you're not.

4 Q. But you agree that that phrase  
5 that you just used, meaningful ligation of  
6 the partial duplex adaptor to both ends,  
7 that's not recited in the claim; right?

8 A. No, I'm giving you my scientific  
9 interpretation.

10 Q. Okay. You also agree that the  
11 data shows that in the instance of the  
12 experiment that the Meyer authors ran,  
13 there was ligation to both ends; right?

14 MS. CIPRIANO: Object to form.

15 THE WITNESS: They found evidence  
16 of the broken cap which would have  
17 only happened with sequencing.

18 BY MR. HOAGLAND-HANSON:

19 Q. They found evidence of the broken  
20 cap which would have only happened if  
21 adaptors were ligated to both ends; right?

22 A. For sequencing.

23 Q. I guess that's just not an answer  
24 to my question. I'm trying to figure out  
25 are you saying -- so let me ask the

1 question again.

2           They found evidence of the broken  
3 cap which would only happen if adaptors  
4 were ligated to both ends for sequencing;  
5 right?

6       A. That is correct. So one of the  
7 things that they did not do is ligate  
8 adaptors to both sides and then go through  
9 the entire extension targeting step;  
10 right? The cap sequencing occurred  
11 through the by-product of ligating  
12 sequencing adaptors to fragments the same  
13 way they get some primer dimers that  
14 weren't targeted. So the way that this  
15 happens in the Meyer experiment, you're  
16 not pushing those cap sequences through  
17 the targeting extension and amplification  
18 so there's no enrichment for cap. There's  
19 no possible way to enrich for cap, given  
20 what they're seeing here. Rather it is a  
21 by-product fully consistent with the large  
22 number of molecules produced and nothing  
23 in my reading of this would say that you  
24 could push those fragments through the  
25 rest of the elements in claim 1.

1 Q. There are other fragments which  
2 do have the binding site for the  
3 oligonucleotide; right?

4 MS. CIPRIANO: Objection, form.

5 THE WITNESS: Yes.

6 BY MR. HOAGLAND-HANSON:

7 Q. And those fragments you agree can  
8 also get adaptors ligated to both ends if  
9 their final blocked cap is truncated;  
10 right?

11 A. We have no evidence of that.

12 Q. Did you discuss this issue with  
13 Dr. Meyer?

14 A. No, I've had no communication  
15 with Dr. Meyer.

16 Q. Do you know why he doesn't offer  
17 an opinion that this doesn't happen?

18 A. I have had no communication with  
19 Dr. Meyer, I don't know why Dr. Meyer does  
20 not put it in his declaration. I can't  
21 speak to that.

22 Q. Did you ask your lawyers to ask  
23 Dr. Meyer for you?

24 A. I had -- I am not at liberty to  
25 discuss conversations we've had under

1 privilege.

2 Q. So you weren't interested in what  
3 Dr. Meyer had to say on this issue?

4 MS. CIPRIANO: Objection, form.

5 THE WITNESS: I did not state  
6 that. I did not -- I had no  
7 communication with Dr. Meyer in any  
8 way.

9 BY MR. HOAGLAND-HANSON:

10 Q. So you did ask your lawyers about  
11 it but you consider that a privileged  
12 communication?

13 MS. CIPRIANO: Objection to the  
14 extent it seeks privileged  
15 information. Carlos, you can answer  
16 yes or no.

17 THE WITNESS: I did not request  
18 that the attorneys ask Dr. Meyer for  
19 additional opinions beyond the  
20 opinions they sought from him.

21 BY MR. HOAGLAND-HANSON:

22 Q. I want to change subjects and ask  
23 you some questions about the claim  
24 construction of enrich.

25 A. Okay.

1           Q.    So if we could go to paragraph  
2   149 of Exhibit 2038.  So in paragraph 149,  
3   Dr. Bustamante, you agree that enrich has  
4   plain and ordinary meaning which is to  
5   process so as to add or increase the  
6   proportion of a desirable ingredient?

7           A.    I agree that the Board has  
8   construed enrich to mean that and the POSA  
9   would have considered the term enrich to  
10  have its plain and ordinary meaning that  
11  the panel's definition reflects.  However,  
12  as I lay out in my declaration, the term  
13  enrich is used in multiple ways in the  
14  patent and for enrichment to occur in the  
15  patent it must occur in a very specific  
16  way.

17          Q.    It's your view then, I think,  
18  that enrich has a plain and ordinary  
19  meaning, but here that plain and ordinary  
20  meaning is modified by context; is that  
21  right?

22          A.    Yes, in that as used in the  
23  patent, enrichment is the result of the  
24  amplification process that includes  
25  necessarily the extension products and

1     their complement. That is how enrichment  
2     has to occur as defined in the patent.

3           Q.    Got it. So in your view the  
4     proper construction of enrich is to  
5     process so as to add or increase the  
6     proportion of a desirable ingredient as  
7     the result of an amplification process  
8     that includes necessarily the  
9     amplification products and their  
10    complement?

11          A.    The target, the extension  
12    products through the targeting step.

13          Q.    Okay. So I want to come back to  
14    that.

15                You agree with me that the  
16    claim -- and that is what you set out in  
17    your report -- has the word enriched in  
18    two places; right?

19          A.    It has the word enriched in the  
20    preamble and it has the word enriched in,  
21    I believe, 1(d).

22          Q.    And then it appears again in 1(f)  
23    but we'll agree that that's the same as  
24    the preamble?

25          A.    Yes, I think the sequencing of

1 the enriched nucleic acid milieu by (f),  
2 the fragments that are made available for  
3 sequencing are the result of the  
4 enrichment process.

5 Q. In your view does the enrichment  
6 that happens as a result of the claimed  
7 method have to be intentional or can it be  
8 accidental?

9 MS. CIPRIANO: Object to form.

10 THE WITNESS: In general when we  
11 undertake molecular biology protocols  
12 like next-generation sequencing,  
13 you've designed the experiment and the  
14 protocols in such a way so that they  
15 are reproducible and intentional. So  
16 it would seem to me to practice the  
17 claimed intention, you would have a  
18 desired outcome based on the target  
19 for which you are enriching. You  
20 could get off-target effects as part  
21 of a design, but I would find it to  
22 still be the result of the intentional  
23 design to target a specific sequence  
24 of interest.

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. Okay, if I come to you and I say  
3 I have an unbiased method for cDNA  
4 sequencing but, in fact, I enrich  
5 exclusively frags of the 3' end, would you  
6 say that's a method of enrichment or not?

7 MS. CIPRIANO: Objection.

8 THE WITNESS: First, that's not  
9 what happens in the Meyer method. The  
10 Meyer method sequences all of the  
11 fragments that have the adaptors  
12 ligated to it including the internal  
13 fragments, so the -- the claims here  
14 are laid out so that a POSA can  
15 practice the claimed invention.  
16 That's the purpose of laying them out.  
17 If you happen to have an experiment  
18 where something went off the rails,  
19 again, no guarantee it's reproducible,  
20 there's no guarantee you know why that  
21 happened so you'd have to troubleshoot  
22 it and I would not consider that in a  
23 meaningful way as anticipating the  
24 claims and that's not what happens in  
25 Meyer anyway.

1 BY MR. HOAGLAND-HANSON:

2 Q. So I guess I just want to follow  
3 up on this one more time to make sure I  
4 understand.

5 If, in fact, I get enrichment,  
6 but that was to your point not part of my  
7 experimental design, I haven't practiced  
8 the claim?

9 MS. CIPRIANO: Objection, form.

10 THE WITNESS: For you to practice  
11 the claim you need to enrich through  
12 the process laid out here where you  
13 are amplifying the extension products  
14 that arise as a result of the  
15 targeting process which includes the  
16 ligation of the adaptors and so on. I  
17 have seen no evidence that has been  
18 presented that somebody has enriched,  
19 including Meyer, in any accidental or  
20 purposeful way, so I can't answer that  
21 hypothetical without understanding the  
22 context in which you would like me to  
23 answer.

24 BY MR. HOAGLAND-HANSON:

25 Q. For purposes of the claim, is it

1 a goal, a result or both?

2 MS. CIPRIANO: Objection, form.

3 THE WITNESS: The purpose of the  
4 claimed invention is to enrich for the  
5 nucleic acid sequence of interest.

6 That's the purpose.

7 BY MR. HOAGLAND-HANSON:

8 Q. So it's enough to just have the  
9 purpose even if I don't get enrichment at  
10 the end?

11 MS. CIPRIANO: Objection, form.

12 THE WITNESS: If you practice the  
13 claimed invention, you will get  
14 enrichment at the end as specified  
15 here because the products available  
16 for sequencing will be the end result  
17 of the extension step through the  
18 amplification of the sequencing  
19 adaptors. Otherwise you won't have  
20 sequencing adaptors. So if you're  
21 able to get sequence data, it will be  
22 coming through the process laid out  
23 here in the claimed invention. In the  
24 Meyer example they have a ton of  
25 additional sequence data that wasn't

1        derived in any meaningful way from  
2        anything that resembles the claim  
3        invention. They were sequencing the  
4        internal fragments, they were  
5        sequencing the 5' capped end. None of  
6        that would meet the requirements here.

7        BY MR. HOAGLAND-HANSON:

8        Q.    You understand that this is  
9        what's called a comprising claim; right?

10       A.    I understand the term comprising.

11       Q.    What does that mean?

12       A.    Including.

13       MS. CIPRIANO: Objection, form.

14       BY MR. HOAGLAND-HANSON:

15       Q.    It means including but not  
16       limited to?

17       A.    But not limited to.

18       Q.    Right?

19       A.    Agreed.

20       Q.    And you agree that these don't  
21       have to be the only primers in the  
22       reaction; right?

23       A.    In my reading, there is nothing  
24       in the claimed invention that prevents you  
25       from having other primers. However, you

1 wouldn't then be enriching as designed  
2 here unless they were multiplex primers  
3 that were enriching for other targets of  
4 interest.

5 Q. You agree these don't have to be  
6 the only adaptors in the reaction; right?

7 MS. CIPRIANO: Objection, form.

8 THE WITNESS: Then it's not this  
9 method.

10 BY MR. HOAGLAND-HANSON:

11 Q. So in your understanding, in your  
12 interpretation of this claim, the only  
13 adaptors that can be used as part of this  
14 method is the adaptor that's recited in  
15 step (a) and it's closed to other  
16 adaptors?

17 MS. CIPRIANO: Objection, form.

18 THE WITNESS: In my reading you  
19 need to practice these steps in order  
20 to enrich in the way laid out in the  
21 claimed invention. If that is the  
22 purpose, and you're looking to enrich  
23 multiple targets, then obviously each  
24 of those adaptors would be different  
25 versions of the adaptor described

1           here.

2       BY MR. HOAGLAND-HANSON:

3           Q.    Going back to our conversation  
4    earlier, you agree that this claim only  
5    speaks to a single fragment; right?

6           MS. CIPRIANO:  Objection, form.

7           THE WITNESS:  A fragment in the  
8    milieu of nucleic acids that are being  
9    put through the protocol for  
10   enrichment.

11   BY MR. HOAGLAND-HANSON:

12          Q.    Okay.  If one fragment in the  
13   solution goes through these steps, but a  
14   hundred other fragments go through other  
15   chemistry steps, am I practicing the  
16   method or not as to that one fragment?

17          MS. CIPRIANO:  Objection, form.

18          THE WITNESS:  You would be  
19   practicing the method if you are going  
20   through all of the steps (a) through  
21   (f).

22   BY MR. HOAGLAND-HANSON:

23          Q.    Is there a threshold amount by  
24   which the fragment has to be enriched at  
25   the end?

1 MS. CIPRIANO: Objection, form.

2 THE WITNESS: There is no  
3 threshold specifically laid out in the  
4 patent.

5 BY MR. HOAGLAND-HANSON:

6 Q. So if I go through the process, I  
7 start with a hundred fragments, and I end  
8 up with 101 fragments, have I enriched for  
9 that one fragment that I've added?

10 A. By the plain and ordinary  
11 meaning, I would say not much, if at all.

12 Q. Have I enriched or not?

13 A. I would consider that not  
14 enrichment in any meaningful way.

15 Q. If I enrich the concentration of  
16 one fragment by 10 percent, is that  
17 enrichment then?

18 MS. CIPRIANO: Objection, form.

19 THE WITNESS: It depends on which  
20 of the definitions of enrichment we  
21 are focusing on. If the enrichment  
22 occurs as a result of the claims as  
23 laid out in (a) through (f), then by  
24 definition that would be enrichment  
25 using this method. In the plain and

1           ordinary meaning going from 1 percent  
2           to 10 percent would be considered  
3           enrichment.

4   BY MR. HOAGLAND-HANSON:

5           Q.   How many cycles of PCR are  
6           required by 1(d)?

7                   MS. CIPRIANO:  Objection, form.

8                   THE WITNESS:  There's no mention  
9           of PCR cycles in 1(d).

10  BY MR. HOAGLAND-HANSON:

11          Q.   So if I do two cycles do I  
12          practice 1(d)?

13          A.   There's no mention of the number  
14          of PCR cycles in 1(d).

15          Q.   So you agree with me that if I do  
16          two cycles in PCR I practice 1(d), that's  
17          amplification; right?

18                   MS. CIPRIANO:  Objection, form.

19                   THE WITNESS:  I would say that  
20          would not.  First, amplification can  
21          occur in 1(d) through PCR.  It's one  
22          method.  It's not the only way that  
23          you can have amplification.  And in my  
24          experience, you would be looking at  
25          dozens of cycles to carry out 1(d) and

1 the POSA would understand that to  
2 include dozens of cycles.

3 BY MR. HOAGLAND-HANSON:

4 Q. Going back to your report in  
5 paragraph 150 of Exhibit 2038, are you  
6 with me, Dr. Bustamante?

7 A. I am.

8 Q. The last sentence here you say,  
9 "A POSA would understand that the  
10 proportion of a nucleic acid fragment in a  
11 sample can only be increased where there  
12 are other fragments in the solution; i.e.,  
13 if a solution contains 100 percent of a  
14 single fragment type, the proportion of  
15 that fragment type cannot be increased any  
16 further."

17 Do you see that?

18 A. I do.

19 Q. What is a fragment type?

20 A. A type of fragment.

21 Q. What does that mean?

22 A. A unique fragment.

23 Q. Unique by sequence?

24 A. It is the only -- if all of the  
25 fragments are of a given chemical

1 composition, then it can't be increased  
2 any further. It's at a hundred percent of  
3 that chemical composition.

4 Q. Okay. I just want to understand  
5 what you mean by fragment type. Is a frag  
6 type like AGACG and if I have an entire  
7 pot of nothing but AGACG, is that one  
8 fragment type?

9 A. I'm not totally following your  
10 sequence there.

11 Q. Whatever. If I have one fragment  
12 in the solution that has a certain  
13 nucleotide sequence, is that a unique  
14 fragment?

15 A. If the sample is composed of a  
16 single chemically identical  
17 polynucleotide, then you can't enrich it  
18 any further. I think that's pretty  
19 straightforward.

20 Q. Okay. I guess I'm just trying to  
21 figure out if what you actually meant was  
22 100 percent of a single fragment type,  
23 i.e., a hundred percent cDNA?

24 A. No.

25 Q. Fragment type here refers to a

1 chemically unique molecule?

2 A. That composes the entire  
3 solution.

4 Q. Okay.

5 A. To be at a hundred percent. Once  
6 you reach a hundred percent it's all  
7 composed of that.

8 Q. In paragraph 152 of Exhibit 2038,  
9 last sentence again, you say, "A POSA  
10 would understand that this term as used  
11 requires that the claimed amplification  
12 process results in the enrichment of the  
13 nucleic acid sequence of interest."

14 Do you see that?

15 A. I do.

16 Q. Is it your opinion that the  
17 amplification step 1(d) has to result in  
18 all of the enrichment or just some of the  
19 enrichment?

20 MS. CIPRIANO: Objection to form.

21 THE WITNESS: In the claimed  
22 invention, enrichment occurs through  
23 process 1(d). That is the enrichment  
24 that is being defined in the claimed  
25 invention.

1 BY MR. HOAGLAND-HANSON:

2 Q. Okay. We talked about it being a  
3 comprising claim earlier.

4 A. We did.

5 Q. If I have a pre-enrichment step  
6 that enriches --

7 A. Target of interest.

8 Q. -- target of interest -- I'll try  
9 starting over.

10 If I have a pre-enrichment step  
11 that enriches the target of interest and  
12 then step 1(d) further enriches for my  
13 target of interest, is -- I'll start over.

14 If I have a pre-enrichment step  
15 that enriches for my target of interest  
16 and then I further enrich for my target of  
17 interest in 1(d), is that practicing claim  
18 1 or not?

19 MS. CIPRIANO: Objection, form.

20 THE WITNESS: If you're carrying  
21 out (a) through (f) of claim 1, you're  
22 practicing claim 1. So if you're  
23 doing enrichment through 1 through  
24 (f), even if you've done some  
25 pre-steps, you're certainly -- for

1           that portion that practices (a)  
2           through (f) you're practicing the  
3           claimed invention.

4   BY MR. HOAGLAND-HANSON:

5           Q.    So claim 1(d) doesn't have to be  
6           solely responsible for the enrichment?

7           A.    It is responsible for the  
8           enrichment described in claim 1.  You have  
9           two definitions of enrichment.

10          Q.    I guess I don't really understand  
11          your answer.  You say there's two  
12          definitions of enrichment; right?  If I  
13          have unrecited steps that also result in  
14          enrichment, does 1(d) have to be solely  
15          responsible for the enrichment or just  
16          partially?

17          A.    I think you are conflating the  
18          two definitions.  The definition of  
19          enrichment that is relevant to the patent  
20          is the enrichment that happens through  
21          1(d).

22                    You could have prior steps as you  
23          do for all molecular biology but the  
24          enrichment that is relevant is with and  
25          without having practiced the claimed

1 invention. So the baseline could be your  
2 pre-enrichment, that's fine, that  
3 pre-enrichment proportion is now enriched  
4 through practicing the claimed invention  
5 and the enrichment that is relevant is the  
6 enrichment relative to where you start.

7 Q. How do you define the baseline  
8 for pre-enrichment?

9 A. The baseline would be without  
10 practicing the claimed invention, what you  
11 would get without the process of targeting  
12 the nucleic acid sequence of interest,  
13 extending and then amplifying the  
14 extension product and its complement.

15 Q. Is the baseline defined as  
16 whatever my solution is prior to ligation  
17 of the adaptors or could it be later in  
18 the reaction?

19 MS. CIPRIANO: Objection, form.

20 THE WITNESS: The baseline would  
21 be what the outcome of -- it's a  
22 method of sequencing, what would be  
23 the outcome of the method of  
24 sequencing had you not practiced the  
25 invention, so if you had not done the

1 enrichment step.

2 BY MR. HOAGLAND-HANSON:

3 Q. Is it just the enrichment step or  
4 the other steps, too?

5 A. It's --

6 MS. CIPRIANO: Objection, form.

7 THE WITNESS: To practice the  
8 claimed invention, you practice the  
9 steps of 1(a) through (f).

10 BY MR. HOAGLAND-HANSON:

11 Q. Right, but are you measuring the  
12 baseline compared to the omission of 1(d)  
13 or the omission of 1(a) through (f)?

14 A. You would measure the baseline  
15 relative to sequencing the unenriched  
16 sample that is the starting material for  
17 (a) through (f).

18 Q. Okay. Can the amplification that  
19 occurs as a result of 1(d) -- let me start  
20 over.

21 Can the enrichment that occurs as  
22 the result of 1(d) be due to differing  
23 efficiency between multiple primers in use  
24 in the PCR reaction?

25 MS. CIPRIANO: Objection, form.

1 THE WITNESS: I'm sorry, could  
2 you just restate that for me?

3 BY MR. HOAGLAND-HANSON:

4 Q. Sure. Can the enrichment that  
5 occurs in 1(d) be the result of differing  
6 efficiencies between multiple primers in  
7 use in the PCR?

8 A. I'm not sure what multiple  
9 primers you're referring to.

10 Q. You agree the claim covers  
11 multiplexing; right?

12 A. The claim covers multiplexing.

13 Q. In the 1(d) PCR I have two gene  
14 specific primers. You with me?

15 MS. CIPRIANO: Objection, form.

16 THE WITNESS: Not fully. Just  
17 would you mind explaining your  
18 hypothetical?

19 BY MR. HOAGLAND-HANSON:

20 Q. Sure. You can have more than  
21 one -- I'll back up.

22 In the process overall, right,  
23 you agree that there can be multiple  
24 primers targeting multiple sequences of  
25 interest; right?

1           A.    I agree with that.

2           Q.    Can the enrichment that I get at  
3   the end be the result of differing  
4   efficiencies between my primers against  
5   target 1 and my primers against target 2  
6   where primer 1 is more efficient and so I  
7   get more target 1 product at the end?

8           A.    You're measuring enrichment  
9   relative to what you would observe without  
10   enrichment so you're measuring enrichment  
11   of target 1 relative to not using a primer  
12   specific to the sequence of interest for  
13   target 1, and you're measuring enrichment  
14   for target 2 relative to what you would  
15   get without the use of the primer specific  
16   to the target of interest for primer 2.  
17   In your example, you would enrich for both  
18   target 1 and target 2 and so you're  
19   practicing the claimed invention and  
20   enriching for both as would be expected  
21   for multiplexing.

22          Q.    If I get more target 1 than  
23   target 2 have I enriched for target 1 over  
24   target 2?

25          A.    You've enriched for target 1

1 relative to what you would get without  
2 enriched for target 1, and you would get  
3 enriched for target 2 relative to what you  
4 would get without enrichment for target 2.  
5 Enrichment is relative to -- is defined  
6 for the target sequence of interest.

7 Q. I thought it was defined against  
8 the proportion of overall fragments in the  
9 system.

10 MS. CIPRIANO: Objection, form.

11 THE WITNESS: Which you would  
12 define for target 1 and target 2  
13 without enrichment for target 1 and  
14 target 2.

15 MR. HOAGLAND-HANSON: Can we look  
16 at paragraph 214 of Exhibit 2038?

17 THE WITNESS: How are we doing on  
18 time?

19 MR. HOAGLAND-HANSON: Do you need  
20 a break?

21 THE WITNESS: I might ask for a  
22 break, if that's okay. Thank you.

23 (Recess taken from 9:09 a.m. to  
24 9:34 a.m.)

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. Okay, Dr. Bustamante, I wanted to  
3 look at paragraph 214 of Exhibit 2038.  
4 Are you with me?

5 A. I'm there.

6 Q. And in this paragraph, you say,  
7 "The '012 and '108 patents require that  
8 the amplification step of claim 1 result  
9 in enrichment"; is that right?

10 A. That's what I wrote.

11 Q. And you say a couple sentences  
12 down, "Because the oligonucleotide  
13 extension products are formed by extending  
14 oligonucleotides specific to the target  
15 sequence - and no other sequence - all  
16 oligonucleotide extension products must  
17 contain sequence complementary to the  
18 sequence of interest."

19 Do you see that?

20 A. I do.

21 Q. The claims don't exclude other  
22 extension products as well; right?

23 MS. CIPRIANO: Objection to form.

24 THE WITNESS: Can you clarify the  
25 question for me?

1 BY MR. HOAGLAND-HANSON:

2 Q. Sure. You said the  
3 oligonucleotide specific to the target  
4 sequence and no other sequence; right?  
5 And I'm just trying to figure out where in  
6 the claims the no other sequence  
7 limitation appears.

8 A. The extension products are formed  
9 by extending the oligonucleotides that are  
10 specific to the target sequence. That's  
11 how the extension product comes about. So  
12 the extension products because in claim 1  
13 you have that specific primer to the  
14 target sequence, if an extension product  
15 is formed, it's formed through ligation of  
16 the primer to the target sequence, the  
17 complementary target sequence.

18 Q. I guess I'm looking at claim 1(c)  
19 of the '012 patent, right, that's the  
20 extension step?

21 A. Um-hum.

22 Q. It doesn't say at the end and no  
23 other sequence; right?

24 A. That's not written in the claim.

25 Q. Is it your view that 1(c)

1 requires that no other sequence be  
2 extended?

3 A. By the chemistry designed here no  
4 other product would be extended since the  
5 primer that is in solution and annealing  
6 to the fragment with the ligated duplex  
7 adaptors is ligate -- is specific to that  
8 nucleic acid fragment. To the extension  
9 product from that nucleic acid fragment  
10 would be the extension product arising  
11 from the target-specific primer and the  
12 subsequent child molecules arising through  
13 PCR or other amplification of that  
14 process.

15 Q. I can add other primers in;  
16 right?

17 MS. CIPRIANO: Objection, form.

18 THE WITNESS: As we've said, you  
19 can do multiplexing as part of this so  
20 there will be other primers in the  
21 solution, but when we're talking about  
22 the extension products arising from  
23 the nucleic acid fragment, there would  
24 be those that are arising from the  
25 annealing of the target-specific

1 primer.

2 BY MR. HOAGLAND-HANSON:

3 Q. There's an amplification step in  
4 (d) that happens using primers that are  
5 complementary to two adaptor sequences;  
6 right?

7 A. That is right.

8 Q. And one adaptor sequence comes  
9 from the ligated partial duplex in step  
10 (a); right?

11 A. That's correct.

12 Q. And one adaptor comes from the  
13 tail of the primary extend in step (c);  
14 right?

15 A. That's correct.

16 Q. Is it your understanding of the  
17 claim that claim 1 requires that the  
18 second adaptor only be added via the tail  
19 of the oligonucleotide that's extended in  
20 step (c)?

21 MS. CIPRIANO: Objection, form.

22 THE WITNESS: Just repeat that  
23 question for me if you don't mind.

24 BY MR. HOAGLAND-HANSON:

25 Q. Sure. Is it your understanding

1 of the claim that claim 1 requires that  
2 the second adaptor only be added via the  
3 tail of the oligonucleotide that's  
4 extended in step (c)?

5 A. So in step (d), as written the  
6 second primer is annealing to the 3' end  
7 of a complement of the second adaptor  
8 sequence. That is coming from the  
9 extension product from 1(c). That's my  
10 read of the claim.

11 Q. I want to talk a little bit about  
12 some of your obviousness opinions.

13 A. Okay.

14 Q. I would like to go to paragraph  
15 365 of your declaration, Exhibit 2038.  
16 Then you say here, "The named inventors  
17 devised the claimed methods despite the  
18 weight of the prior teaching away from and  
19 expressing scepticism towards the path  
20 they took."

21 Do you see that?

22 A. I do.

23 Q. What is the path the inventors  
24 took?

25 MS. CIPRIANO: Objection, form.

1           THE WITNESS: The claims as laid  
2           out in the '012 and '108 patents and  
3           the disclosures of the methods to  
4           enable a single primer extension  
5           targeting system for enriching nucleic  
6           acid sequence of interest.

7   BY MR. HOAGLAND-HANSON:

8           Q.    So you referred to a single  
9           primer extension targeting system. What  
10          is that?

11          A.    That is my shorthand for the  
12          technology described in the '012 and the  
13          '108 patent.

14          Q.    Why is it a single primer?

15          A.    Because it is a single primer  
16          that is being used to target the sequence  
17          of interest as opposed to two primers  
18          which you would use in traditional  
19          amplicon sequencing.

20          Q.    Does the claim exclude the use of  
21          two target-specific primers?

22          A.    The claim as we discussed is a  
23          comprising claim but when we think about a  
24          dual primer system, you have one primer  
25          designed to, let's call it Watson strand

1 and one primer designed to Crick strand.  
2 So the system here, if it were to use two  
3 targeting primers would both be on the  
4 same as they lay out sort of tiling  
5 strategies so you would still be on the  
6 same orientation by the design of the  
7 ligated adaptors.

8 Q. Sorry to jump around so much but  
9 in paragraph 65 of your declaration,  
10 Exhibit 2038, you talk about some prior  
11 art methods of PCR; is that right?

12 A. I discuss different methods of  
13 PCR in paragraph 65.

14 Q. Okay. PCR suppression vector at  
15 PCR splinkerette PCR and nested PCR;  
16 right?

17 A. That is correct.

18 Q. And it's your opinion that the  
19 field had moved beyond these methods by  
20 2012?

21 MS. CIPRIANO: Objection to form.

22 THE WITNESS: What I wrote is  
23 that many of these methods which are  
24 pre-NGS methods were quite challenging  
25 to scale to a genome wide multiplexing

1 approach first and foremost, and in  
2 and of themselves really required  
3 extensive optimization and so the  
4 field by this time was looking at  
5 other approaches for multiplex  
6 targeting.

7 BY MR. HOAGLAND-HANSON:

8 Q. And so you agree that for NGS  
9 purposes the field had moved beyond nested  
10 PCR by January 2012?

11 MS. CIPRIANO: Objection, form.

12 THE WITNESS: Nested PCR requires  
13 careful optimization and there are  
14 certainly examples of nested PCR being  
15 used with NGS. However, it was not at  
16 a state of development where you could  
17 create the kind of programmable  
18 technology described here.

19 BY MR. HOAGLAND-HANSON:

20 Q. You agree that nested PCR is not  
21 the route the inventors took?

22 A. They took the route described in  
23 the patents so there are clear examples of  
24 where what we consider nested PCR are very  
25 different than what is in the claimed

1 inventions.

2 Q. So you would agree with me that  
3 the single primer extension targeting  
4 system that's recited in the claims is  
5 different than nested PCR; right?

6 MS. CIPRIANO: Objection, form,  
7 scope.

8 THE WITNESS: I'm not sure that  
9 there's a definition for claim  
10 construction in this proceeding for  
11 nested PCR.

12 BY MR. HOAGLAND-HANSON:

13 Q. What does it mean to you?

14 MS. CIPRIANO: Objection to form.

15 THE WITNESS: That to me nested  
16 PCR uses multiple rounds, usually two  
17 rounds, to create amplicons where the  
18 first set of PCR primers are chosen so  
19 that the internal fragments can be  
20 differentiated from other genomic  
21 regions that may show similarity, but  
22 where the nested PCR allows you to  
23 target that region of the genome.

24 BY MR. HOAGLAND-HANSON:

25 Q. Is that process recited in the

1 claims of the '012 and '108 patents or  
2 not?

3 MS. CIPRIANO: Objection to form,  
4 scope.

5 THE WITNESS: As I said, the  
6 claims are as written using the  
7 partial duplex adaptors and single  
8 primer extension to enrich with a  
9 target sequence in regions of  
10 interest.

11 BY MR. HOAGLAND-HANSON:

12 Q. So the process recited in the  
13 claims of the '012 and '108 patents is  
14 different than the nested PCR?

15 MS. CIPRIANO: Objection scope,  
16 asked and answered.

17 THE WITNESS: As I said, there's  
18 no definition that I've been provided  
19 for how nested PCR would be construed.  
20 In my understanding of nested PCR, it  
21 would require at least two dual primer  
22 systems -- two pairs of primers that  
23 target an internal region for  
24 amplification based on a knowledge of  
25 sequence homology and it's usually

1 specific to a region of interest.

2 BY MR. HOAGLAND-HANSON:

3 Q. And that's not what's recited in  
4 the claims of the '012 and '108 patents;  
5 right?

6 MS. CIPRIANO: Objection, form.

7 THE WITNESS: As laid out, I  
8 don't believe one would use the term  
9 nested PCR but again, there's no  
10 construction of the term as I  
11 understand it for this proceeding.

12 BY MR. HOAGLAND-HANSON:

13 Q. I want to go to paragraph 101 of  
14 Exhibit 2038. Are you with me,  
15 Dr. Bustamante?

16 A. I am.

17 Q. And you wrote in paragraph 101,  
18 "The prior art at the time taught that it  
19 was necessary to use primer pairs rather  
20 than a single target-specific primer";  
21 right?

22 A. That's what I wrote.

23 Q. And at the end of this paragraph  
24 on the next page, you say, "Before the  
25 claimed inventions, the widely held view

1 in the field was that primer pairs were  
2 required to facilitate effective  
3 enrichment through amplification,  
4 especially PCR amplification."

5 And then you said, "In fact, I am  
6 aware of no instances before the priority  
7 date in which one target-specific primer  
8 was used in connection with PCR  
9 amplification to enrich for target  
10 sequences."

11 Do you see that?

12 A. That's what I wrote.

13 Q. And you rely on this background  
14 in your obviousness opinions. If we go to  
15 paragraph 208, for example, in connection  
16 with the Bronner reference and you go to  
17 the end of paragraph 208, you say,  
18 "Bronner fails to disclose any library  
19 preparation methods directed to the use of  
20 a single target-specific primer."

21 Do you see that?

22 A. I do.

23 Q. And in paragraph 316 of Exhibit  
24 2038 you say at the top of the next page,  
25 page 176, "Siebert teaches away from

1    amplification with single target-specific  
2    primers where no other safeguards are  
3    available."

4                    Do you see that?

5            A.    That's what I wrote.

6            Q.    And again in paragraph 327, about  
7    the Caruccio reference, you write,  
8    "Caruccio fails to teach the use of  
9    target-specific primers, let alone a  
10   single target-specific primer, or the use  
11   of selective amplification to enrich for  
12   target sequences"; right?

13          A.    That's right because Caruccio is  
14   really teaching a method for transposon  
15   introduction of the sequencing adaptors.

16          Q.    And then again in paragraph 333  
17   at the end of your obviousness opinions,  
18   you say, "But there is no reference in any  
19   of these references to any method that  
20   enriches a target sequence using a single  
21   target-specific primer"; right?

22          A.    That's what I wrote.

23          Q.    Okay. It's fair to say that your  
24   obviousness opinions depend on your  
25   analysis that the prior art doesn't teach

1 the use of a single target-specific  
2 primer; right?

3 MS. CIPRIANO: Objection, form.

4 THE WITNESS: What I've written  
5 is that by the time of the claimed  
6 invention, the approaches that had  
7 been considered in the '90s were  
8 difficult and labor intensive so that  
9 a POSA would not have been motivated  
10 to try and adapt them for use in  
11 next-generation sequencing and in the  
12 context of enriching for a target  
13 using a single primer. That's the  
14 context in which this is written.

15 BY MR. HOAGLAND-HANSON:

16 Q. What's the relevance of the  
17 single target-specific primer to your  
18 obviousness opinions?

19 A. That at the time the prevailing  
20 view in the field is that to do targeted  
21 enrichment via PCR, you need two primers  
22 that target the amplicons, the amplicon of  
23 interest and for multiplexing, multiple  
24 primers that could be used in conjunction  
25 to enable multiplex amplicon sequencing.

1 Q. So do you still have the claim of  
2 the '012 patent?

3 A. I do.

4 Q. Okay. Where does it -- where  
5 does the claim recite a single  
6 target-specific primer?

7 A. The claim as written out here is  
8 using one target-specific primer in (a).

9 Q. But it doesn't exclude the use of  
10 two target-specific primers; right?

11 A. The design of the chemistry here  
12 has an orientation such that the extension  
13 product and its complement alone are  
14 sufficient for the enrichment through the  
15 amplification step. You can tile multiple  
16 sequences of interest across a genomic  
17 region, if that's what you mean by  
18 multiple primers, but there's no need for  
19 a second primer in the reverse orientation  
20 as is traditionally used in amplicon  
21 sequencing.

22 Q. What if I used two primers in the  
23 same orientation?

24 A. That would still be single primer  
25 extension.

1 Q. Why?

2 A. Because you are -- traditional  
3 PCR has them in different orientations.

4 Q. I guess I'm just trying to  
5 understand your opinion. Is the  
6 distinction between this method and the  
7 prior art the use of just one primer or  
8 the use of just one direction of the  
9 primer?

10 MS. CIPRIANO: Objection, form.

11 THE WITNESS: It is the need for  
12 only one primer targeting a specific  
13 region of interest, whereas the  
14 prevailing understanding at the time  
15 was if you only used one primer,  
16 you're going to be getting many  
17 off-target effects that will prevent  
18 you from enriching the target region  
19 of interest. And that was all of the  
20 literature that we discuss here around  
21 how do you mitigate the off-target  
22 effects if you're trying to carry out  
23 a reaction with only one targeting  
24 primer.

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. Okay. Did you consider in  
3 reaching your opinions whether the  
4 off-target effects that you talk about  
5 could have been addressed by using two  
6 nested PCR reactions?

7 MS. CIPRIANO: Objection to form.

8 THE WITNESS: My goal was to  
9 evaluate the knowledge at the time of  
10 the invention and to understand the  
11 claimed invention in the context of  
12 what a person of ordinary skill in the  
13 art would have understood at the time  
14 of the invention. To my  
15 understanding, there was no argument  
16 in your petition around nested primers  
17 in the same orientation or similar or  
18 I was certainly not asked to address  
19 that in my declaration or I would have  
20 addressed it.

21 BY MR. HOAGLAND-HANSON:

22 Q. So you offer some opinions in  
23 your declaration about objective indicia  
24 of nonobviousness. Do you recall that?

25 A. I do.

1 Q. And you offer some opinions about  
2 teaching away and scepticism long-felt but  
3 unmet need and praise; right?

4 A. That's correct.

5 Q. And you say the patents, sort of  
6 the inventions claimed in the patents  
7 addressed that teaching away scepticism  
8 and the unmet need and are the basis for  
9 the praise?

10 A. Correct. The products are the  
11 embodiment to those patents.

12 Q. In paragraph 138 you also rely on  
13 a declaration from a Dr. Brooks. Do you  
14 recall that?

15 A. I do.

16 Q. Dr. Brooks in his declaration  
17 offered opinions on scepticism and  
18 unexpected results; right?

19 A. We can bring up the Brooks  
20 declaration so that I answer your question  
21 accurately.

22 MR. HOAGLAND-HANSON: Let's take  
23 a break.

24 (Discussion off the record.)

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. Dr. Bustamante, I'm going to hand  
3 you a portion of what's been previously  
4 marked as Exhibit 1016 in this proceeding  
5 and what I'm handing you is just pages 300  
6 through 304 of Exhibit 1016.

7 A. I need my glasses.

8 MR. HOAGLAND-HANSON: Let's take  
9 that break after all.

10 (Recess taken from 10:06 a.m. to  
11 10:17 a.m.)

12 BY MR. HOAGLAND-HANSON:

13 Q. Okay, Dr. Bustamante, before we  
14 took a break we were starting to look at  
15 Exhibit 1016. Are you with me?

16 A. I am.

17 Q. And this is the declaration of  
18 Andrew Brooks you talk about in your  
19 declaration; right?

20 A. That's correct.

21 Q. Okay. And I just --

22 A. Pending all the exhibits I assume  
23 this is a faithful reproduction of the  
24 Brooks deposition. It appears to be.

25 Q. If you go to the third page, he

1 has a heading that says Unexpected

2 Results. Do you see that?

3 A. I do.

4 Q. And you don't offer your own  
5 opinions in your declaration on unexpected  
6 results; right?

7 A. I -- when I speak about the  
8 Brooks declaration and unexpected results,  
9 I'm talking about his statements about  
10 unexpected results.

11 Q. Okay. But you didn't do your own  
12 independent analysis of whether the  
13 claimed methods resulted in unexpected  
14 results; right?

15 A. I was not asked to prepare a  
16 section of the report on unexpected  
17 results outside of what I discuss here.

18 Q. And you weren't able to speak to  
19 Dr. Brooks in connection with preparing  
20 your declaration; right?

21 A. He had unfortunately passed away.

22 Q. You agree that there's no data in  
23 the '012 or the '108 patents showing what  
24 happens when you sequence a sample  
25 according to the methods disclosed in

1     those patents; right?

2                   MS. CIPRIANO:  Objection to form.

3                   THE WITNESS:  As I read the  
4           patents, they lay out the examples  
5           that are in the patents and I don't  
6           believe that there are sequencing  
7           results as part of that -- part of  
8           those sections of the patent.

9     BY MR. HOAGLAND-HANSON:

10           Q.     Okay.  And there's no other data  
11    other than sequencing results; right?  
12    There's no like this is how much  
13    enrichment we got as a quantitative  
14    matter; right?

15                   MS. CIPRIANO:  Objection, form.

16                   THE WITNESS:  The patents contain  
17           what they contain and in my reading, I  
18           don't recall seeing anything specific  
19           to that effect.

20    BY MR. HOAGLAND-HANSON:

21           Q.     Okay.  Is there any data in the  
22    patents, in the '012 and '108 patents  
23    showing that the methods recited in the  
24    patents avoid the off-target effects that  
25    you talk about in your declaration?

1 MS. CIPRIANO: Objection to form.

2 THE WITNESS: The patents and the  
3 claims make clear that the enrichment  
4 occurs through the amplification of  
5 the targeted regions and based on an  
6 understanding of the chemistry, the  
7 adaptors that would be available for  
8 sequencing are those that are the end  
9 result of the processes laid out in 1  
10 through (f).

11 BY MR. HOAGLAND-HANSON:

12 Q. Is there any data in the '012 and  
13 '108 patents showing that the methods  
14 recited in the patents avoid the  
15 off-target effects associated with single  
16 primer methods that you talk about in the  
17 prior art?

18 A. I think as I mentioned the  
19 examples lay out what they lay out and I  
20 don't believe that is something that is  
21 addressed in those examples.

22 Q. Okay. In your report, you talk  
23 about two different Tecan products, the  
24 Ovation product and the Allegro product.

25 A. Are we moving on from Brooks?

1 Q. You can set that aside.

2 A. Okay, thank you. So we're back  
3 to secondary considerations?

4 Q. Sure. So if you want me to --  
5 I'll direct you to paragraph 340 and 341  
6 of your declaration. Are you with me,  
7 Dr. Bustamante?

8 A. Give me a minute to get there.

9 Q. Sure.

10 A. Okay.

11 Q. And you'd agree with me you talk  
12 about two different Tecan products in your  
13 declaration, the Ovation product and the  
14 Allegro product; right?

15 A. Yes, I mention the Ovation Custom  
16 Target Enrichment System, the Ovation Gene  
17 Fusion Target Enrichment System and the  
18 Allegro Targeted Genotyping by Sequencing,  
19 as well as the Allegro Targeted Genotyping  
20 V2.

21 Q. Have you ever personally used any  
22 Ovation product?

23 A. As I think I mention, I don't  
24 recall us having used this in my  
25 laboratory at Stanford or other

1 laboratories that I've directed. We may  
2 have collaborated with others that have  
3 used this in the past but I can't speak to  
4 it in any publication that I recall at the  
5 moment.

6 Q. So it's --

7 A. From my lab. There are  
8 publications I discuss here.

9 Q. So it's fair to say you didn't  
10 perform any testing of the Ovation product  
11 to render your opinions in your  
12 declaration; right?

13 A. I was not asked to.

14 Q. And similarly, you didn't perform  
15 any testing of the Allegro product to  
16 render your opinions in your declaration;  
17 right?

18 A. I was not asked.

19 Q. You understand that there needs  
20 to be a nexus between the objective  
21 indicia that you identify in the claims;  
22 right?

23 A. I do.

24 Q. And so in paragraph 339 -- well,  
25 above paragraph 339 you reproduce a figure

1 showing the workflow for the Ovation  
2 Target Enrichment System. Do you see  
3 that?

4 A. I do.

5 Q. And in paragraph 339 you say,  
6 "This illustration is coextensive with  
7 steps 1(a) through 1(f) of the '012 patent  
8 and 1(a) through 1(c) of the '108 patent";  
9 is that right?

10 A. That's correct, that's what I  
11 wrote.

12 Q. Okay. What does coextensive  
13 mean?

14 A. That these steps as laid out in  
15 Figure 1 correspond to the claims in 1(a)  
16 through 1(f).

17 Q. You'd agree with me that  
18 coextensive means corresponding exactly;  
19 right?

20 MS. CIPRIANO: Objection, form.

21 THE WITNESS: As I said they  
22 correspond to those steps and steps  
23 1(a) through 1(f) are the '012 and  
24 steps 1(a) through 1(c) the '108.

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. You would agree with me that  
3 steps 1(a) through 1(f) and steps 1(a)  
4 through 1(c) aren't limited to what's  
5 shown in the figure above paragraph 339;  
6 right?

7 MS. CIPRIANO: Objection, form.

8 THE WITNESS: As we've indicated  
9 with a comprising claim, they are  
10 included here.

11 BY MR. HOAGLAND-HANSON:

12 Q. But the claims are not limited to  
13 the steps shown in Figure 1 above; right?

14 MS. CIPRIANO: Objection, form.

15 THE WITNESS: Figure 1 above is a  
16 schematic that represents the approach  
17 that's laid out in the publication.

18 BY MR. HOAGLAND-HANSON:

19 Q. But this is not the only approach  
20 that can be used to practice the claims;  
21 right?

22 MS. CIPRIANO: Same objection.

23 THE WITNESS: As I've indicated,  
24 as long as you are performing steps  
25 1(a) through 1(f) of the '012 and 1(a)

1 through 1(c) of the '108, you are  
2 practicing the claimed invention.

3 BY MR. HOAGLAND-HANSON:

4 Q. But if I practice steps 1(a)  
5 through 1(f) and also five more additional  
6 steps, I'm no longer coextensive with  
7 Figure 1; right?

8 MS. CIPRIANO: Objection to form.

9 THE WITNESS: I need to  
10 understand what you have in mind.

11 BY MR. HOAGLAND-HANSON:

12 Q. Okay. Maybe we'll come back to  
13 that.

14 You'd agree with me that the  
15 patents don't tell the person of skill  
16 anything about how to design primers for  
17 using these methods; right?

18 A. I would have to double-check but  
19 I don't recall a specific section on  
20 primer design. There is, of course, the  
21 inclusion by reference of all the  
22 references in there so I presume there are  
23 citations that include primer design as  
24 part of the publication.

25 Q. Right. You'd agree with me that

1 primer design is important to the success  
2 of the target enrichment method?

3 MR. BEAVERS: Objection to form.

4 THE WITNESS: I couldn't disagree  
5 with that.

6 BY MR. HOAGLAND-HANSON:

7 Q. You'd also agree with me that  
8 primer design is not easy to do?

9 MS. CIPRIANO: Objection, form.

10 THE WITNESS: I would agree that  
11 primer design is important and  
12 requires skill and practice.

13 BY MR. HOAGLAND-HANSON:

14 Q. It can be a significant challenge  
15 in a target enrichment method?

16 A. I wouldn't disagree with that  
17 statement.

18 Q. In paragraph 360 of your  
19 report --

20 A. Give me a minute to get there,  
21 please.

22 Q. Sure. In paragraph 360 of your  
23 declaration, Dr. Bustamante, you discuss  
24 an article about the Allegro product by  
25 Caitlin Smith. Do you see that?

1           A.    I do.

2           Q.    And you have a portion of the  
3 article in block quotes. Do you see that?

4           A.    I do.

5           Q.    It says, "Enzymatically  
6 fragmented sample DNA is ligated to  
7 adaptors containing barcodes with their  
8 DimerFree," and there's a little trademark  
9 symbol, "technology."

10                   Do you see that?

11          A.    I do.

12          Q.    Is that technology described in  
13 the '012 and '108 patent somewhere?

14          A.    I can't tell you that. We'd need  
15 to look at when the DimerFree trademark  
16 was registered and additional materials in  
17 order to understand when that was  
18 developed.

19          Q.    Do you know what the DimerFree  
20 technology is?

21          A.    It's referenced here in the  
22 publication, presumably part of the  
23 system.

24          Q.    Do you know what part of the  
25 system it is?

1           A.    My understanding would be it's  
2   part of the adaptors that are ligated on.  
3   We could look at it in detail if you wish.

4           Q.    I don't understand you to have  
5   such an opinion but do you,  
6   Dr. Bustamante, have any opinion as to  
7   whether the Ovation and Allegro  
8   embodiments that you identify are  
9   reasonably commensurate with the scope of  
10   the claims?

11          A.    I don't recall being asked to  
12   prepare a section on whether they are  
13   commensurate.

14          Q.    The praise you're identifying in  
15   this section is praise for the commercial  
16   Ovation and Allegro products; right?

17          A.    And the embodiments of the  
18   patents through that product.

19          Q.    You don't identify any articles  
20   that praise the '012 and '108 patent  
21   methods specifically; right?

22                MS. CIPRIANO:  Objection to form.

23                THE WITNESS:  What I reference is  
24   the patent owners have publicly stated  
25   that these products are the embodiment

1 of the patent.

2 BY MR. HOAGLAND-HANSON:

3 Q. But it's not your opinion that  
4 the patent claims are limited to the  
5 methods when practiced according to the  
6 Ovation or Allegro products; right?

7 MS. CIPRIANO: Objection to form.

8 THE WITNESS: I'm sorry, I just  
9 need you to repeat that.

10 BY MR. HOAGLAND-HANSON:

11 Q. Sure. The claims aren't limited  
12 to the embodiments that are the Ovation  
13 and Allegro products; right?

14 A. No, there can be other  
15 embodiments.

16 Q. Have you done any analysis or  
17 offered any opinions about what other  
18 embodiments fall within the scope of these  
19 claims?

20 MS. CIPRIANO: Objection to form.

21 THE WITNESS: Are you asking me  
22 about other products or are you asking  
23 me about other -- what specifically  
24 are you asking me about in terms of  
25 other embodiments?

1 BY MR. HOAGLAND-HANSON:

2 Q. Other products or other ways of  
3 using these methods.

4 A. The sections that I prepared for  
5 this declaration were the sections I was  
6 asked to prepare in connection with the  
7 strategy laid out by counsel.

8 Q. Okay. Do you recall you also  
9 submitted declarations in some IPR  
10 petitions that were filed relating to the  
11 '012 and '108 patents by QIAGEN?

12 A. I do recall that.

13 Q. And do you recall that in your  
14 declarations relating to the QIAGEN  
15 products you offered a lengthy discussion  
16 of what you said was copying by QIAGEN of  
17 those patents?

18 A. I do recall there being a section  
19 to that effect in the QIAGEN declarations  
20 I prepared.

21 Q. Why don't you assert -- I'll ask  
22 it again.

23 Why don't you assert copying as  
24 an objective indicia of nonobviousness in  
25 this proceeding?

1           A.    As I mentioned before, I'm not an  
2 attorney, I don't set the legal strategy.  
3 I wasn't asked to prepare such a section  
4 for this report.

5           Q.    Why do you think that is?

6           A.    I would not speculate on that and  
7 cannot speculate on that.

8           Q.    Does it surprise you?

9           MS. CIPRIANO:  Objection to form.

10          THE WITNESS:  Sir, as I said, I'm  
11 not going to speculate to that effect.  
12 I wasn't part of the legal strategy.

13 BY MR. HOAGLAND-HANSON:

14          Q.    So in preparing your opinions on  
15 objective indicia in this proceeding, is  
16 it fair to say you only considered the  
17 specific objective indicia to which  
18 counsel directed you?

19          MS. CIPRIANO:  Objection to form.

20          THE WITNESS:  I gave my  
21 scientific opinions and guidance to  
22 understand the material in response to  
23 the petition that counsel felt was  
24 important in addressing their strategy  
25 in responding to the petition.

1 BY MR. HOAGLAND-HANSON:

2 Q. So you felt that copying was  
3 relevant in responding to QIAGEN's  
4 obviousness argument but not  
5 scientifically relevant to responding to  
6 IDT's arguments?

7 MS. CIPRIANO: Objection to form,  
8 misstates the record.

9 THE WITNESS: That's not what I  
10 stated, sir. I said I prepared the  
11 sections I was asked to prepare in  
12 line with the legal strategy set forth  
13 by counsel. Conversations about what  
14 to include or not to include I would  
15 consider part of the privileged  
16 communication. I don't want to run a  
17 breach of that.

18 BY MR. HOAGLAND-HANSON:

19 Q. I just want to look then at the  
20 instructions that your counsel provided  
21 you which are in paragraph 36 of your  
22 declaration, Dr. Bustamante. And in  
23 paragraph 36 you write, I understand from  
24 counsel "that the following additional  
25 factors are probative - and at times the

1 most probative evidence - in assessing  
2 obviousness: (1) the prior art taught  
3 away from the claimed methods, (2) the art  
4 expressed skepticism towards the claimed  
5 inventions, (3) a long-felt, unmet need  
6 existed that was resolved by the claimed  
7 inventions, and (4) the industry praised  
8 the claimed inventions."

9 Do you see that?

10 A. That's what I wrote.

11 Q. And so it's fair to say your  
12 counsel asked you to consider these  
13 factors but didn't ask you to consider a  
14 broader list of factors from which you  
15 identified the ones that are relevant?

16 MS. CIPRIANO: Objection to the  
17 form. To the extent it calls for  
18 privileged information, you're not  
19 entitled to know what we talked to him  
20 about. If you can answer the question  
21 without discussing conversations with  
22 counsel.

23 THE WITNESS: As I said, I cannot  
24 discuss conversations with counsel.

25 MR. HOAGLAND-HANSON: Are you

1           instructing him not to answer?

2                   MS. CIPRIANO: I said if he can  
3           answer without disclosing  
4           conversations he had with counsel then  
5           he can answer.

6 BY MR. HOAGLAND-HANSON:

7           Q. Do you know the answer to my  
8           question?

9           A. Would you restate your question?

10          Q. Sure. It's fair to say that your  
11       counsel asked you to consider the factors  
12       listed in paragraph 36 and not a broader  
13       set of factors; right?

14       A. I can't say that.

15       Q. So this is a yes or no question.  
16       Were you asked to consider a larger set of  
17       factors for objective indicia of  
18       nonobviousness?

19       A. I cannot answer that question  
20       without running a breach of privileged  
21       communication with counsel.

22                   MS. CIPRIANO: You can answer yes  
23       or no, if you know the answer to the  
24       question.

25                   THE WITNESS: I'm not -- I'm

1       trying to recall. I spoke to these  
2       sections because that's what I was  
3       asked to prepare, period.

4               (IDT Exhibit 1123, library  
5       preparation method, marked for  
6       identification.)

7               MR. HOAGLAND-HANSON: I'm going  
8       to hand you what I've crudely marked  
9       and hopefully legibly marked as  
10      Petitioner's Exhibit 1123.

11              MS. CIPRIANO: For the record  
12      I'll object to hearsay, authenticity  
13      and relevance.

14   BY MR. HOAGLAND-HANSON:

15       Q.    There's a library preparation  
16      method shown on Exhibit 1123. Do you see  
17      that?

18       A.    I see 1123 and this is my first  
19      time seeing this document as presented  
20      here.

21       Q.    Great. Let's walk through it  
22      together.

23              We're starting with a library of  
24      DNA fragments. Do you see that?

25       A.    I see that you have dscDNA or

1     dsgDNA written at the top of the figure  
2     and you're representing that to library;  
3     is that correct?

4             Q.     Sure.

5             A.     One fragment or a library of  
6     fragments or what does that figure  
7     represent?

8             Q.     It's a library of fragments.

9             A.     Okay.

10            Q.     And we're tracking one fragment  
11    through its chemical path through this  
12    particular set of manipulations. Do you  
13    think you can follow that with me?

14            A.     Without a lot of information  
15    regarding the experiment, I can only  
16    surmise and guess at what you're trying to  
17    get at.

18            Q.     Okay.

19            A.     I'll do my best in trying to  
20    answer your question, sir.

21            Q.     Let's see. So we end repair and  
22    we A tail. Do you know what that refers  
23    to?

24            A.     I understand end repair and I  
25    understand A tailing. Again, I'm not sure

1 exactly what specific protocol you're  
2 utilizing here.

3 Q. You understand those concepts  
4 generally?

5 A. I do.

6 Q. Those are familiar to someone  
7 with expertise in next-generation  
8 sequencing library preparation?

9 A. They are but much like primer  
10 design the devil's in the detail.

11 Q. And then we have an adaptor  
12 ligation step. Do you see that?

13 A. I see where you've written  
14 adaptor ligation.

15 Q. And there's a schematic  
16 representation of a partial duplex  
17 adaptor. Do you see that?

18 A. You're representing it as a  
19 partial duplex adaptor, that's fine. I  
20 don't have any other details as to the  
21 composition of that adaptor.

22 Q. Okay. That's fine. Maybe we'll  
23 see what happens to it as we work our way  
24 through.

25 And there's two PCR reactions

1 depicted schematically below that adaptor  
2 ligation. Do you see that?

3 A. I see the schematic. I see PCR1,  
4 PCR2. Again, seeing this for the first  
5 time, not having any time to analyze this  
6 or prepare for this, given that this is  
7 the first time I'm seeing this document.

8 Q. It's fair to say this wasn't  
9 among the selected documents that your  
10 counsel provided to you to reach your  
11 opinions in your declaration; right?

12 A. This particular document as  
13 presented here is not what I prepared for  
14 to comment on today.

15 Q. Do you recognize this schematic?

16 A. I may or may not. I'm not sure  
17 exactly where it's drawn from. I've seen  
18 similar schematics in the past.

19 Q. Where?

20 A. I don't want to speak without  
21 being accurate so I've seen it in other  
22 documents that I've reviewed in the past.

23 Q. What documents?

24 A. Sitting here right here right now  
25 I can't recall and you're giving me a

1 document without additional context. I'm  
2 saying it's reminiscent of documents I've  
3 seen before. I can't tell you if it's a  
4 faithful reproduction of what I've seen in  
5 the past. I'm saying it looks familiar.  
6 I can't point to something right here  
7 right now, given I'm seeing this for the  
8 first time as a new exhibit.

9 Q. Okay. There's two PCR reactions  
10 shown. Do you see that?

11 A. I see where you write PCR1 and  
12 PCR2.

13 Q. And it's not unusual to  
14 schematize PCR reactions in the way that  
15 I've schematized them here, is it?

16 MS. CIPRIANO: Objection to form.

17 THE WITNESS: Cartoons are used  
18 in molecular biology as a way to  
19 convey concepts.

20 BY MR. HOAGLAND-HANSON:

21 Q. For example, there's several  
22 cartoons in the '012 patent that you offer  
23 opinions about; right?

24 A. There are schematics that I offer  
25 opinions on.

1           Q.    In the first PCR reaction,  
2   there's one primer that's shown as  
3   complementary to the ligated adaptor and  
4   one primer that's complementary to my  
5   fragment. Do you see that?

6           A.    Could you again just give me a  
7   minute and walk me through exactly where  
8   in the figure you're pointing to.

9           Q.    It's a routine convention to  
10   depict primers using that single-headed  
11   arrow, right, as shown in Exhibit 1123?

12          A.    Are we talking about the left or  
13   the right or both, top or bottom?

14          Q.    Whichever you prefer.

15          A.    You tell me. It's your question.  
16   I want to make sure I can give you an  
17   accurate answer.

18          Q.    Are you right-handed or  
19   left-handed?

20          A.    I'm right-handed.

21          Q.    Let's talk about the right side.

22          A.    Okay.

23          Q.    You have a first PCR reaction,  
24   right, with two primers. Do you see that?

25          A.    Do you mean the green arrow and

1 the black and brown arrow?

2 Q. Is that how you want to interpret  
3 this?

4 A. I would interpret this as  
5 primers. Is that accurate in your  
6 depiction?

7 Q. Let's assume that they are  
8 primers.

9 A. Okay.

10 Q. Then do you see there's a second  
11 PCR?

12 A. So that the first arrow flows  
13 into the second arrow going down and you  
14 have a black arrow with a red component.  
15 Is that the second PCR reaction you're  
16 referring to?

17 Q. Yes.

18 A. Okay, I do see that.

19 Q. Okay. And there's a third primer  
20 in my second PCR reaction that's the red,  
21 yellow, purple. Do you see that?

22 A. Okay, I wasn't sure if that  
23 was --

24 Q. It's missing its head.

25 A. Okay.

1 Q. Do you want to draw a little head  
2 on it?

3 A. It's okay, it's your figure.

4 Q. Here (indicating), why don't you  
5 draw the head where you would draw the  
6 head if that was meant to be a primer.

7 MS. CIPRIANO: Objection to form.

8 THE WITNESS: Why don't you draw  
9 the head and tell me where you want it  
10 to bind so I can better understand.

11 BY MR. HOAGLAND-HANSON:

12 Q. Let's assume it's complementary  
13 to the tail of the red primer.

14 A. I don't want to misread your --

15 Q. It's your hypothetical.

16 A. It's not my hypothetical. It's  
17 your hypothetical. You gave it to me. I  
18 can't build a hypothetical with you, sir.  
19 I can answer questions based on what you  
20 want me to answer so if you can tell me  
21 exactly what reaction you're referring to  
22 and how you want me to interpret the  
23 reaction, I would be happy to answer your  
24 question. I don't want to misunderstand  
25 your question.

1 Q. Let's say it's complementary to  
2 the --

3 A. Why don't you draw it for me so I  
4 understand where you would like it to go.

5 Q. It's complementary to the red  
6 tail. Does that make sense to you?

7 A. I don't want to misinterpret your  
8 figures so why don't you re-prepare the  
9 figure for me so I can answer your  
10 question.

11 Q. I'm not the expert. How would  
12 you draw such a primer?

13 MS. CIPRIANO: Objection to form.

14 THE WITNESS: Sir, I can't answer  
15 a question with a figure that's  
16 incomplete that I'm seeing for the  
17 first time. I'm simply asking you to  
18 please prepare this for me so I can  
19 answer the questions you have for me.

20 BY MR. HOAGLAND-HANSON:

21 Q. So let's ask a different  
22 question. In the hypothetical as we've  
23 talked about it so far, let's omit that  
24 other primer, pretend it's not there.  
25 We're just doing two PCR reaction.

1           A.    Okay.  Are we going back to this  
2   figure?

3           Q.    Sure.  Do I have a single primer  
4   extension step?

5                   MS. CIPRIANO:  Objection, form.

6                   THE WITNESS:  Sir, I don't know  
7   what you have because you're providing  
8   me a cartoon with no additional  
9   details.  I need you to explain to me  
10  exactly what the experiment is for me  
11  to answer your question.

12  BY MR. HOAGLAND-HANSON:

13          Q.    If I have an extension step as  
14  part of a PCR reaction, is that the same  
15  thing as steps 1(b) and 1(c) of the '012  
16  patent or not?

17                   MS. CIPRIANO:  Objection, form.

18                   THE WITNESS:  You need to be more  
19  specific.  You need to give me more  
20  details.

21  BY MR. HOAGLAND-HANSON:

22          Q.    What other details do you need?

23          A.    I need the details as to the  
24  design of the experiment.  I have no  
25  context in which to evaluate this.

1 Q. Let's just put that aside.

2 A. Okay.

3 Q. You can put 1123 aside.

4 A. Okay.

5 Q. And I'll take back my pen because  
6 unfortunately --

7 A. You can have your pen back.

8 Q. Let's just talk about claim 1 of  
9 the '012 patent.

10 A. Okay, we're back to claim 1 of  
11 the '012 patent.

12 Q. You'd agree with me that step  
13 1(d) is a PCR reaction; right?

14 MS. CIPRIANO: Objection, form.

15 THE WITNESS: As we've indicated  
16 and I believe it's written in the  
17 patent, it can be PCR, it can be  
18 isothermal, if I recall correctly.  
19 Let me double-check that. I believe  
20 in column 27 it says suitable  
21 amplification reactions can be  
22 exponential or isothermal. Can  
23 include any DNA amplification reaction  
24 including, but not limited to, PCR.  
25 Strands placement amplification and so

1 on and so forth.

2 BY MR. HOAGLAND-HANSON:

3 Q. Okay. There's also steps (b) and  
4 (c)?

5 A. There are also steps (b) and (c)  
6 in the claim language.

7 Q. And in your summary of the  
8 invention, this is the single primer  
9 extension portion; right?

10 MS. CIPRIANO: Objection, form.

11 THE WITNESS: As I've indicated,  
12 I would consider the claimed invention  
13 to include all of claim 1(a) through  
14 (f). Extension occurs so the  
15 annealing occurs in step (b),  
16 extension occurs in step (c), and then  
17 in step (d), you have amplification of  
18 the extension product and its  
19 complement.

20 BY MR. HOAGLAND-HANSON:

21 Q. And I'm just trying to understand  
22 can steps (b) and (c) occur as part of a  
23 prior PCR reaction?

24 MS. CIPRIANO: Objection to form.

25 THE WITNESS: Prior to what, sir?

1 MR. HOAGLAND-HANSON: Prior to  
2 the PCR in step (d).

3 MS. CIPRIANO: Same objection.

4 THE WITNESS: Well, it's a  
5 comprising claim but I guess I'd need  
6 to understand the PCR reaction you  
7 have in mind.

8 BY MR. HOAGLAND-HANSON:

9 Q. Could steps (b), (c) and (d) all  
10 be happening in a single PCR reaction?

11 A. I'm not sure you'd call that  
12 traditional PCR. So again, it depends on  
13 what type of PCR reaction you are asking  
14 me about and how you're characterizing  
15 that.

16 Q. There's one primer referred to in  
17 (b) and (c). You'd agree with me; right?

18 A. It says annealing one or more  
19 polynucleotides and solution to the  
20 nucleic acid sequence of interest so  
21 there's at least one.

22 Q. And there's two primers in (d);  
23 right?

24 A. Well, it mentions using a first  
25 primer that anneals to the complement of

1 the first adaptor sequence and a second  
2 primer that anneals to 3' end to  
3 complement the second adaptor sequence, so  
4 there would be two primers in (d) as  
5 written.

6 Q. And so can I do this reaction all  
7 in one pot in one step?

8 MS. CIPRIANO: Objection, form.

9 THE WITNESS: Whether you or  
10 whether a POSA could carry this out,  
11 is the question about whether a POSA  
12 could carry this out?

13 BY MR. HOAGLAND-HANSON:

14 Q. It seems you have a low opinion  
15 of my laboratory skills but fine.

16 A. I can't speak to whether you're a  
17 POSA, sir, or not.

18 Q. Can a reasonably competent  
19 laboratory technician do this reaction all  
20 in one pot in one step or not?

21 A. I'm not sure if a technician  
22 would meet the definition of a POSA but  
23 let's consider it from the point of view  
24 of a POSA. May or may not. I need to  
25 think about it, to be frank.

1 Q. That's not a scenario that you  
2 contemplated in offering your opinions in  
3 your declaration?

4 MS. CIPRIANO: Objection to form.

5 THE WITNESS: As I said, I'd need  
6 time to think about that.

7 BY MR. HOAGLAND-HANSON:

8 Q. And you have not prior to today  
9 thought about it?

10 A. I didn't say that. I said I'd  
11 need some time to think about it to be  
12 able to give you an accurate answer.

13 Q. Do you have an opinion today or  
14 not?

15 MS. CIPRIANO: Objection to form.

16 THE WITNESS: I said I'd need  
17 some time to think about that.

18 BY MR. HOAGLAND-HANSON:

19 Q. Where in your declaration do you  
20 offer opinions about this scenario?

21 MS. CIPRIANO: Objection to form.

22 THE WITNESS: I don't believe I  
23 was asked to prepare an opinion about  
24 whether it could be one or two  
25 reactions or needs to be separate

1 reactions. So I'm not sure I've  
2 contemplated all of the relevant  
3 material. I'd need to think through  
4 that in detail so I could give you an  
5 accurate answer.

6 BY MR. HOAGLAND-HANSON:

7 Q. You also considered at various  
8 times declarations from Dr. Matz and  
9 Dr. Meyer in reaching your opinions, do  
10 you recall that?

11 A. I do.

12 Q. Your opinions at one point relied  
13 on Dr. Matz, and now they rely on  
14 Dr. Meyer; right?

15 A. This declaration is based on  
16 Dr. Meyer's.

17 Q. When did you learn that Dr. Matz  
18 had been summarily dismissed and replaced  
19 with Dr. Meyer?

20 A. At some point shortly after  
21 counsel received the decision from the  
22 court I was informed that Dr. Matz was no  
23 longer going to be providing his report.

24 Q. Do you know why that happened?

25 A. I don't know a lot of the details

1 behind why that decision was reached.

2 Q. Did your lawyers tell you that  
3 Dr. Matz lied to us and he lied to them?

4 MS. CIPRIANO: Objection to form.

5 THE WITNESS: I certainly can't  
6 speak to how that was -- that came  
7 about. I don't know much about that.

8 BY MR. HOAGLAND-HANSON:

9 Q. Would it surprise you to learn  
10 that you were basing your opinions on a  
11 twice proven liar?

12 MS. CIPRIANO: Objection to form.

13 THE WITNESS: Sir, I don't know a  
14 lot of the details about the  
15 conversations Dr. Matz had with  
16 counsel. I can't speak to it.

17 BY MR. HOAGLAND-HANSON:

18 Q. Do you know Dr. Matz?

19 A. I do not.

20 Q. You've never met him?

21 A. To the best of my knowledge, I've  
22 never met Dr. Matz.

23 Q. And you didn't talk to him in the  
24 course of this case?

25 A. I have never spoken to him that I

1 know of.

2 Q. You mentioned that you signed an  
3 amended declaration recently that we've  
4 been looking at, Exhibit 2038?

5 A. That's correct.

6 Q. There's one thing that confused  
7 me. If you go to the very last page of  
8 Exhibit 2038 there's a date here and  
9 there's your signature?

10 A. Yes.

11 Q. It's dated July 18, 2025?

12 A. That's correct.

13 Q. That's not the date that you  
14 signed 2038, right, the amended version?

15 A. That is the date I signed the  
16 original declaration.

17 Q. What's the right date that should  
18 be when you signed the amended  
19 declaration?

20 A. It would have been when it was  
21 submitted by counsel.

22 Q. So you don't know?

23 A. It would have been in the last --  
24 I don't remember when it was submitted.

25 Q. Okay. If you look right above

1     that paragraph 336 you say, "I declare  
2     under penalty of perjury that the  
3     foregoing is true and correct"?

4           A.     That's right.

5           Q.     Did your lawyers give you any  
6     instructions about what that means?

7           A.     In general, I understand what  
8     perjury means.

9           Q.     So you understood that you can go  
10    to jail if you lie to me?

11           MS. CIPRIANO:  Objection.

12           THE WITNESS:  Sir, I'm not -- in  
13    what sense am I -- I have given you my  
14    truthful responses, sir.

15           MR. HOAGLAND-HANSON:  Okay.  Just  
16    want to make sure you understand the  
17    stakes of the proceeding for you  
18    personally but not for me.

19           MS. CIPRIANO:  Objection.

20           THE WITNESS:  I appreciate that,  
21    sir.

22    BY MR. HOAGLAND-HANSON:

23           Q.     We talked a little bit about your  
24    process.  Did you ever speak to Dr. Meyer?

25           A.     No, I don't recall ever speaking

1 to Dr. Meyer.

2 Q. When did you first receive  
3 Dr. Matz's declaration?

4 A. It was at some point during -- I  
5 can't give you the exact date. It was  
6 sometime during the preparation of the  
7 original report.

8 Q. Did you see a draft of that  
9 declaration?

10 MS. CIPRIANO: Objection to form.

11 THE WITNESS: I don't recall  
12 seeing a draft. I recall receiving  
13 the declaration. Yes, I recall  
14 receiving the final declaration as I  
15 recall.

16 BY MR. HOAGLAND-HANSON:

17 Q. Did you get it before you'd  
18 arrived at your opinions or after?

19 A. If I relied on it here, it would  
20 have been during the production of this  
21 document.

22 Q. Were you offered the opportunity  
23 to ask Dr. Matz questions via your  
24 lawyers? That's a yes or no question.

25 A. I don't recall.

1 Q. Were you involved in the drafting  
2 of Dr. Matz's declaration?

3 A. Not -- not -- not that I -- not  
4 in any way that I can recall, no, not at  
5 all.

6 Q. Okay. It's fair to say that you  
7 weren't involved in the selection of the  
8 points on which Dr. Matz and then  
9 Dr. Meyer would opine; right?

10 MS. CIPRIANO: Objection.

11 THE WITNESS: I was asked to  
12 prepare this document based on my  
13 discussions with counsel. I had  
14 nothing to do with the preparation of  
15 their reports.

16 BY MR. HOAGLAND-HANSON:

17 Q. Okay. I just want to understand  
18 what role Dr. Meyer's opinions play in  
19 your opinions today, okay?

20 A. I rely on Dr. Meyer as the first  
21 author of the paper for his scientific  
22 description of what they were attempting  
23 to do in the paper, the purpose of the  
24 paper being to generate unbiased  
25 transcriptome sequencing from a non-model

1 organism and that is the extent to which  
2 I've relied on his declaration.

3 Q. If Dr. Meyer's declaration is  
4 removed from the case, does that change  
5 your opinions in any way?

6 MS. CIPRIANO: Objection to form.

7 THE WITNESS: I'd have to think  
8 about that. I'd have to think about  
9 that.

10 BY MR. HOAGLAND-HANSON:

11 Q. Okay. So in other words, you're  
12 not prepared sitting here today to offer  
13 opinions in the absence of Dr. Meyer's  
14 declaration; is that fair?

15 MS. CIPRIANO: Objection to form.

16 THE WITNESS: I have prepared my  
17 opinions using Dr. Meyer as one source  
18 to reach my scientific opinion on the  
19 matter.

20 BY MR. HOAGLAND-HANSON:

21 Q. And it's cited liberally  
22 throughout your declaration it's fair to  
23 say?

24 MS. CIPRIANO: Objection to form.

25 THE WITNESS: He was the main

1 author of the document you rely on for  
2 your petition so it's important to  
3 understand what they were motivated to  
4 do as part of that project. And it's  
5 a critical reference to understand and  
6 no better source than the authors of  
7 the paper.

8 BY MR. HOAGLAND-HANSON:

9 Q. You don't offer separate opinions  
10 in your declaration that are your opinions  
11 absent Dr. Meyer's involvement; right?

12 MS. CIPRIANO: Objection,  
13 misstates the testimony.

14 THE WITNESS: I don't believe  
15 that is accurate. I formed my own  
16 opinion about the Meyer paper and have  
17 relied on his declaration to  
18 understand parts of what isn't a  
19 hundred percent clear from the paper  
20 alone.

21 BY MR. HOAGLAND-HANSON:

22 Q. Do you think it matters what  
23 Dr. Meyer thinks about his paper?

24 MS. CIPRIANO: Objection to form.

25 THE WITNESS: Yes, I think it

1 matters to understand the context in  
2 which they were carrying out their  
3 experiments.

4 BY MR. HOAGLAND-HANSON:

5 Q. Do you think Dr. Meyer is better  
6 situated than you to talk about his paper?

7 MS. CIPRIANO: Objection to form.

8 THE WITNESS: Dr. Meyer has a lot  
9 of information that I don't have about  
10 how they carried out the experiments.  
11 I can understand the paper as a person  
12 of ordinary skill in the art and can  
13 opine on the science as they have  
14 written it, but there's a lot of  
15 background information or additional  
16 information in context that he  
17 provides that I can't be privy to  
18 because I wasn't there. I wasn't an  
19 author on the paper. I had nothing to  
20 do with it.

21 BY MR. HOAGLAND-HANSON:

22 Q. You're aware that Dr. Meyer  
23 didn't have access to any confidential  
24 information from his time at Texas; right?

25 MS. CIPRIANO: Objection to form.

1           THE WITNESS: What I understand  
2           is from what's in the Meyer  
3           declaration and from his testimony.

4   BY MR. HOAGLAND-HANSON:

5       Q. And were you aware that it's  
6   Dr. Meyer's view that he's only offering  
7   opinions on what the POSA can ascertain  
8   from the reference itself?

9       A. We can look at the Meyer  
10   declaration to make sure we're accurate in  
11   what he is speaking to in his declaration.

12      Q. Were you aware that Dr. Meyer was  
13   deposed prior to you?

14      A. I understand he was deposed last  
15   week, I think.

16      Q. Have you reviewed that  
17   transcript?

18      A. I've seen a rough version of the  
19   transcript.

20      Q. Are you aware that some of the  
21   things he said in his deposition are  
22   inconsistent with what's in his  
23   declaration?

24           MS. CIPRIANO: Objection to form,  
25           misstates the record.

1           THE WITNESS: I was provided a  
2           rough copy of the transcript.

3   BY MR. HOAGLAND-HANSON:

4           Q.   You're aware that Dr. Meyer  
5           didn't have access to any of his lab  
6           notebooks or any underlying data from the  
7           Matz lab in preparing his declaration;  
8           right?

9           A.   What I understand I understand  
10          from what is in his declaration and in his  
11          testimony.

12          Q.   You're aware that Dr. Meyer  
13          didn't have access to any of his lab  
14          notebooks or data from the Matz lab in  
15          preparing his declaration; right?

16          A.   I think that's accurate. I'm  
17          not -- I believe he was asked questions  
18          about this in the deposition. I don't  
19          have the transcript in front of me so I  
20          don't want to misstate and give you an  
21          inaccurate answer. I remember you or  
22          someone from your team asked him questions  
23          regarding this.

24          Q.   How is what Dr. Meyer did here  
25          different than what you did?

1 MS. CIPRIANO: Objection to form,  
2 speculation.

3 THE WITNESS: I was asked to  
4 opine as I lay out in my report the  
5 IPR petition and the questions set  
6 forth in the declaration. He was to  
7 my understanding asked to opine about  
8 his paper alone and did not have  
9 broader information regarding the  
10 proceedings. As I understand it, I  
11 don't -- I wasn't part of any  
12 conversation with Dr. Meyer so I can't  
13 tell you what else he may or may not  
14 have known.

15 BY MR. HOAGLAND-HANSON:

16 Q. You agree that the relevant legal  
17 inquiry is what the POSA reading the paper  
18 understands; right?

19 MS. CIPRIANO: Objection to form.

20 THE WITNESS: My understanding is  
21 that what is important is what a POSA  
22 would have known and understood at the  
23 time of the priority date and any  
24 prior art preceding the priority date.

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. And is that understanding based  
3 on what's in the reference or what's in  
4 the reference plus what's in Dr. Meyer's  
5 head?

6 A. It's what's in the reference and  
7 whatever is in the POSA's background,  
8 understanding and knowledge. I do think  
9 Dr. Meyer gives an important perspective  
10 on what the purpose of the experiment was  
11 and what they were aiming to do so that we  
12 could evaluate it in the context of the  
13 claimed invention. And in my reading,  
14 they were not looking to enrich in any  
15 way, shape or form. They were looking to  
16 get an unbiased view of the transcriptome,  
17 the non-model organism. That was the  
18 purpose of the paper and clearly stated as  
19 he states in his report as well.

20 Q. So I guess I'm just still  
21 confused. Why is Dr. Meyer's perspective  
22 important?

23 MS. CIPRIANO: Objection to form.

24 THE WITNESS: He is the first  
25 author of the paper you rely on for

1 anticipation in your petition.

2 BY MR. HOAGLAND-HANSON:

3 Q. Does it matter what he thinks if  
4 he didn't write it down in the paper?

5 MS. CIPRIANO: Objection to form.

6 THE WITNESS: I think it's  
7 important to understand what the  
8 authors of the paper knew and  
9 understood and were aiming to do in  
10 the publication that is important for  
11 evaluating anticipation in this  
12 proceeding.

13 BY MR. HOAGLAND-HANSON:

14 Q. And I think I have to go back to  
15 something that we went over earlier  
16 because I don't think I got an answer to  
17 my question. Do your opinions change in  
18 the absence of Dr. Meyer's testimony or  
19 not?

20 A. My opinions about the Meyer paper  
21 are based largely on my reading of the  
22 Meyer paper and the Meyer report confirms  
23 many of my opinions regarding what they  
24 were aiming to do, why the experiments  
25 were run the way they were and why it does

1 not anticipate the claimed invention in my  
2 opinion.

3 Q. In paragraph 115 of your  
4 declaration, Exhibit 2038, you say, "I  
5 have reviewed the qualifications and  
6 background of Dr. Eli Meyer. Under this  
7 definition of a POSA, Dr. Meyer possessed  
8 the relevant qualifications as of January  
9 26, 2012. His views reflect those of a  
10 POSA at the time."

11 Do you see that?

12 A. I do.

13 Q. Do you know what legal standard  
14 Dr. Meyer applied in reaching his  
15 opinions?

16 MS. CIPRIANO: Objection, form,  
17 scope.

18 THE WITNESS: My understanding is  
19 that he was asked to -- and again, we  
20 could turn to the Meyer declaration to  
21 specifically address what he was asked  
22 to do in his report.

23 BY MR. HOAGLAND-HANSON:

24 Q. Is it your understanding that  
25 offering opinions from the perspective of

1 the POSA, a sort of hypothetical legal  
2 construct, is the same as being a POSA at  
3 the relevant time?

4 MS. CIPRIANO: Objection to form.

5 THE WITNESS: I've got to think  
6 about your question. Could you kind  
7 of clarify it for me again? Sorry.

8 BY MR. HOAGLAND-HANSON:

9 Q. Sure. And I apologize for it  
10 being a bit metaphysical but it's the most  
11 metaphysical court of appeals in the land.  
12 Is it your opinion that offering opinions  
13 from the perspective of the POSA, the  
14 hypothetical legal contract, is the same  
15 as being a POSA at the relevant time?

16 MS. CIPRIANO: Objection, form.

17 THE WITNESS: I guess in keeping  
18 with the metaphysical nature of your  
19 question, in order to offer an opinion  
20 as a POSA, wouldn't one need to be a  
21 POSA? Otherwise one couldn't offer  
22 the opinion of a POSA without being a  
23 POSA.

24 MR. HOAGLAND-HANSON: I want to  
25 move on to a slightly different topic

1           here.

2                   MS. CIPRIANO: We've been going  
3           about an hour. Do you want to take a  
4           break?

5                   MR. HOAGLAND-HANSON:  
6           Dr. Bustamante?

7                   THE WITNESS: Probably. What  
8           time is it?

9                   MR. HOAGLAND-HANSON: 11:15.

10                  THE WITNESS: 11:15. Why don't  
11           we go to about 11:30 and break then.  
12           Does that work and we can break at  
13           about 11:30 for what would be the  
14           lunch break?

15                  MR. HOAGLAND-HANSON: Sure.

16   BY MR. HOAGLAND-HANSON:

17           Q. I want to ask about some of your  
18           other opinions about the claim.

19           A. Okay.

20           Q. And in paragraph 121 of your  
21           declaration, Exhibit 2038 --

22           A. Give me a minute to get there,  
23           please.

24           Q. You have a section that's titled  
25           the Illustration of the Claimed

1     Inventions. Do you see that?

2             A. I do.

3             Q. And in paragraph 121, you have a  
4     reproduction of what's Figure 1 of the  
5     '012 patent; right?

6             A. That's correct, it's based on  
7     Figure 1.

8             Q. What's the relationship between  
9     Figure 1 and the claims of the '012  
10    patent?

11            MS. CIPRIANO: Objection to form.

12            THE WITNESS: Well, the claims  
13    are the claims as they are written out  
14    and Figure 1 is meant to illustrate  
15    the schematic behind how the process  
16    is undertaken by a person of ordinary  
17    skill in the art, so it's meant to  
18    illustrate how the technology is  
19    implemented in Figure 1. Not exactly  
20    a one-to-one mapping but we could look  
21    through claim 1 and see where those  
22    elements are shown in Figure 1.

23    BY MR. HOAGLAND-HANSON:

24            Q. It's fair to say that in  
25    paragraph 121 this reaction is also drawn

1     schematically again; right?

2           A.     It's a schematic. I would agree  
3     with that.

4           Q.     So you're not averse to using and  
5     offering opinions on schematics where  
6     appropriate?

7           A.     Where I've had time to understand  
8     the schematic in the context of text that  
9     explains the steps, I'm happy to do so.

10          Q.     You agree that the claim's not  
11     limited to the steps you show in the  
12     figure in paragraph 121; right?

13          A.     The claims are as laid out in the  
14     claim language.

15          Q.     And in this section C, the  
16     illustration of the claimed inventions,  
17     you don't go through any other embodiments  
18     that would be different chemical ways of  
19     practicing the invention; right?

20                 MS. CIPRIANO: Objection to form.

21                 THE WITNESS: I go through this  
22                 as an illustration of the steps  
23                 involved in carrying out the claimed  
24                 invention in one embodiment.

25     ///

1 BY MR. HOAGLAND-HANSON:

2 Q. And I'm just trying to understand  
3 the relationship between what you call the  
4 illustration of the claimed invention and  
5 the claims. Were your opinions based on  
6 this particular embodiment?

7 A. This embodiment informed my  
8 opinions of the claims as did the entirety  
9 of the patent and my background as a POSA.

10 Q. Are there any other embodiments  
11 other than this that were disclosed in the  
12 patents?

13 MS. CIPRIANO: Objection to form.

14 THE WITNESS: This is one  
15 illustration of the claimed invention  
16 that I go through in detail and I  
17 would be happy to discuss in more  
18 detail. There are aspects that are  
19 unclear.

20 BY MR. HOAGLAND-HANSEN:

21 Q. In the '012 patent you rely on  
22 Figure 1, right, in this section?

23 MS. CIPRIANO: Objection, form.

24 THE WITNESS: I rely on Figure 1  
25 from the '012 patent in this section.

1 BY MR. HOAGLAND-HANSON:

2 Q. Are there any other schematics of  
3 embodiments of the claims in the '012  
4 patent?

5 A. Well, there are fairly additional  
6 materials in the remainders of the figures  
7 and the examples that speak to the many  
8 embodiments that are discussed in the  
9 invention disclosure.

10 Q. Okay. Have you undertaken an  
11 analysis to talk about other embodiments  
12 that are set out in the patent other than  
13 Figure 1?

14 MS. CIPRIANO: Objection, form,  
15 scope.

16 THE WITNESS: What I've laid out  
17 here is a description of this  
18 particular workflow as illustrated in  
19 Figure 1.

20 BY MR. HOAGLAND-HANSON:

21 Q. Have you undertaken an analysis  
22 anywhere in your declaration of any other  
23 embodiments other than the one in Figure  
24 1?

25 MS. CIPRIANO: Objection to form.

1           THE WITNESS: We certainly talked  
2           about additional aspects of the  
3           claims. I discuss elements related to  
4           fragmentation and RNA sequencing and  
5           so on, so this is a step by step so  
6           that we understand how an enrichment  
7           comes about through the primer  
8           extension and amplification that is  
9           described in Figure 1 and in the  
10          patent, including the claims and the  
11          rest of the materials therein.

12        BY MR. HOAGLAND-HANSON:

13          Q. Do you discuss any other  
14          embodiments through which the enrichment  
15          comes about through primer extension and  
16          amplification other than what's described  
17          in Figure 1?

18                MS. CIPRIANO: Objection to form.

19                THE WITNESS: This is a general  
20          description of the process by which  
21          enrichment occurs using one fragment  
22          as an example that walks through  
23          elements of the claims.

24        BY MR. HOAGLAND-HANSON:

25          Q. What's shown is the third step in

1 paragraph 124.

2 A. Sorry, is that a question?

3 Q. I was just directing you to make  
4 sure we're on the same page.

5 A. I wasn't sure if you were asking  
6 me a question, I apologize.

7 Q. That's fair.

8 Paragraph 124, the figure  
9 associated with it is actually at the top  
10 of the next page.

11 A. Okay.

12 Q. This is the extension step;  
13 right?

14 A. Occurring in front of the figure.

15 Q. This extension that's shown in  
16 Figure 1 is not part of a PCR reaction;  
17 right?

18 MS. CIPRIANO: Objection to form.

19 THE WITNESS: It's an extension  
20 step in the figure as labeled.

21 BY MR. HOAGLAND-HANSON:

22 Q. That's not a PCR reaction; right?

23 MS. CIPRIANO: Objection, form.

24 THE WITNESS: In my opinion, PCR  
25 stands for polymerase chain reaction

1       and it involves cycling through  
2       different stages of denaturation,  
3       extension, re-annealing and so on that  
4       produce the exponential amplification  
5       of the fragment of interest based on  
6       the template and its complement in  
7       subsequent cycles being used as  
8       template and additional templates  
9       created that create the chain reaction  
10      for a portion of polymerase chain  
11      reaction, so this is one step of  
12      extension. An extension is a part of  
13      PCR but this obviously is not a PCR in  
14      toto.

15   BY MR. HOAGLAND-HANSON:

16       Q.   It's fair to say that if somebody  
17   came to you and they said I've got this  
18   library preparation method with an  
19   extension step in it, you wouldn't  
20   understand them to be referring to PCR?

21           MS. CIPRIANO:  Objection to form.

22           THE WITNESS:  May or may not  
23   involve PCR but extension is  
24   extension.

25   ///

1 BY MR. HOAGLAND-HANSON:

2 Q. It's something different than  
3 amplification?

4 A. Extension is extension,  
5 amplification is amplification.

6 Amplification can involve extension.  
7 Extension doesn't always involve or  
8 qualify as amplification unless it's a  
9 process by which you're using the  
10 templates and its complemented subsequent  
11 rounds to create new templates which by  
12 definition then would be PCR.

13 Q. In paragraph -- well, let's see.  
14 I want to go to paragraph 170 of your  
15 declaration, Exhibit 2038. Are you with  
16 me, Dr. Bustamante?

17 A. Let me turn to there. And how  
18 are we doing on time?

19 MS. CIPRIANO: 11:25.

20 THE WITNESS: Would you mind if  
21 we broke here and then reconvened  
22 after?

23 MR. HOAGLAND-HANSON: Do you want  
24 to take a half hour?

25 THE WITNESS: That would be ideal

1           for me, if that's okay.

2                   MR. HOAGLAND-HANSON: It's your  
3           deposition.

4                   THE WITNESS: It's your  
5           deposition.

6                   (Lunch recess taken at  
7           11:25 a.m.)

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1           A F T E R N O O N       S E S S I O N

2                   (Time noted: 12:19 p.m.)

3   D R.   C A R L O S       B U S T A M A N T E,

4           resumed and testified as follows:

5   CONTINUED EXAMINATION

6   BY MR. HOAGLAND-HANSON:

7           Q.   All right, Dr. Bustamante, this  
8   is a yes or no question. You met with  
9   counsel to prepare for your deposition?

10          A.   I did.

11          Q.   And you met with Ms. Cipriano?

12          A.   When?

13          Q.   To prepare for your deposition.

14          A.   Yes.

15          Q.   And you met with Mr. Beavers?

16          A.   I did.

17          Q.   Did you meet with your counsel  
18   last night to prepare for your deposition?

19          A.   No.

20          Q.   I want to go back to paragraph

21   170 --

22          A.   Okay.

23          Q.   -- of your declaration, Exhibit  
24   2038. Well, actually, why don't we start  
25   with paragraph 169.

1 A. Okay.

2 Q. And do you still have your copy  
3 of the Meyer reference Exhibit 1009  
4 somewhere? If not, I have another one.

5 A. I believe it's here.

6 Q. Good.

7 A. I think this is it.

8 MR. HOAGLAND-HANSON: And do you  
9 need a copy?

10 MS. CIPRIANO: No.

11 BY MR. HOAGLAND-HANSON:

12 Q. You'd agree with me,  
13 Dr. Bustamante, that the Meyer reference  
14 as you discuss in paragraph 169 identifies  
15 certain features in its sequencing method  
16 that solve certain problems with 454  
17 sequencing; right?

18 A. I would agree with that and in  
19 general.

20 Q. And at page 9 of the Meyer  
21 reference, Exhibit 1006 --

22 A. Let me turn to that, please.  
23 Okay.

24 Q. There are two specific issues  
25 that Meyer identifies. Do you see that?

1           A.    I see page 9. Give me a second  
2 just to -- so the two issues that you're  
3 referring to are the homopolymer problem  
4 and the concatenation problem?

5           Q.    Those are the two problems that  
6 Meyer specifically identifies in the  
7 paper; right?

8           A.    Those are two of the problems  
9 that they identify, that's correct.

10          Q.    And the first problem they say,  
11 "Because 454 sequencing does not  
12 efficiently process homopolymer regions  
13 greater than eight base pairs in length,  
14 the polyA tails at the 3' ends of intact  
15 transcripts present a problem, and would  
16 be expected to result in  
17 underrepresentation of the 3' ends of  
18 transcripts"; right?

19          A.    That's what they wrote.

20          Q.    The first problem they identify  
21 is this underrepresentation of the 3' ends  
22 of fragments; right?

23          A.    The first problem they solve is  
24 the 454 homopolymer problem, which in this  
25 context they surmise could lead to a 3'

1 end underrepresentation, but it's really  
2 about the homopolymer problem.

3 Q. And then the second difficulty  
4 they identify is concatenation of adaptors  
5 during cDNA preparation; correct?

6 A. That's what they list.

7 Q. And those are the two problems  
8 that you discuss in paragraph 169 of your  
9 declaration; right?

10 A. Those are the -- I point to those  
11 two and reference page 9 of the 1006  
12 exhibit which is the Meyer paper.

13 Q. In paragraph 170 of your  
14 declaration, Dr. Bustamante, you talk  
15 about some other concerns expressed by  
16 Meyer that dictated specific design  
17 choices. Do you see that?

18 A. I do.

19 Q. And you cite a paragraph of  
20 Dr. Meyer's declaration, Exhibit 2287. Do  
21 you see that?

22 A. I see Exhibit 2287. I believe  
23 that's Meyer, if I could get a copy of the  
24 Meyer reference.

25 Q. Sure. I'll hand you what's

1 previously marked as patent owner's  
2 Exhibit 2287.

3 A. Thank you. I have it in front of  
4 me.

5 Q. Okay. So and I just want to go  
6 back to what you were saying in paragraph  
7 170 of your declaration. You say, "there  
8 were other concerns expressed by Meyer  
9 that dictated specific design choices."

10 Do you see that?

11 A. I do.

12 Q. And you cite to Exhibit 2287,  
13 paragraph 22. Do you see that?

14 A. I do.

15 Q. And you have that open now as  
16 well?

17 A. I do.

18 Q. Okay. In paragraph 22, Dr. Meyer  
19 doesn't cite his reference, right, except  
20 for the first sentence. Do you see that?

21 A. I do. He cites the first page of  
22 the paper.

23 Q. Okay. And when Dr. Meyer says  
24 our biggest challenge would be to avoid --  
25 and then in bold and italics -- avoid the

1 preferential sequencing of certain genes  
2 or transcript regions and to ensure that  
3 the whole transcript done was covered as  
4 evenly as possible and so on, there's no  
5 citation to his paper; right?

6 A. Well, I think he's referencing  
7 the Meyer paper in that paragraph.

8 Q. None of the words that you rely  
9 on from paragraph 22 of Exhibit 2287  
10 appear in the Meyer reference, Exhibit  
11 1006; right?

12 MS. CIPRIANO: Objection, form.

13 THE WITNESS: This is all  
14 occurring in a section how we overcame  
15 challenges to sequence an entire  
16 transcriptome and further broken down  
17 into overcoming bias towards -- so  
18 Roman III is the section, how we  
19 overcame challenges to sequence an  
20 entire transcriptome and it further  
21 goes on to section (a), overcoming  
22 bias towards highly abundant  
23 transcripts, section (b) -- or  
24 subsection (b), overcoming bias  
25 towards 3' ends of transcripts,

1 section (c), overcoming bias towards  
2 shorter transcripts, section (d),  
3 avoiding -- or subsection (d),  
4 avoiding nonproductive sequence of  
5 artificial adaptors, subsection (e),  
6 avoiding blinding the 454 sequencer  
7 with polyA tails.

8 And I've further gone to  
9 reference specific paragraphs in Roman  
10 numeral section III of his  
11 declaration.

12 BY MR. HOAGLAND-HANSON:

13 Q. Not even remotely the question I  
14 asked, Dr. Bustamante.

15 A. Okay. I was trying to put it  
16 into context.

17 Q. None of the words in paragraph 22  
18 of Exhibit 2287 appear anywhere in Exhibit  
19 1006; right?

20 MS. CIPRIANO: Objection, form.

21 THE WITNESS: We would have to  
22 compare them directly. Again, I'm  
23 citing to a declaration and my  
24 understanding of the challenges as a  
25 POSA in trying to implement their goal

1 of sequencing as evenly as possible in  
2 the entire transcript region.

3 BY MR. HOAGLAND-HANSON:

4 Q. Are the words in paragraph 22 of  
5 Exhibit 2287 in Exhibit 1006 or not?

6 MS. CIPRIANO: Objection to form.

7 THE WITNESS: We can -- I mean  
8 depends on how you -- the word  
9 transcriptome appears, overcoming a  
10 bias appears, 3' ends appear, they  
11 talk about shorter transcripts, the  
12 454 homopolymer problem appears. So  
13 I'm not quoting verbatim but I am  
14 summarizing the issues that are  
15 presented in both the Meyer paper and  
16 in Meyer's declaration about his  
17 paper.

18 BY MR. HOAGLAND-HANSON:

19 Q. Where in exhibit -- well, in  
20 paragraph 170 you go on to say, you go on  
21 to refer to an overrepresentation of the  
22 3' end. Do you see that, Dr. Bustamante?

23 A. Yes.

24 Q. Okay. And you cite --

25 A. Yeah.

1 Q. And you cite paragraphs 24 and 25  
2 of Exhibit 2287.

3 A. I do.

4 Q. And Dr. Meyer in paragraphs 24  
5 and 27 -- I'll ask it again.

6 You cite paragraphs 24 and 25 of  
7 Exhibit 2287 in paragraph 170 of your  
8 declaration; right?

9 A. That's right. And the subsection  
10 (b), overcoming bias towards 3' ends of  
11 transcripts.

12 Q. And Dr. Meyer has this section in  
13 his declaration paragraphs 24 and 25 of  
14 Exhibit 2287 called overcoming bias  
15 towards 3' ends of transcripts; right?

16 A. Yes, I believe I just said that  
17 but yes.

18 Q. I think we're in agreement.

19 A. Good.

20 Q. In this section he doesn't cite  
21 to the Meyer paper; right?

22 A. In paragraph 25 he cites to Meyer  
23 paper page 13.

24 Q. Okay. We'll look at that. Does  
25 he cite to any other page?

1 A. He cites to Exhibit 1034.

2 Q. That's a different reference;  
3 right?

4 A. I understand. I would agree with  
5 you. We could pull up that reference as  
6 well.

7 Q. Is there anywhere in the actual  
8 reference Exhibit 1006 that talks about  
9 overrepresentation of 3' end fragments?

10 A. Well, they mention broadly the  
11 problem of when you start the sequence  
12 from the 3' end you may not get complete  
13 transcript and so you would underrepresent  
14 internal fragments of 5' ends. I'm not  
15 sure they characterize it as  
16 overrepresentation of 3' ends, but it's  
17 part of what they discuss, for example, at  
18 the top of page 9.

19 Q. Where at the top of page 9 do  
20 they refer to overrepresentation of 3'  
21 transfers?

22 MS. CIPRIANO: Objection.

23 THE WITNESS: Well, they talk  
24 about the problem of sequencing from  
25 the 3' end and discuss solving the

1 homopolymer problem relative to the  
2 underrepresentation of 3' ends. And  
3 then if you follow that logic through  
4 and you're not able to efficiently get  
5 the rest of the cDNA, then you're  
6 potentially in that world of  
7 overrepresentation of 3' end.

8 BY MR. HOAGLAND-HANSON:

9 Q. Can you point me to what section  
10 of page 9 you're talking about?

11 A. So at page 9, they are discussing  
12 the issues with how to undertake -- really  
13 they are beginning their discussion  
14 section of the paper. And in the  
15 discussion section of the paper, they  
16 begin by discussing solving the  
17 homopolymer problem. That homopolymer  
18 problem has to do with two issues. Issue  
19 one is too much sequencing real estate if  
20 you can efficiently sequence, and problem  
21 two is flooding the sequencer so that it  
22 can't read through the homopolymer. So  
23 they make a decision through their broken  
24 T adaptor modification of the clone tech  
25 protocol to do their full cDNA reverse

1 transcription starting from as close to  
2 the end as possible and then sequencing  
3 internal fragments towards the -- from the  
4 inside of the fragments as opposed to from  
5 the end. So if they don't get through  
6 complete cDNA, then this is part of what  
7 they are discussing with the 3'  
8 overrepresentation as they also clearly  
9 lay out in his declaration.

10 Q. What part of Exhibit 1006 at page  
11 9 talks about overrepresentation of the 3'  
12 end?

13 MS. CIPRIANO: Objection.

14 THE WITNESS: Not in -- as I  
15 said, not in exactly that. There's no  
16 heading that says that. There's no --  
17 it is part of the general discussion  
18 and a POSA reading this and  
19 understanding the process of cDNA  
20 production would understand that if  
21 you're beginning from the 3' end and  
22 not able to resolve all the way  
23 through to the 5' end, then you will  
24 have overrepresentation.

25 ///

1 BY MR. HOAGLAND-HANSON:

2 Q. What part of Exhibit 1006 is the  
3 POSA reading to draw that understanding  
4 from?

5 A. From the discussion section that  
6 starts on page 9.

7 Q. The whole thing?

8 A. The discussion section goes  
9 through and explains their understanding  
10 of the results of the paper.

11 Q. You'd agree with me then in the  
12 first paragraph of the discussion section,  
13 they only talk about underrepresentation  
14 of the 3' ends; right?

15 A. And in solving that  
16 underrepresentation, they need to then  
17 deal with does this then create  
18 overrepresentation.

19 Q. Where does it say that?

20 A. It stands to reason as part of  
21 the logic of how the cDNA is produced.

22 Q. So it stands to reason to you and  
23 Dr. Meyer, right, but it doesn't say that  
24 in the reference anywhere?

25 MS. CIPRIANO: Objection, form.

1           THE WITNESS: You're asking me  
2           for my interpretation. I've held that  
3           interpretation, given that their whole  
4           goal, and I think this is unambiguous,  
5           their whole goal is to get an unbiased  
6           representation of the transcript of a  
7           non-model organism. So as they are  
8           trying to undertake that objective,  
9           they are thinking about how do I  
10          ensure that I have an experiment where  
11          I'm getting as much full cDNA as  
12          possible and use the 454 instrument as  
13          the readout which is why they have  
14          undertaken the set of experiments that  
15          they lay out here, including trying to  
16          get to as much internal sequence as  
17          possible to then sequence into the 3'  
18          and 5' ends where they go through the  
19          process of creating scaffolding  
20          molecules, they discuss the singletons  
21          and in that entire set of discussions,  
22          they want to ensure themselves and  
23          make a strong claim to and Meyer  
24          reiterates that claim that they have  
25          produced a method that gives you an

1 unbiased view of the transcriptome.

2 BY MR. HOAGLAND-HANSON:

3 Q. You can't point me to anywhere  
4 more specifically than the entire  
5 discussion section of the Meyer paper  
6 where the Meyer authors refer to  
7 overrepresentation of the 3' ends?

8 MS. CIPRIANO: Objection, form.

9 THE WITNESS: As I said, there's  
10 no specific section where they call  
11 that out but it is a logical problem  
12 to be resolved as Meyer points out in  
13 his declaration.

14 BY MR. HOAGLAND-HANSON:

15 Q. It's your opinion that the  
16 overrepresentation issue to the extent one  
17 existed is resolved by the use of the  
18 SMART kit; right?

19 MS. CIPRIANO: Objection to form.

20 THE WITNESS: The modification of  
21 the SMART kit with the broken T  
22 modification.

23 BY MR. HOAGLAND-HANSON:

24 Q. That's the underrepresentation.  
25 The SMART kit also resolves the

1 overrepresentation; right?

2 A. In successful application of the  
3 broken T they claim and show data that  
4 they are getting what they expect in terms  
5 of sequencing real estate allocated to the  
6 fragments, and that's what they claim and  
7 that's what they demonstrate.

8 Q. And it's your opinion the use of  
9 a SMART kit is outside the claimed method?

10 A. Any --

11 MS. CIPRIANO: Objection, form.

12 THE WITNESS: The SMART kit is  
13 occurring before fragmentation and the  
14 method begins with fragmented nucleic  
15 acids.

16 BY MR. HOAGLAND-HANSON:

17 Q. So and it's your opinion that any  
18 manipulation that happened prior to  
19 fragmentation can't be part of the method?

20 MS. CIPRIANO: Objection to form.

21 THE WITNESS: Depends on what  
22 modifications you're talking about but  
23 in this case, you're asking me about  
24 the clone tech kit. The clone tech  
25 kit is a full cDNA kit and they don't

1 do fragmentation until after they've  
2 done the kit and put on the cap end  
3 primer -- the cap ends.

4 BY MR. HOAGLAND-HANSON:

5 Q. At the end of paragraph 170 you  
6 say, "all of these processes occurred  
7 before the cDNA strands were fragmented  
8 and before any partial duplex adaptors  
9 were ligated to the cDNA fragments."

10 Do you see that?

11 A. I do.

12 Q. Why does this matter to your  
13 opinions?

14 MS. CIPRIANO: Objection to form.

15 THE WITNESS: It matters to my  
16 opinion because the method outlined  
17 here begins with fragments of nucleic  
18 acids to which partial duplex adaptors  
19 are ligated. So all this is happening  
20 before the partial duplex adaptors are  
21 ligated.

22 BY MR. HOAGLAND-HANSON:

23 Q. Is there a step in the Meyer  
24 process where the RNA fragments are  
25 discarded?

1           A.    There are steps in the Meyer  
2   protocol where they do a fair amount of  
3   cleanup.

4           Q.    Is it your opinion that the  
5   original RNA fragments are no longer  
6   present at the end of the Meyer method?

7                   MS. CIPRIANO:  Objection to form.

8                   THE WITNESS:  Whether or not they  
9           are present, they are not made visible  
10          to the sequencing readout which is the  
11          goal of the Meyer method.  So to the  
12          extent their cleanup or use of  
13          additional enzymes in the workflow,  
14          the purpose of the experiment is to  
15          get to sequence libraries and that's  
16          the focus of their analysis.

17   BY MR. HOAGLAND-HANSON:

18          Q.    We were talking about the claim  
19   earlier.  Is it your opinion the  
20   enrichment that happens as a result of the  
21   steps in the method has to be compared to  
22   other things that are visible in the  
23   sequencing readout?

24          A.    Yes, to the sequencing readout as  
25   it would occur were enrichment not carried

1 out, to be specific.

2 Q. Is it your opinion that the  
3 enrichment that happens in the claim is  
4 something that's only observed in the  
5 sequencing readout?

6 MS. CIPRIANO: Objection to form.

7 THE WITNESS: The enrichment  
8 isn't observed through the sequencing  
9 readout.

10 BY MR. HOAGLAND-HANSON:

11 Q. Okay.

12 A. I'm --

13 Q. Go ahead.

14 A. No, please.

15 Q. I just want to understand your  
16 opinion then. Is it your opinion you  
17 don't practice the claim if you increase  
18 the number of fragments in the sample but  
19 then those fragments are not picked up on  
20 the sequencing readout?

21 MS. CIPRIANO: Objection, form.

22 THE WITNESS: If the fragments  
23 are not amenable to sequencing and  
24 this is a method for sequencing, then  
25 what is relevant are the fragments

1           that are amenable for sequencing.

2   BY MR. HOAGLAND-HANSON:

3           Q.    You agree with me though the  
4   proper place to look to see if I've  
5   enriched the method as recited in the  
6   claims is in the sequencing data and not  
7   in what's in the tube; right?

8                   MS. CIPRIANO:  Objection to form.

9                   THE WITNESS:  It's in the  
10    sequencing data but to properly  
11    estimate enrichment, you would need to  
12    have baseline data without enrichment  
13    which is never presented in the paper.

14  BY MR. HOAGLAND-HANSON:

15           Q.    I'm hearing your disagreement  
16  with the Meyer argument loud and clear.  
17  I'm just trying to ask you what the claim  
18  requires.  What is the proper place where  
19  I look to see if I've enriched for  
20  purposes of the claim in the sequencing  
21  data or is it in the tube?

22           A.    It is in the sequencing data and  
23  in a -- in the sequencing data as compared  
24  to what you would observe without  
25  enrichment.  So to give you an example, in

1     exome capture or similar you often talk  
2     about reads that are on target or  
3     background and the much higher depth of  
4     coverage that is achieved in the on target  
5     regions versus background. So you are  
6     looking to have a baseline to compare to  
7     and that baseline comes from not  
8     practicing the enrichment step.

9           Q.    Okay. So in order to figure out  
10    if I've practiced the method, do I need to  
11    sequence my sample without target  
12    enrichment first to create the baseline?

13          A.    If you've practiced method, then  
14    the fragments that are carried through  
15    that have the sequencing adaptors would be  
16    those that are the result of the extension  
17    product and its complement that are then  
18    subsequently amplified in step 1(d).

19          Q.    How do I know if I've amplified  
20    against the baseline without knowing what  
21    the baseline is?

22                MS. CIPRIANO: Objection to form.

23                THE WITNESS: As I've indicated,  
24    the design of this protocol, the  
25    enrichment step as occurring through

1       the extension and its complement and  
2       the amplification steps are creating  
3       the sequencing library with the  
4       necessary adaptors to do the  
5       sequencing. So if you were to have  
6       either existing data from not having  
7       carried out the enrichment step, or if  
8       in your sequencing data you're seeing  
9       the vast majority of the material  
10      being from your enrichment, then you  
11      will have understood that you've  
12      practiced the claimed invention.

13   BY MR. HOAGLAND-HANSON:

14       Q.    So I guess I want to understand  
15      those two options. One option it seems  
16      like you say if you have some expectation  
17      or data about what you would have had  
18      without the enrichment step, then you  
19      could compare that to what you got after  
20      your enrichment step to determine if you  
21      enriched?

22       A.    The extent to which you've  
23      enriched and the extent to which you are  
24      enriched.

25       Q.    I want to go to the next

1 paragraph of your declaration, paragraph  
2 171. And at the bottom of that paragraph,  
3 which is on the next page, there's  
4 figure -- you've reproduced Figure 1 of  
5 the Meyer method; right?

6 A. Figure 1 from the Meyer  
7 publication, yes.

8 Q. I just want to talk about the  
9 method at a high level first.

10 A. Okay.

11 Q. We start with RNA and then we  
12 have the cap kit; right?

13 A. The modified clone text mark.

14 Q. Different people have different  
15 preferred nomenclatures. And that creates  
16 a library of double-stranded cDNA; right?

17 MS. CIPRIANO: Objection to form.

18 THE WITNESS: That creates a pool  
19 of cDNAs with capped ends.

20 BY MR. HOAGLAND-HANSON:

21 Q. That are double-stranded?

22 A. They are double-stranded, agreed.

23 Q. And then those double-stranded  
24 fragments are -- let me start over.

25 Those double-stranded cDNAs are

1 fragmented; right?

2 A. That's correct.

3 Q. And then there's adaptor  
4 ligation?

5 A. There's adaptor ligation that  
6 follows to the classes of molecules  
7 created by the fragmentation which  
8 includes the capped 5' end fragments, the  
9 internal that do not have caps and the 3'  
10 ends which also have a cap.

11 Q. And then there is a PCR reaction?

12 A. Then there's PCR with multiple  
13 primers, yeah.

14 Q. I could do the same chemistry on  
15 genomic DNA; right?

16 A. Depends on what you mean by the  
17 same chemistry. You couldn't do the cDNA  
18 synthesis for genomic DNA, could you?

19 Q. You can do the rest of the steps  
20 though; right?

21 MS. CIPRIANO: Objection to form.

22 THE WITNESS: You wouldn't -- so  
23 the cap ends require you to leverage  
24 the cDNA chemistries so the end -- I  
25 don't mean to question your molecular

1 biology skills, I'm not sure how you  
2 would modify the protocol to put the  
3 caps on, if someone could or would, I  
4 don't know. But you could certainly  
5 start with genomic DNA and fragmented  
6 genomic DNA.

7 BY MR. HOAGLAND-HANSON:

8 Q. And then I could ligate these  
9 adaptors to it?

10 A. You could ligate these adaptors  
11 to them but in that case most of what  
12 you'd have would be equivalent to the  
13 internal fragments.

14 Q. Right. And then I could put  
15 those genomic DNA fragments with the  
16 ligated adaptors through the amplification  
17 step?

18 A. You could. Again, now I would  
19 need you to explain to me what the set of  
20 primers are that you're utilizing but --

21 Q. I could do it with these primers.  
22 My cap primer is just not doing very much  
23 for me.

24 MS. CIPRIANO: Objection to form.

25 THE WITNESS: Yeah, again we're

1 kind of venturing into a set of  
2 hypotheticals.

3 BY MR. HOAGLAND-HANSON:

4 Q. There's no chemical  
5 incompatibility between genomic DNA and  
6 these processes?

7 MS. CIPRIANO: Objection to form.

8 THE WITNESS: Again, you could --  
9 one could carry out all kinds of PCR  
10 reactions. What you would get, hard  
11 to predict unless you thought hard  
12 about why you're carrying out the  
13 steps you're carrying out but you could  
14 do it, sure. You could do it. I'm  
15 not sure you would want to do it but  
16 you could do it.

17 BY MR. HOAGLAND-HANSON:

18 Q. In this method as Meyer depicts  
19 it, you agree there's a primer that is  
20 specific to the cap sequence; right?

21 A. There's a primer that binds the  
22 cap sequence.

23 Q. Some of the fragments only get  
24 the adaptor from the cap primer; right?

25 MS. CIPRIANO: Objection to form.

1 BY MR. HOAGLAND-HANSON:

2 Q. I'll ask a better question. If I  
3 omit the cap primer, the blue and yellow  
4 primer, right, then I will get no 5' or 3'  
5 end primer; right?

6 A. Barring off target, that would be  
7 my supposition.

8 Q. And you agree that in this  
9 reaction as drawn with the cap primer,  
10 I'll have increased the number of cap  
11 primer containing fragments from where I  
12 was at the start of the process?

13 MS. CIPRIANO: Objection to form.

14 THE WITNESS: Now I'm not sure  
15 what process you're talking about.  
16 Are we talking about the genomic DNA  
17 process?

18 BY MR. HOAGLAND-HANSON:

19 Q. No, let's go back to the process  
20 as shown in Figure 1.

21 A. Okay. So now we're back to Meyer  
22 Figure 1, method 1. Okay. I just want to  
23 make sure I understand so I can fairly  
24 answer the question.

25 Q. At the end of this process --

1 well, let's start from post-fragmentation.

2 A. We start at post-fragmentation,  
3 Meyer Figure 1, method 1.

4 Q. Via the PCR reaction that's shown  
5 in figure 1.

6 A. Where we're ligating the  
7 adaptors?

8 Q. We fragment, you ligate the  
9 adaptors as shown here.

10 A. Okay.

11 Q. And we do the PCR exactly as  
12 shown.

13 A. So we're doing Meyer method 1.

14 Q. Yes.

15 A. Okay.

16 Q. As a result of Meyer method 1,  
17 have I increased the absolute number of 5'  
18 and 3' end fragments in the sample?

19 A. The absolute number?

20 Q. Yes.

21 A. You've increased the absolute  
22 number of all the molecules that undergo  
23 PCR. That's the point of PCR. So all the  
24 molecules that are going to be amenable to  
25 PCR will have PCR copies made depending on

1 the number of cycles and you run that  
2 exponentially for each of the fragments  
3 that you can successfully PCR.

4 Q. I want to talk about the modified  
5 method in additional file 4 that you talk  
6 about in paragraph 185 of Exhibit 2038.

7 A. I'm at paragraph 185 on page 114  
8 where I have the reproduction of the  
9 figure and then I believe this is a Meyer  
10 supplement area here so it's in the  
11 additional file 4.

12 Q. You agree the Meyer reference  
13 recommends that the POSA use the  
14 additional file 4 method?

15 MS. CIPRIANO: Objection to form.

16 THE WITNESS: They present no  
17 data in this paper on this method.

18 BY MR. HOAGLAND-HANSON:

19 Q. You agree that the data generated  
20 with the Figure 1 method is representative  
21 of what the results would be with  
22 additional file 4; right?

23 MS. CIPRIANO: Objection to form.

24 THE WITNESS: No, it can't be.

25 It's different than method 1.

1 BY MR. HOAGLAND-HANSON:

2 Q. You agree that you would get very  
3 similar and comparable results with the  
4 additional file 4 method as compared to  
5 the Figure 1 method?

6 MR. BEAVERS: Objection to form.

7 THE WITNESS: To be frank, I'm  
8 not sure because I haven't seen any  
9 data on the implementation of this  
10 method. So as a skeptical POSA I'm  
11 not sure what you'd expect, although I  
12 understand the setup.

13 BY MR. HOAGLAND-HANSON:

14 Q. So do you agree that you would  
15 get very similar and comparable results  
16 with the additional file 4 method or not?

17 A. I can't know until I see the  
18 data. I understand what they are trying  
19 to accomplish here and I understand why  
20 they present it as a potential improvement  
21 over the method, but you know, proof in  
22 the pudding. Until you carry it out and  
23 demonstrate it, it's a more complicated  
24 reaction and a lot of competing primers  
25 going on. So I can't tell you with

1     certainty what you would expect to see,  
2     how similar it would be to the original  
3     method, but they present the method in  
4     their paper and I know you rely on this  
5     method as a part of your petition so I  
6     spent time thinking about the method.

7           Q.    Do you think the changes to  
8     additional file 4 would significantly  
9     affect the results?

10           MS. CIPRIANO:  Objection, form.

11           THE WITNESS:  Again as I said, I  
12     can't know until you've run the  
13     experiment.  It might make a modest  
14     improvement.  It might make other  
15     biases creep up.  Hard to know until  
16     you've implemented.

17     BY MR. HOAGLAND-HANSON:

18           Q.    Would you expect to get a  
19     different distribution of 3' end fragments  
20     if you used the additional file 4 method?

21           A.    I can't guess at that.  It  
22     depends on the efficiency of the competing  
23     primers.  Hopefully it works as well.  
24     Maybe it works better.  Hard to honestly  
25     know.

1 Q. So you can't tell me how the  
2 sequencing data you would generate would  
3 differ if you had used additional file 4  
4 compared to Figure 1?

5 MS. CIPRIANO: Objection to form.

6 THE WITNESS: I'm not going to  
7 speculate on exactly what the  
8 sequencing data would look like.  
9 That's also got a random component of  
10 what material they started with, how  
11 well the cDNA process worked the  
12 second time and so on. It's a  
13 hypothetical as put forth here with a  
14 lot of components that are competing  
15 for the limited pool of reagents. So  
16 in theory we could go through and  
17 understand how each of the products  
18 that's made available for sequencing  
19 comes about, but until you run the  
20 experiment, you can't know. That's  
21 why you run the experiment.

22 BY MR. HOAGLAND-HANSON:

23 Q. Do you have some reason to think  
24 that Figure 1 results in  
25 overrepresentation of the 3' ends that

1 additional file 4 results in less  
2 overrepresentation of 3' ends?

3 MS. CIPRIANO: Objection to form.

4 THE WITNESS: Well, I -- sitting  
5 here today right now, I can't tell you  
6 if one would overrepresent more than  
7 the other, whether there would be  
8 overrepresentation. I think they are  
9 hoping this would help with the  
10 protocol. They've worked on this  
11 before so if I were interested in  
12 unbiased transcriptome sequencing of a  
13 non-model organism, I'd certainly  
14 consider using their protocol. May  
15 run protocols and see which one did  
16 better.

17 BY MR. HOAGLAND-HANSON:

18 Q. In both of these methods there's  
19 a PCR suppression feature that's included;  
20 right?

21 A. That's what I understand.

22 Q. And that results in the fragments  
23 that get the same adaptor, either the  
24 yellow or the red, don't get amplified;  
25 right?

1           A.    They are greatly suppressed.

2   That is accurate. By the creation of the  
3   hairpin loop.

4           Q.    There are many more of the  
5   fragments that get the red and yellow  
6   adaptors created than of the fragments  
7   that got the yellow and the red; right?

8           MS. CIPRIANO: Objection, form.

9           THE WITNESS: I'm sorry, repeat  
10       your question.

11   BY MR. HOAGLAND-HANSON:

12       Q.    Sure. There are three groups of  
13   fragments in here; right? Red-yellow,  
14   yellow-yellow and red-red.

15       A.    Just slow down for me. There's  
16   three groups, the 5' end fragments,  
17   internal fragments which represent more  
18   fragments than 5' end and 3' end, and then  
19   there's the ligation step which ligates on  
20   the yellow and red adaptors. And in  
21   ligating the red and yellow adaptors, half  
22   the time you get a yellow, half the time  
23   you'd get a red and so if you get a  
24   yellow-yellow or a red-red, you suppress.  
25   Half the time you get a yellow and a red,

1     you sequence. And so half of the internal  
2     fragments, which are most of the  
3     fragments, get a yellow and a red.

4         Q. After the ligation step, right,  
5     you have some fragments with a red and  
6     yellow, you have some fragments with two  
7     of the same adaptors; right?

8         A. That is correct.

9         Q. And at the end of the  
10    amplification step, you have many more of  
11    the red-yellow fragments than you have of  
12    the yellow-yellow and the red-red?

13        A. That is correct because you can  
14    only amplify those that have a red and a  
15    yellow.

16        Q. You'd agree that the red-red and  
17    the yellow-yellow don't go anywhere. They  
18    are still in the --

19        A. They aren't filtered out or  
20    cleaned in some way to my understanding,  
21    but they are not amenable to sequencing  
22    because they don't have adaptor ligated on  
23    their sequencing.

24        Q. In paragraph --

25        A. You can't sequence those

1 fragments because they are essentially  
2 invisible. The ones that are PCR  
3 suppressed.

4 Q. In paragraph 237 of Exhibit 2038  
5 you have a paragraph above which there's a  
6 heading, The Purpose of Meyer Reinforces  
7 that it Does Not Disclose Enrichment.

8 Do you see that?

9 A. I do.

10 Q. Why does the purpose of Meyer  
11 matter to your opinions?

12 A. Are we back to the metaphysical  
13 questions or? I think it matters because  
14 it demonstrates that they weren't aiming  
15 to do enrichment, they didn't do  
16 enrichment, their goal was to get an  
17 unbiased view of the transcriptome.  
18 That's what they wrote about. That's what  
19 they set up their experiment to do, and  
20 that's what they spoke to in their paper.

21 Q. You agree that if the Meyer  
22 authors set out to not enrich but did, in  
23 fact, enrich, right, it wouldn't matter if  
24 they didn't mean to?

25 MS. CIPRIANO: Object to form.

1           THE WITNESS: I think this goes  
2           to the question of sequencing and bias  
3           in sequencing. So if they see an  
4           overrepresentation of fragments based  
5           on the design of their protocol, is it  
6           a feature or is it a bug. In their  
7           case they would consider that a bug.  
8           They really want to get as clean a  
9           representation, as I've iterated  
10          throughout my testimony, as possible.  
11          If they have a bug, do they want to  
12          hunt down that bug and understand why  
13          that bug happened. Is it a problem  
14          that's going to cloud their analysis,  
15          for example, primer dimers; right?  
16          They didn't seek to find primer  
17          dimers. They did what they could to  
18          reduce the number of primer dimers.  
19          If they found some primer dimers, do  
20          they spend any time thinking about  
21          that and teaching more importantly to  
22          a POSA anything about the bug or the  
23          feature. And I would say they teach  
24          nothing here that a POSA would take  
25          and want to use as a means of

1 enrichment. A POSA would read this  
2 paper and say I'm interested in the  
3 method for doing full cDNA sequencing  
4 in a non-model organism. This seems  
5 to do a reasonable job. I'm going to  
6 try the method. That's why I think  
7 it's important. You asked me why do I  
8 think that purpose is important  
9 because is it a feature or is it a  
10 bug.

11 BY MR. HOAGLAND-HANSON:

12 Q. Is it your understanding that  
13 only features can anticipate the claims  
14 and not bugs?

15 MS. CIPRIANO: Objection to form.

16 THE WITNESS: It is my  
17 understanding that for prior art to  
18 anticipate, it must contain all of the  
19 elements of the claim in the same way,  
20 order, et cetera as laid out in the  
21 claims. So if it is such an  
22 interesting finding that it is an  
23 invention, then presumably someone  
24 would take that and build on it and  
25 demonstrate why it's a feature and not

1 a bug. To my knowledge no one carried  
2 this through and said clearly this  
3 demonstrates a massively interesting  
4 way to do target enrichment, which to  
5 me means it was a bug, it doesn't  
6 disclose and anticipate the claimed  
7 invention because it doesn't contain  
8 all of the elements of the claimed  
9 invention.

10 BY MR. HOAGLAND-HANSON:

11 Q. Okay. I guess I'm just trying to  
12 understand if the prior art teaches a way  
13 of doing something but not a very good  
14 way, does that not anticipate because the  
15 POSA is not interested in not a very good  
16 way?

17 MS. CIPRIANO: Objection, legal  
18 conclusion.

19 THE WITNESS: As I said, in my  
20 opinion again, I'm giving my  
21 scientific opinion. In my opinion, if  
22 the teaching of the paper is that you  
23 can create an unbiased representation  
24 of the transcriptome, sometimes it  
25 teaches away from doing enrichment.

1       There's no enrichment that's happening  
2       here. So why would you read this  
3       paper and say clearly there's  
4       enrichment, I'm going to modify this  
5       to now go do enrichment. It's not the  
6       paper. I think you have to torture it  
7       to get to that conclusion that it's  
8       teaching you enrichment.

9       BY MR. HOAGLAND-HANSON:

10       Q. So is it your understanding that  
11       if a reference teaches away from the  
12       invention, it can't anticipate the claims?

13       MS. CIPRIANO: Objection, same  
14       objection.

15       THE WITNESS: As I said, and just  
16       to reiterate, I'm not a lawyer, I'm a  
17       scientist. I'm giving you my  
18       scientific opinion. My understanding  
19       is that for a prior art to anticipate  
20       it must clearly lay out all of the  
21       elements of the claim in the same way  
22       in one embodiment and I don't see that  
23       here. And if anything, I would read  
24       Meyer's as a way to do transcriptome  
25       sequencing and solve problems with it,

1        454 potentially and consider it for  
2        use in other non-model organisms. I  
3        would not use it to do any target  
4        enrichment because the vast majority  
5        of fragments or sequencing here, the  
6        internal sequence that's made up here.  
7        So there's really no enrichment  
8        happening. That's what's made up here  
9        so there's really no enrichment  
10       happening as part of this method and  
11       that's their goal. They don't want to  
12       enrich, they want faithful  
13       representation.

14    BY MR. HOAGLAND-HANSON:

15        Q.    So I guess I'm just still trying  
16        to figure out, what is your opinion if  
17        Meyer does result in an increased  
18        proportion of 3' end fragments, does it  
19        still not anticipate?

20        A.    First of all, I don't believe it  
21        produced an increased proportion of 3'  
22        ends. I don't read that in Meyer at all  
23        first and foremost. Secondly, there is no  
24        enrichment as defined in the claims  
25        because enrichment must occur through the

1 extension, its complement, carried through  
2 the amplification. Here and as I laid out  
3 in my declaration, you're sequencing by  
4 design many fragments that don't contain  
5 anything resembling a target of interest.  
6 Most of what's being sequenced is the  
7 internal fragments and 5' end. So there's  
8 no enrichment happening if 3' end is  
9 relative to baseline and certainly no  
10 enrichment relative to the other fragments  
11 in the soup.

12 Q. Do you understand the claims to  
13 exclude the simultaneous sequencing of  
14 things that are not the target of  
15 interest?

16 MS. CIPRIANO: Objection to form.

17 THE WITNESS: As we've discussed,  
18 the claims allow for multiplexing. So  
19 you can have multiple targets of  
20 interest and still practice the  
21 claimed invention. You're practicing  
22 it for each of the targets of  
23 interest. And if sequencing allows  
24 you to do multiplexing, it allows to  
25 do -- multiplexing of samples, it

1 allows you to run similar types of  
2 samples, not all samples but you can  
3 sometimes run samples that are  
4 prepared in similar ways on the same  
5 lane or flow cell. And so if somebody  
6 wanted to create a system where you  
7 were doing targeting and another step  
8 and pooled those libraries, there's  
9 nothing here that prohibits that from  
10 happening.

11 BY MR. HOAGLAND-HANSON:

12 Q. In other words, if I practiced  
13 the steps of the claim to enrich for a  
14 sequence of interest and at the same time  
15 I decide because I've got a space on my  
16 Illumina to shotgun the rest of my sample,  
17 I'm not outside the scope of the claim;  
18 right?

19 A. For the portion that you're  
20 targeting, you're practicing the claimed  
21 invention.

22 Q. And I haven't taken myself  
23 outside the claimed invention by also  
24 shotgunning a bunch of other stuff, too;  
25 right?

1           A.     That would be my read given that  
2     it's a comprising step.

3           MS. CIPRIANO:  We've been going  
4     about an hour.  Do you want to take a  
5     break?

6           MR. HOAGLAND-HANSON:  Do you want  
7     to take a break?

8           THE WITNESS:  Sure.  I can take a  
9     short break.  I want to make sure that  
10    I've made myself available for all the  
11    questions that you have for me.

12          MR. HOAGLAND-HANSON:  Why don't  
13    we go off.

14          (Recess taken from 1:17 p.m. to  
15    1:28 p.m.)

16  BY MR. HOAGLAND-HANSON:

17       Q.    You ready, Dr. Bustamante?

18       A.    I am.

19       Q.    We were just talking briefly  
20    before the break, shotgun sequencing is  
21    just a method where you sequence all of  
22    the particular fragments in a sample; is  
23    that fair?

24          MS. CIPRIANO:  Objection, form.

25          THE WITNESS:  Shotgun sequencing

1 depends on the technology you're using  
2 but in general, when we refer to  
3 shotgun sequencing we're referring to  
4 sequencing of genomic DNA, and that  
5 genomic DNA is usually treated in such  
6 a way so that it is representative of  
7 the whole of the genome, but doesn't  
8 mean you get equal representation,  
9 given the biases of sequencing but  
10 oftentimes what you do is use adaptors  
11 that would allow you to sequence the  
12 fragments that are in the whole genome  
13 sequencing extract.

14 BY MR. HOAGLAND-HANSON:

15 Q. In paragraph 238 of Exhibit 2038,  
16 you with me, Dr. Bustamante?

17 A. I am.

18 Q. You say in the second half of the  
19 paragraph that starts at the top of the  
20 next page --

21 A. Give me a minute.

22 (Witness perusing document.)

23 Okay, I'm at the top of the page  
24 142.

25 Q. You say, "As Dr. Meyer explains,

1 their concern with the 3' end fragments  
2 being underrepresented in the sequencing  
3 data was based on the homopolymer optical  
4 issue"; is that right?

5 A. That's what I wrote.

6 Q. "They fixed that issue by  
7 breaking the polyT chain through the  
8 substitution of one 'T' nucleotide for a  
9 'C' nucleotide"; right?

10 A. I agree.

11 Q. "That substitution did not enrich  
12 for anything. It only reduced an issue  
13 with pyrosequencing"; right?

14 A. That's what I wrote.

15 Q. There was also a primer in both  
16 the Figure 1 method and the additional  
17 file 4 method that's directed to the cap  
18 sequence; right?

19 A. We can turn back to Figure 1. In  
20 Figure 1 there's a primer that targets the  
21 cap end sequences.

22 Q. Do you have any opinion as to the  
23 relative efficiency of that primer versus  
24 the red and yellow primers in the reaction  
25 in Figure 1?

1           A.    I don't recall speaking to them  
2    in my declaration and sitting here right  
3    now today, I'm not sure I could speak to  
4    the relevant efficiencies.

5           Q.    Okay. There's a calculation that  
6    you talk about on page 9 of Exhibit 1006,  
7    the Meyer reference.

8           A.    Let me turn to that.  
9                   I'm at that section of the paper  
10   and the general section of that in my  
11   report.

12          Q.    Okay. And what it says in  
13   Exhibit 1006 at page 9 is "A single copy  
14   of this 'broken T' adaptor was found in  
15   98,276 of the raw reads (16 percent of the  
16   total), slightly more than the expectation  
17   (approximately 10 percent of the reads),  
18   based on average read length of 232 base  
19   pairs and assuming an average transcript  
20   size of 2200 base pairs."

21                Do you see that?

22          A.    I do.

23          Q.    Do you agree that this  
24   calculation was based on reasonable  
25   assumptions?

1 MS. CIPRIANO: Objection to form.

2 THE WITNESS: This calculation is  
3 the subject of a lot of discussion so  
4 I'm going to ask you to please break  
5 that into a more specific question.

6 BY MR. HOAGLAND-HANSON:

7 Q. Do you agree the calculation was  
8 based on reasonable assumptions?

9 A. I'm not sure we know all of the  
10 assumptions that went into that  
11 calculation, including the transcript size  
12 of 2200 base pairs and the use of the  
13 average read length versus other measures  
14 of central tendency, and whether in a  
15 meaningful way that 10 percent is  
16 different from the 16 percent, given that  
17 it's very much a back of envelope  
18 calculation or a ballpark figure as  
19 they -- as Meyer says in his declaration.

20 Q. You agree that the calculation  
21 was designed to demonstrate that the Meyer  
22 authors had resolved the  
23 underrepresentation of the 3' ends; right?

24 A. In some way it's a way to check  
25 whether they were in the right ballpark.

1 Q. There's a statement that you just  
2 referred to about 2200 being the overall  
3 transcript length; right?

4 A. The average transcript length.  
5 Average transcript size is what they  
6 write.

7 Q. You agree that's a reasonable  
8 assumption as the average transcript size  
9 for the coral being studied here; right?

10 A. I do not agree that that's  
11 necessarily a reasonable assumption. I  
12 think this is a value they didn't make  
13 clear where it came from in the paper and  
14 even in the declaration its origin in a  
15 textbook based on mammals. So we actually  
16 have no quantitative estimate of what the  
17 actual average transcript size is in the  
18 coral species they are studying. So they  
19 picked a number and I don't think they or  
20 I would use that number today, and even  
21 back then, I'm not sure it was a  
22 reasonable estimate.

23 Q. Okay. Do you have an opinion as  
24 to what number should be used for the  
25 denominator instead of 2200?

1           A.    So I don't have an exact number  
2   for you but I do think it should be  
3   smaller than 2200 based on the actual  
4   distribution of the assemblies they saw  
5   and the fact that that's a number picked  
6   out for mammals, so they really need a  
7   better number based on corals, which is  
8   part of what they were trying to get to,  
9   to be frank. I think the number is  
10  probably smaller than 22.

11          Q.    Do you understand the POSA to  
12  read this number as it's set out in  
13  Exhibit 1006 and assume that that's the  
14  transcript length for mammals?

15               MS. CIPRIANO:  Objection to form.

16               THE WITNESS:  They don't make a  
17       specific reference at all to where  
18       that number comes from.

19  BY MR. HOAGLAND-HANSON:

20          Q.    In the paper, it's posited as the  
21  average transcript length; right?

22          A.    They claim it is but they don't  
23  give a reference to it. Assuming an  
24  average transcript size of 2200, it's an  
25  assumption.

1 Q. Okay. And what number do you  
2 think the POSA reading this reference  
3 would substitute for 2200?

4 A. I think a POSA would read this as  
5 saying uh, it's close to the 10 percent  
6 they are expecting, it's in the right  
7 ballpark. I don't think this was meant to  
8 be in any way a statement about  
9 enrichment, it's a statement that says  
10 we're in the right ballpark. It's an  
11 order of magnitude statement, it's not  
12 2 percent or 80 percent.

13 Q. Where does it say in the right  
14 ballpark?

15 MS. CIPRIANO: Objection to form.

16 THE WITNESS: It doesn't state  
17 that. What I'm saying in this section  
18 of the discussion, I think they are  
19 basically saying we're in the -- we're  
20 in the order of magnitude that you  
21 would expect. They don't make in any  
22 way, shape or form a statement, whoa,  
23 we've wildly increased over the  
24 10 percent. Right? It's near the  
25 expectation. Slightly more than the

1 expectation but near the expectation.

2 They got what they expected.

3 BY MR. HOAGLAND-HANSON:

4 Q. There's two percentages here,  
5 16 percent and 10 percent; right?

6 A. That's correct.

7 Q. Do you have an opinion that the  
8 POSA reading Exhibit 1006 would substitute  
9 some other percentages here?

10 A. There is no error bar. There is  
11 no measure of noise given. Approximately  
12 10 percent is given as the number. It's  
13 not even a solid 10 percent.  
14 Approximately 10 percent. So a POSA would  
15 read this and say they are near the  
16 expectation.

17 Q. You don't have an opinion where  
18 you say actually it should be 13 percent  
19 and 12 percent; right?

20 MS. CIPRIANO: Objection, form.

21 THE WITNESS: I give opinions as  
22 to the measures of central tendency  
23 that would perhaps be more appropriate  
24 to use to get at the expectation but  
25 again, I think this is not meant to be

1       a true -- a true quantitative  
2       assessment, rather it is an assessment  
3       of being near the expected value.  
4       Without a measure of error. There's  
5       no standard deviation given because  
6       they don't have true data. They have  
7       a ballpark figure based on mammals.  
8       That we find out later. It's not even  
9       written here saying it came from  
10      mammals.

11     BY MR. HOAGLAND-HANSON:

12         Q.    What percentage would be the more  
13     appropriate one to use as the expectation,  
14     Dr. Bustamante?

15               MS. CIPRIANO:  Objection to form.

16               THE WITNESS:  I would be  
17     hard-pressed given I don't have the  
18     actual data.  I just have the  
19     published distributions, but my sense  
20     is it is perhaps closer to 13 or  
21     14 percent, but again, that's a  
22     guesstimate.  I have -- and I think  
23     nobody has given the data that they  
24     have actually produced a reasonable  
25     way to differentiate whether the value

1           here is demonstrating  
2           overrepresentation at all. I think  
3           it's about what they would have  
4           expected to see and that's what they  
5           claim and move on.

6           MR. HOAGLAND-HANSON: Why don't  
7           we take a quick break.

8           MS. CIPRIANO: Okay.

9           (Recess taken from 1:44 p.m. to  
10          2:05 p.m.)

11          MR. HOAGLAND-HANSON: Welcome  
12          back, Dr. Bustamante. We have no  
13          further questions for you today.

14          MS. CIPRIANO: And I have no  
15          questions today. Thank you.

16          THE WITNESS: Thank you.

17          (Time noted: 2:05 p.m.)

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## 1 C E R T I F I C A T E

2 STATE OF NEW YORK )

3 : ss.

4 COUNTY OF NASSAU )

5

6 I, CATHI IRISH, a Registered  
7 Professional Reporter, Certified Realtime  
8 Reporter, and Notary Public within and for  
the State of New York, do hereby certify:

9 That DR. CARLOS BUSTAMANTE, the  
witness whose deposition is hereinbefore  
10 set forth, was duly sworn by me and that  
such deposition is a true record of the  
11 testimony given by the witness.

12 I further certify that I am not  
13 related to any of the parties to this  
14 action by blood or marriage, and that I am  
15 in no way interested in the outcome of  
16 this matter.

17 IN WITNESS WHEREOF, I have hereunto  
18 set my hand this 23rd day of  
19 October, 2025.

20

21

22

23

24

25

  
CATHI IRISH, RPR, CRR, CLVS

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1 Case: Integrated DNA Tech., Inc. vs Tecan Genomics, Inc.

2 Witness Name: Dr. Carlos Bustamante, Vol II

3 Deposition Date: 10/23/2025

4

5

6 Please be advised that the transcript in the above  
7 referenced matter is now complete and ready for signature.

8 The deponent may come to this office to sign the transcript,  
9 a copy may be purchased for the witness to review and sign,  
10 or the deponent and/or counsel may waive the option of  
11 signing. Please advise us of the option selected.

12 Please forward the errata sheet and the original signed  
13 signature page to counsel noticing the deposition, noting the  
14 applicable time period allowed for such by the governing  
15 Rules of Procedure. If you have any questions, please do  
16 not hesitate to call our office at (202)-232-0646.

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6 Witness Name: Dr. Carlos Bustamante, Vol II

7 Deposition Date: 10/23/2025

8 I do hereby acknowledge that I have read

9 and examined the foregoing pages

10 of the transcript of my deposition and that:

11 (Check appropriate box):

12 ( ) The same is a true, correct and

13 complete transcription of the answers given by

14 me to the questions therein recorded.

15 ( ) Except for the changes noted in the

16 attached Errata Sheet, the same is a true,

17 correct and complete transcription of the

18 answers given by me to the questions therein

19 recorded.

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1 Errata Sheet

2 NAME OF CASE: Integrated DNA Tech., Inc. vs Tecan Genomics, Inc.

3 DATE OF DEPOSITION: 10/23/2025

4 NAME OF WITNESS: Dr. Carlos Bustamante, Vol II

5 Reason Codes: 1. To clarify the record.

6 2. To conform to the facts.

7 3. To correct transcription errors.

8 Page \_\_\_\_\_ Line \_\_\_\_\_ Reason \_\_\_\_\_

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